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ORIGINAL REPORT

The Vaccine Safety Datalink project[†]

Frank DeStefano MD, MPH* for the Vaccine Safety Datalink Research Group[‡]

National Immunization Program, Centers for Disease Control and Prevention, Atlanta, GA, USA

SUMMARY

The Vaccine Safety Datalink (VSD) is a collaborative project between the National Immunization Program of the Centers for Disease Control and Prevention (CDC) and several large health maintenance organizations (HMOs) in the United States. 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. hospital discharge, outpatient visits, emergency room visits, and deaths), and covariate data (e.g. birth certificates and census) are prospectively collected at multiple HMOs (initially four) and linked under joint protocol for analyses. Approximately 6 million people (2% of the US population) are members of HMOs participating in the VSD. The VSD has proven to be a valuable resource that has provided important information on a number of vaccine safety issues. The databases and infrastructure created for the VSD have also provided opportunities to address other immunization questions including vaccination coverage and cost-effectiveness. In a recent investigation of intussusception following rotavirus vaccination, the VSD methodology was expanded to include 10 managed care organizations. A cohort study was conducted that allowed estimation of incidence rates of intussusception and attributable risks associated with rotavirus vaccine. Published in 2001 by John Wiley & Sons, Ltd.

KEY WORDS — surveillance; vaccines; immunization; safety; adverse events; intussusception

INTRODUCTION

As immunizations successfully reduce the incidence of vaccine-preventable diseases, there is increasing interest on vaccine safety concerns. There are several inherent limitations of pre-licensure clinical trials including sample size, duration of follow-up, and population heterogeneity. As a result, postlicensure (also called postmarketing) evaluation of safety once vaccines are given to millions of persons is needed to

* Correspondence to: Frank DeStefano MD, MPH, National Immunization Program (MS-F34), Centers for Disease Control and Prevention, Atlanta, GA 30341, USA. E-mail: fxd1@cdc.gov

[‡]Other members of the Vaccine Safety Datalink team (by site): Robert T. Chen MD, MA; John Glasser PhD, MPH; Philip H. Rhodes PhD; Piotr Kramarz MD; Thomas Verstraeten MD; David Walker MPH; Catherine Okoro (National Immunization Program, Centers for Disease Control and Prevention, Atlanta, Georgia); Robert S. Thompson MD; Lisa A. Jackson MD, MPH; Robert L. Davis MD, MPH; William E. Barlow PhD; Kari Bohlke ScD; Patti Benson MPH; Barbara Carste MPH; Jo Ann Habakangas BA; Christi Hanson BA; Minqi Jiang MS; Paula Lee Poy BA; Darren Malais BS; Viviana Rebolledo BS; Wendy Rogers BA; David Rubanowice BS; Dennis Sheeran MS; Onchee Yu MS; Ann Zavitkovsky MPH, MPA (Group Health Cooperative, Seattle, Washington); John P. Mullooly PhD; Julie E. Maher PhD, MS; Sheila Weinman PhD; Lois Drew BA; Jill Mesa; Kim Olson; Heather Houston RN; Colleen Chun MD; Steven Gancher MD; John A. Pearson MD; Jerry Slepak MD; Alan Bauck BS; Teresa Kimes MS; Joseph Murphy BA; Nadia Redmond MSPH; Karen Riedlinger MPH; Carol Sullivan; Gayle Thomas-Monk (Kaiser Permanente Northwest Region, Portland, Oregon); Steve B. Black MD; Henry R. Shinefield MD; Paula Ray MPH; Edwin Lewis MPH; Bruce H. Fireman MA; Joan Schwalbe; Ajit De Silva; Patti Hallam (Kaiser Permanente of Northern California, Oakland, California); Joel I. Ward MD; Connie M. Vadheim PhD; Hang Lee PhD; Ken Zangwill MD; Eileen Eriksen MPH; Tracy Zhang MS; Jennifer Lee MS; Jennie Jing MA; Nancy Goff; Jeffrey Perlman MD (Center for Vaccine Research Harbor-UCLA Medical Center, Torrance, California); S. Michael Marcy MD; Marlene Lugg DrPH (Southern California Kaiser Permanente, Los Angeles, CA); M. Miles Braun MD, MPH; Robert P. Wise MD, MPH, Robert Ball MD, MPH (Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD); Vito Caserta MD, MPH; Geoffrey Evans MD (Division of Vaccine Injury Compensation, Health Resources and Services Administration, Rockville, MD).

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evaluate rare, delayed, or unusual reactions. Postlicensure safety monitoring is also critical to maintaining public confidence, as vaccines are almost always given to healthy persons (mostly children) with few alternatives.

Historically, postlicensure monitoring in most countries, including the US, has relied on passive surveillance systems such as the VAERS. Because of the methodological limitations in passive surveillance for adverse events from drugs, during the 1980s pharmacoepidemiologists began turning to large databases that link computerized pharmacy prescription (and later, immunization) and medical outcome records. These databases derive from defined populations such as members of HMOs, single-provider health care systems, and Medicaid programs. As the databases are usually generated in the routine administration of such programs and do not require completion of a vaccine adverse event reporting form, the problems of underreporting or recall bias are reduced. Because these programs have enrollees numbering from thousands to millions, large populations can be examined for relatively infrequent adverse events. Denominator data on doses given and the ready availability of appropriate comparison groups also make these databases ideal for studying vaccine safety.

Recognition of the need for improved monitoring of vaccine safety prompted CDC to initiate the VSD project in 1990.[1] The following is a brief review of the VSD methodology and a few of the studies that have been completed thus far. We also present an example in which the VSD methodology was rapidly expanded to conduct a large cohort study of intussusception following rotavirus vaccination.

METHODS

The National Immunization Program of the Centers for Disease Control and Prevention (CDC) created the VSD in 1991. The project links medical event information, vaccine history, and selected demographic information from the computerized clinical databases of four staff model HMOs: Group Health Cooperative of Puget Sound (GHC) in Seattle, Washington; Kaiser Permanente Northwest (NWK) in Portland, Oregon; Kaiser Permanente Medical Care Program of Northern California (NCK) in Oakland, California; and Southern California Kaiser Permanente (SCK) in Los Angeles, California. HMO members have unique identification numbers that can be used to link data on their medical services within the HMO. Initially, the project obtained data only on infants and children from birth through 6 years of age, but data collection has since been expanded to include older children, adolescents, and adults, and now totals about 6 million members.

Computerized databases are the initial source of data for most VSD studies. Vaccination data are derived from computerized immunization tracking systems that are maintained by each of the HMOs. Quality control comparisons of the computerized immunization data with information recorded in paper medical records have shown high levels of agreement.[2] For medical encounters, each of the HMOs 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 are also available if needed. Paper medical records are often abstracted to confirm diagnoses and vaccination histories. Occasionally, patients or their parents are interviewed to obtain additional information. Each site encodes their patients' clinical data with unique study identifiers before sending data to CDC annually for merging and analysis, thereby preserving patient confidentiality.

RESULTS FROM SELECTED STUDIES

Several studies from the VSD have been published to date. In addition to vaccine safety, study topics have also addressed issues of vaccine coverage, disease incidence, methodology, and cost-effectiveness. Highlights of selected published vaccine safety studies follow.

Risk of hospitalization because of aseptic meningitis after measles-mumps-rubella (MMR) vaccination in 1- to 2-year-old children

Vaccines containing the Urabe strain of mumps vaccine have been shown to be associated with an increased risk of aseptic meningitis. However, an analysis in VSD showed that the MMR vaccine used in the United States, containing the Jeryl-Lynn strain of mumps vaccine, is not associated with an increased risk of aseptic meningitis.[3] A matched case–control study was performed using cases of aseptic meningitis that were ascertained by reviewing hospitalization data files from 1984 through 1993 among children 1 to 2 years of age. Of the 59 confirmed cases hospitalized for aseptic meningitis, three had received MMR vaccine within 30 days before vaccination compared with seven of the 118 matched controls, resulting in an odds ratio (95% confidence interval (CI)) of 0.8 (0.2–3.5).

Safety of second MMR vaccination at 4–6 years and 10–11 years of age

A comparison of adverse event rates in the VSD project found that children 10 to 12 years of age were more likely to have a clinical event after a second MMR vaccination than were children who received their second MMR at 4 to 6 years of age.[4] These results favored policy recommendations to give the second MMR at 4 to 6 years. To determine whether there was an increased frequency of clinical events after, and possibly related to, the second MMR dose in children aged 10 to 12 years compared with those aged 4 to 6 years, we took advantage of procedural differences in vaccine administration at two HMOs. A cohort of children who had received MMR vaccination was identified at each of the HMOs and the rates of medical encounters overall and for specific conditions was compared for the 30-day period following vaccination with a 30-day period before vaccination. The rates of medical encounters increased by about 45% after vaccination in the HMO that gave the second MMR at 10–12 years of age, compared with encounter rates before vaccination, whereas encounter rates decreased after vaccination in the HMO that gave the vaccine at 4–6 years. The increased encounter rates in the 10–12-year-old age group was typically for rashes and joint pains. In addition, there appeared to be an increase in visits for seizures from the computerized data, but chart review revealed that these were mostly for follow-up or well-child care visits among children with a pre-existing seizure disorder.

Risk of chronic arthropathy among women after rubella vaccination

Acute joint complaints following rubella vaccination occur in about 25% of women. A review by the Institute of Medicine found a possible causal relationship between rubella vaccination and chronic arthritis in women.[5] To evaluate a possible association, a study was conducted at one of the VSD HMOs with a regional laboratory database to identify and select women according to rubella serologic status. Detailed chart review was conducted to verify diagnoses of arthropathies, to determine their onset dates, and to obtain rubella vaccination histories. Overall, records of 4884 women were reviewed. After at least 1 year of follow-up, there was no evidence of an increased risk of chronic joint problems associated with vaccination.[6]

Population-based cohort study of intussusception and rotavirus vaccination

In the spring of 1999, the VAERS received a number of reports of intussusception following rhesus rotavirus tetravalent (RRV-TV) vaccination. Intussusception is a rare disorder and too few doses of rotavirus vaccine had been given in the four VSD HMOs to study the potential association adequately. Ten managed care organizations, including two from the VSD project, were enrolled to study this issue.[7] Cases of intussusception were identified by searching electronic databases for diagnoses of intussusception (ICD-9-CM code 560.0) in infants 1–11 months of age and confirmed by medical chart review. Of 463 277 children, 56 253 had been vaccinated with a total of 91 371 doses of RRV-TV. The incidence rate of intussusception was 25/100 000 person-years among unexposed infants and 340/100 000 person-years in infants 3–7 days after vaccination. In the interval 3–7 days after vaccination, the age-adjusted rate ratio was 16.0 (95% CI: 5.5–46.7) for all doses combined and 30.4 (95% CI: 8.8–104.9) after the first dose. The attributable risk was one case of intussusception per 11 073 children vaccinated. These results (along with a concurrent case–control study) were instrumental in CDC's Advisory Committee on Immunization Practices deciding to withdraw its recommendation for RRV-TV. The study also illustrates that managed care organizations can quickly respond to emerging vaccine safety concerns by providing timely data on large populations.

KEY POINTS

- The Vaccine Safety Datalink (VSD) project capitalizes on the advantages of health maintenance organizations (HMOs) for efficient population-based health research
- The VSD evaluates vaccine safety hypotheses arising from the medical literature, from passive surveillance such as the Vaccine Adverse Event Reporting System (VAERS), and from changes in immunization schedules or the introduction of new vaccines
- The VSD methodology can be adapted quickly to address important vaccine safety concerns as they arise
- VSD studies have provided important information on the safety of vaccines and have contributed to immunization policy decisions

CONCLUSION

The VSD project was established to capitalize on the advantages offered by HMOs for efficient population-based health research. The VSD is being used to evaluate vaccine safety hypotheses that might arise from the medical literature, from passive surveillance like the VAERS, and from changes in immunization schedules or the introduction of new vaccines. Many of the completed VSD studies have informed United States vaccination policy. The number and scope of studies in the project has continued to grow along with the recognition by immunization programs and policy makers of the increasing importance of vaccine safety monitoring in maintaining the public's confidence in vaccines. The recent expansion of the VSD infrastructure to conduct a timely cohort investigation of the risk of intussusception associated with rotavirus vaccine illustrates the potential of the VSD methodology to be adapted quickly, to address important vaccine safety concerns as they arise.

REFERENCES

1. Chen RT, Glasser J, Rhodes P, *et al*. The Vaccine Safety Datalink Project: a new tool for improving vaccine safety monitoring in the United States. *Pediatrics* 1997; **99**: 765–773.
2. Mullooly J, Drew L, DeStefano F, *et al*. Quality of HMO vaccination databases used to monitor childhood vaccine safety. *Am J Epidemiol* 1999; **149**: 186–194.
3. Black S, Shinefield H, Ray P, *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 Infect Dis J* 1997; **16**: 500–503.
4. Davis RL, Marcuse E, Black S, *et al*. MMMR2 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.
5. Institute of Medicine. *Adverse Effects of Pertussis and Rubella Vaccines.* National Academy Press: Washington, DC; 1991.
6. Ray P, Black S, Shinefield H, *et al*. Risk of chronic arthropathy among women after rubella vaccination. *JAMA* 1997; **278**: 551–556.
7. Kramarz P, France EK, DeStefano F, *et al*. Population based study of rotavirus vaccination and intussusception. *Pediatric Infect Dis J* 2001; **20**: 410–416.