THE VACCINE SAFETY DATALINK (VSD) PROJECT

Annual Report for 2003

AHIP
America's Health Insurance Plans

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Vision/Mission

The vision of the Vaccine Safety Datalink (VSD) project is to provide a powerful and cost-effective resource for the ongoing evaluation of vaccine safety. The mission of the VSD project is to carefully monitor vaccine safety through planned vaccine safety studies and timely investigations of hypotheses.

"Sound immunization policies and recommendations affecting the health of our nation depend upon the consistent monitoring of vaccines and ongoing assessment of immunization benefits and risks. The Vaccine Safety Datalink project is one of our most important tools to ensure the safety and efficacy of vaccines."

Centers for Disease Control and Prevention

Table of Contents

Vaccines are important allies in the effort to prevent illness and control the spread of many diseases. Yet, each year there are reports that highlight possible side effects or other adverse events related to vaccines. Such reports can lead to unwarranted public concern about the risks of vaccines and lead to potential avoidance of vaccinations. Such public actions can have a deleterious effect on the health of the nation.

It is critical to the health of our nation to have a scientific system for collecting vaccine safety information from a large population. The Vaccine Safety Datalink (VSD) project, with the ultimate goal of protecting the public's health through the ongoing monitoring of vaccine safety, provides just such a system.

America's Health Insurance Plans (AHIP), providing health benefits to over 200 million Americans, is proud to be a part of the CDC's VSD project. For more than 20 years—predating the VSD project—researchers in health plans have been involved in vaccine safety and efficacy studies. Since the inception of the VSD project, researchers affiliated with eight health plans have worked collaboratively with CDC researchers to continue studying vaccine safety.

Health plans and insurers have long championed the use of preventive services, especially vaccines, to improve health and prevent disease. AHIP member plans consider vaccination to be an essential component for ensuring a healthy nation and have been innovators in the design of immunization programs to increase rates and timeliness of immunization among infants, children, adolescents and adults.

This annual report highlights the continuing contributions being made to vaccine safety by health plans serving as VSD participating sites.

Karen M. Ignagni
President and CEO, America's Health Insurance Plans (AHIP)

Vaccines are among the most successful and cost-effective public health tools for preventing disease and death in the modern era. The National Immunization Program (NIP) is devoted to undertaking and promoting a wide range of scientific activities to support immunization and prevent disease worldwide. However, no vaccine is 100% safe. When the majority of the population has been vaccinated and the disease risk becomes rare, both real and perceived vaccine side effects increase, which result in heightened public concern about the safety of vaccines. A loss of public confidence in vaccines could result in decreased vaccination levels, followed by epidemics of disease. A timely, credible and effective immunization safety monitoring system to determine which illnesses are caused by vaccines, and which are not, must exist to maintain public confidence in immunizations and prevent the return of disease epidemics.

Within NIP's Immunization Safety Branch (ISB), we are engaged in many programs and activities to monitor the safety of vaccines. The Vaccine Adverse Event Reporting System (VAERS), in collaboration with the Food and Drug Administration, serves as an early warning system to detect problems that may be related to vaccines. The Clinical Immunization Safety Assessment (CISA) Network provides in-depth, standardized clinical evaluations for individuals with unusual or severe vaccine adverse events that might be reported to VAERS. The Brighton Collaboration is a global collaboration which was established to standardize case definitions for study of vaccines, thereby creating a common "vocabulary" for vaccine safety research.

Further vaccine safety research for causal relationships is conducted within ISB through the Vaccine Safety Datalink (VSD) Project, a large-linked database containing comprehensive medical and immunization histories of over 7.5 million people. The VSD enables population-based vaccine safety research studies to compare the incidence of health problems between vaccinated and unvaccinated people. In addition, the VSD established a data sharing process to allow external researchers access to datasets created through the VSD. Research conducted by the Vaccine Acceptance Risk Perceptions (VARP) group determines how best to disseminate information on the benefits and risks of vaccinations, and the Vaccine Development (VAXDEV) activity works to develop safer vaccines and delivery methods, especially needle-free jet injectors for mass immunization campaigns.

I am proud of the accomplishments we have made to monitor the safety of vaccines as documented in this report, conducted by CDC and in collaboration with the various external partners like America's Health Insurance Plans (AHIP). I hope you will join me in supporting the research projects conducted through our vaccine safety programs and activities. I thank you for your contributions and your support in the past year, and welcome the opportunity to continue our collaboration in the coming year.

Sincerely,

Stephen L. Cochi, MD, MPH
Captain, United States Public Health Service
Acting Director, National Immunization Program

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Introduction

Immunization is one of the greatest public health success stories of all time. Every year, many serious childhood diseases are prevented by using vaccines routinely recommended for newborns, infants and children. Since the introduction of these vaccines, reported cases of vaccine-preventable childhood diseases have decreased dramatically in the United States and millions of lives have been saved. As a result, most Americans today have only vague memories of diseases such as polio, rubella, measles, diphtheria, meningitis and pertussis. Without vaccines, the diseases we are now protected from could return to cause serious illness or even death in many infants and children.

Before Vaccines, Parents in the United States Could Expect that Every Year:

- Polio would paralyze about 15,000 children.
- Rubella ("German measles") would cause birth defects and mental retardation in as many as 20,000 newborns;
- Measles would infect about 4 million children, killing 3,000.
- Diphtheria would be one of the most common causes of death in school-aged children.
- A bacterium called Hib would cause meningitis in 15,000 children, leaving many with permanent brain damage.
- Pertussis ("whooping cough") would kill 8,000 children.

Source: Offit, Paul and Bell, Louis, Vaccines: What You Should Know (Third Edition); (page 3); John Wiley & Sons, Inc. 2003.

Although vaccines are widely considered to be important and safe allies in the effort to prevent many serious diseases, vaccines are not completely without risk of side effects or other adverse outcomes. At several points in time during the past decade, the public has expressed concern about possible side effects of vaccines and questioned the safety of specific vaccines. Most recently, there has been public concern over the use of thimerosal (a mercury-containing preservative) in vaccines, reports of severe side effects associated with the smallpox vaccine, and studies suggesting a link between the measles-mumps-rubella (MMR) vaccine and autism. In most instances, concerns about the risks of specific vaccines can be addressed and reduced by providing empirically-based information that allows the public to see that the benefits of a specific vaccine outweigh its risks. However, such information is dependent on a systematic approach for continually monitoring and assessing the safety of specific vaccines in a variety of populations.

Do the Benefits Outweigh the Risks? The Case of Hepatitis B Vaccine

Each year in the United States about 5,000 people die soon after contracting hepatitis B virus. In addition, every year about 10,000 people become chronically infected with hepatitis B virus, putting them at high risk for developing cirrhosis and liver cancer. In fact, with the exception of influenza virus, hepatitis B virus causes more severe disease and death in the United States than any other vaccine-preventable disease.

On the other hand, severe side effects associated with hepatitis B vaccine are extremely rare. One of every 600,000 doses of the hepatitis B vaccine will cause a severe allergic reaction called anaphylaxis. Anaphylaxis usually occurs within 15 minutes of receiving the vaccine and is treatable. To date, no one has died from this reaction.

Because hepatitis B virus is a common cause of severe disease and death in the United States, and the hepatitis B vaccine does not cause permanent damage or death, the benefits of the hepatitis B vaccine clearly outweigh its risks.

Source: Adapted from The Children's Hospital of Philadelphia's Vaccine Education Center at www.chop.edu/consumers/jsp/division/generic.jsp?id=75730

The Vaccine Safety Datalink (VSD) Project

The CDC/NIP Immunization Safety Branch

The Immunization Safety Branch of the CDC's National Immunization Program is charged with enhancing the nation's capacity to monitor and evaluate vaccine safety. Projects underway within the CDC/NIP Immunization Safety Branch include:

- **Vaccine Safety Datalink (VSD) Project.** To collaborate with researchers in the private sector for the purpose of conducting studies that monitor the safety of vaccines commonly used in the United States.
- **Clinical Immunization Safety Assessment (CISA) Network.** To improve scientific understanding of vaccine safety issues at the patient level and develop protocols to assist healthcare providers to better manage situations in which adverse vaccine events occur.
- **Vaccine Adverse Event Reporting System (VAERS).** To monitor reports of post-vaccination adverse events from health professionals, vaccine manufacturers, and the general public for the purpose of identifying new or rare vaccine side effects, increases in the occurrence of known side effects, and patient risk factors for specific adverse events.
- **Brighton Collaboration.** The Brighton Collaboration is an international voluntary collaboration to facilitate the development, evaluation, and dissemination of high quality information about the safety of human vaccines and to develop globally accepted and implemented standardized case definitions of Adverse Events Following Immunization (AEFIs).
- **The Vaccine Acceptance Research Program (VARP).** The Vaccine Acceptance Research Program was conceived to better understand the way in which individuals interpret risks and make decisions about vaccination. The primary goal of this program is to develop and evaluate interventions that help individuals make informed decisions about vaccinations and help people understand the potential increased risk of disease if a significant number of people refuse to be vaccinated because of the current low disease prevalence.
- **The Vaccine Development (VAXDEV).** Unit promotes safer vaccine administration methods such as needle-free injection technology, through contract R&D for high-speed jet injectors, clinical studies, and an information database, website, and news service. VAXDEV also monitors new vaccines and technologies in development, and promotes guidelines for improved vaccine labeling and packaging to minimize medical errors, improve recordkeeping, and enhance surveillance of vaccination adverse events.

The Vaccine Safety Datalink (VSD) was established in 1990 as a crucial part of the federal government's systematic effort to monitor the safety of vaccines commonly used in the United States and to reassure public confidence in vaccines. Through the VSD project, researchers from the private and public sectors work together on studies designed to monitor the safety of vaccines administered to infants, children, adolescents and adults. Based at one of eight participating sites or the Centers for Disease Control and Prevention (CDC), the VSD researchers conduct studies that provide vital information about the short and long-term effects of specific vaccines on various populations. Collectively, the data from the VSD studies are based on active surveillance of approximately seven million people (2.5% of the total U.S. population).

Although all VSD studies are designed to answer critical questions about vaccine safety, each year a select number of studies is given a special "priority" designation that indicates their vital importance to the nation's health. VSD priority studies focus on vaccine safety, are generally based on data collected from multiple sites, and are allocated highest priority in the event that time or financial resources become limited. In this report, we highlight ten priority studies.

The CDC's National Immunization Program (NIP) is charged with the responsibility of providing leadership, expertise and ongoing education about the development and delivery of an effective immunization delivery program for the United States. As part of its mission, NIP's Immunization Safety Branch supports epidemiologic research to evaluate the safety, immunogenicity and efficacy of vaccines recommended for routine human use after licensure by the U.S. Food and Drug Administration (FDA). NIP provides leadership for the planning, coordination and conduct of immunization activities across the nation. Such activities include the provision of consultation, training, statistical, promotional, educational and technical services to assist health departments and other entities to implement effective immunization programs.

America's Health Insurance Plan (AHIP) (formerly known as the American Association of Health Plans) was selected by CDC to provide overall management and coordination for the VSD project. As part of its role in the VSD project, AHIP's responsibilities include:

- Maintain the strategic direction of the VSD projects;
- Monitor and review the quality of work associated with VSD projects and studies;
- Verify that all fiduciary responsibilities and budget specifications are met; and
- Assure timely completion of all work and efforts associated with the scope of the VSD project.

Participating VSD Sites

- **Centers for Disease Control and Prevention**
  National Immunization Program
  Immunization Safety Branch
  Atlanta, Georgia
- **Group Health Cooperative**
  Center for Health Studies
  Seattle, Washington
- **Harvard Pilgrim Health Care, Harvard Medical School and Harvard Vanguard**
  Department of Ambulatory Care and Prevention
  Boston, Massachusetts
- **HealthPartners Research Foundation**
  Minneapolis, Minnesota
- **Kaiser Permanente Colorado**
  Clinical Research Unit
  Denver, Colorado
- **Kaiser Permanente Northwest**
  Center for Health Research
  Portland, Oregon
- **Marshfield Clinic Research Foundation**
  Marshfield, Wisconsin
- **Northern California Kaiser Permanente**
  Kaiser Permanente Vaccine Study Center
  Oakland, California
- **UCLA Center for Vaccine Research / Southern California Kaiser Permanente Health Care Plan**
  Los Angeles, California

Hepatitis B: An Overview

Hepatitis B is a virus that infects the liver. Each year in the United States, approximately 300,000 people become infected with hepatitis B. Among people who contract hepatitis B, about 5,000 die soon after they are infected and another 10,000 develop long-term hepatitis that puts them at risk for cirrhosis and cancer of the liver.

A vaccine for hepatitis B was first licensed for use in the United States in 1982. Since that time, millions of adults, infants, and children have received the hepatitis B vaccine. Side effects are rare. About three percent of children develop pain and tenderness where the shot was given and one percent develop low-grade fevers. An extremely rare side effect of hepatitis B vaccine is anaphylaxis, which is treatable and estimated to occur only once in every 600,000 doses.

Vaccination and Risk of Autoimmune Thyroid Disorder: Is Hepatitis B Vaccine Associated with Graves' Disease or Hashimoto's Thyroiditis?

ISSUE

Recent concerns have been raised about a possible association between hepatitis B vaccine and occurrences of autoimmune thyroid diseases (ATD), such as Graves' disease and Hashimoto's thyroiditis. The concerns are based in part on case reports. Information from such reports is insufficient to infer a causal link between hepatitis B vaccine and ATD because reported cases may simply represent coincidental timing between vaccination and the onset of ATD. Thus far, only a single case-control study, published as an abstract in Pharmacoepidemiology and Drug Safety, has addressed this question. Given the sparse data currently available, and the potential implications of public concern regarding these early reports of a possible association between hepatitis B vaccine and ATD, confirmatory studies are needed.

VSD RESPONSE

A group of VSD researchers has begun a collaborative study to evaluate the association between receipt of hepatitis B vaccine and risk of ATD, specifically Graves' disease or Hashimoto's thyroiditis. As part of the study, researchers will simultaneously conduct two case-control studies among the adult populations of three HMOs participating in the VSD project (Group Health Cooperative, Kaiser Permanente Northwest, and Northern California Kaiser Permanente). At each participating site, automated data sources will be used to identify persons with Graves' disease or Hashimoto's thyroiditis (cases) and persons with no history of thyroid disease (controls). Data will be confirmed by chart review, and persons identified as eligible cases and controls will be contacted by telephone to obtain additional information about vaccinations, identify relevant covariates (i.e., family and personal history of select autoimmune conditions), and estimate date of symptom onset among persons with ATD.

The specific objectives of this VSD priority study are to:

- Evaluate the association between having ever received a hepatitis B vaccine and risk of Graves' disease or Hashimoto's thyroiditis;
- Assess the association between receipt of hepatitis B vaccine within intervals of <1 year, 1-5 years, and >5 years of the index date and risk of Graves' disease or Hashimoto's thyroiditis;
- Evaluate the association between other adult vaccines and the risk of Graves' disease or Hashimoto's thyroiditis;
- Assess the association between receipt of other adult vaccines within intervals of <1 year, 1-5 years, and >5 years of the index date and risk of Graves' disease or Hashimoto's thyroiditis.

The results from this VSD priority study will provide the data necessary to determine whether receipt of hepatitis B vaccine is associated with an increased risk of autoimmune thyroid disease. The study will also fill a gap in the study of autoimmune disorders currently ongoing or recently completed through the VSD project.

VSD Priority Study Research Team:

KARI BOHLKE, ScD
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"By collecting complete information about hepatitis B vaccination history from a well-defined study population, this study will confirm or refute concerns raised by case reports."

Kari Bohlke, ScD, Principal Investigator, Group Health Cooperative

VSD Priority Study Research Team:

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Principal Investigator
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BARBARA CARSTE, MPH
Group Health Cooperative

Alopecia Following Hepatitis B Vaccine in Adults and Adolescents: Is Hepatitis B Vaccine Associated with an Increased Risk of Alopecia?

ISSUE

Recent reports submitted to VAERS suggest that alopecia areata (hair loss) may rarely occur in persons who have received hepatitis B vaccine. While the mechanisms responsible for alopecia following vaccination are not certain, the condition could be immune-mediated. Therefore, CDC continues to conduct research to examine the effects vaccines may have on the immune system in general and alopecia in particular.

VSD RESPONSE

At Group Health Cooperative (GHC), VSD researchers have been working on a matched case-control study to assess the association between receipt of hepatitis B vaccine and the risk of alopecia in adults and adolescents. Chart reviews were used to validate outcome and exposure status for cases and exposure status for controls. In the first phase of the study, cases were drawn from those identified for an earlier retrospective matched case-control analysis that GHC conducted using automated data and controls were matched to cases 5:1 by age, sex, and length of enrollment in GHC prior to the index date. Analyses from the first phase were based on 206 cases and 610 controls, and there was inadequate power to detect an association between alopecia and vaccination (if one exists). Since some associations between alopecia and vaccination have been suggested, the VSD Adult Studies Work Group approved GHC's proposal to expand the analysis to include at least two additional years of data. This second phase of the study is currently underway.

The specific objective of this VSD priority study is to:

- Evaluate the association between receipt of hepatitis B vaccine and risk of alopecia.

The results from this VSD priority study will increase our knowledge about vaccine side effects and contribute to a greater understanding of the impact vaccines may have on the immune system.

Risk of Alopecia Following Hepatitis B Vaccination: A Preliminary Cohort Analysis of 15-59 Year Olds

ISSUE

Recent studies suggest that alopecia areata (hair loss) may rarely occur in persons who have received hepatitis B vaccine. While the mechanisms responsible for alopecia following vaccination are not certain, the condition could be immune-mediated. Therefore, CDC continues to conduct research to examine the effects vaccines may have on the immune system in general and alopecia in particular.

VSD RESPONSE

Researchers at Northern California Kaiser Permanente (NCKP) are conducting a cohort study to assess the risk of alopecia following hepatitis B vaccination among persons aged 15 to 59 years. The study has involved a cohort of persons continuously enrolled in NCKP from 1/1/95 to 12/31/99. Automated data on clinic visits were collected for the cohort and persons with visits for hair loss prior to their follow-up start date were excluded. Vaccine data were collected from an automated immunization database, and the relative risk for alopecia by type of vaccine exposure (i.e., hepatitus B, tetanus/diptheria, influenza) was estimated.

Although a statistically significant association was seen for alopecia in persons exposed to hepatitis B vaccine, similar results were seen in comparisons between persons exposed vs. unexposed to Td. These same results were not found in persons exposed to flu vaccine. The similarities in alopecia rates in the HepB and Td vaccine exposed groups suggest the possibility of unidentified confounders, possibly related to utilization patterns. Further analyses will be necessary to identify potential confounders.

The relatively high incidence of alopecia diagnoses seen in the NCKP automated clinic data compared to published incidence rates for alopecia as well as results of earlier chart review studies suggest a possible lack of specificity in the automated data for alopecia. Chart reviews will be necessary to verify rates of alopecia in exposed vs. unexposed groups.

VSD Priority Study Research Team:

STEVEN B. BLACK, MD
Principal Investigator
Northern California
Kaiser Permanente

HENRY SHINEFIELD, MD
Northern California
Kaiser Permanente

"This study is a good example of the pairing of the VAERS and the VSD for evaluations of vaccine safety. In this case, VAERS reports suggested a possible link between hepatitis B vaccine, or other vaccines, and alopecia areata in children and adults. As a follow-up to this signal, a controlled epidemiologic study was initiated in the VSD."

Lisa Jackson, MD, MPH, Principal Investigator, Group Health Cooperative

VSD Priority Study Research Team:

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Influenza: An Overview

Commonly known as the flu, influenza is a virus that infects the respiratory system. Every year in the United States, about 115,000 people are hospitalized and about 20,000 people die from severe pneumonia caused by influenza. Most of the deaths caused by influenza occur in people 65 or older. However, young children are more likely than adults to be hospitalized with infections caused by influenza.

An influenza vaccine is given to people who are at high risk for developing severe influenza. Recently, CDC advised that all children between 6 months and 23 months of age should also receive the influenza vaccine. Known side effects from influenza vaccine are extremely rare. The influenza vaccine causes fever, muscle aches and fatigue in less than one percent of people given the vaccine.

Influenza Vaccine and Bell's Palsy: Does Influenza Vaccine Increase the Risk of Bell's Palsy?

ISSUE

Bell's palsy is a common neurological disorder that accounts for up to 75% of all peripheral facial palsies. Although the etiology of Bell's palsy is not clear, one of the theories put forward involves an autoimmune etiology. Following the introduction of a newly licensed intranasal influenza vaccine in Switzerland in October 2000, 46 cases of Bell's palsy were noted among people who received the vaccine. The situation warranted a thorough investigation to determine whether there is any association between influenza vaccine and Bell's palsy.

VSD RESPONSE

A group of VSD researchers are currently conducting a case-control study to investigate the possible association between use of the intranasal influenza vaccine and Bell's palsy. As part of the study, researchers will identify people with Bell's palsy who are members of HMOs participating in the VSD project. At each participating site, medical records of persons with Bell's palsy will be reviewed to assess exposure to influenza vaccine, hepatitis B vaccine, Td vaccine, and other vaccines. Data will be analyzed to calculate relative risk of Bell's palsy following vaccination and the incidence of Bell's palsy will be assessed in vaccinated and unvaccinated populations.

The specific objectives of this VSD priority study are to:

- Investigate whether or not receipt of influenza vaccine increases the risk for Bell's palsy;
- Assess the extent to which receipt of other vaccines are risk factors for Bell's palsy.

The results from this VSD priority study will contribute to the ongoing investigation of the association between influenza vaccine and Bell's palsy. The study will also contribute to our understanding of the interaction between autoimmune disorders and vaccines.

"This study will investigate any association between influenza vaccine and Bell's palsy to ensure the safety of the general public."

Lisa Jackson, MD, MPH, Group Health Cooperative

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Safety of the Trivalent Inactivated Influenza Vaccine Among Children Ages 6-23 Months: A Population-Based Study, 1993-2003

ISSUE

During the influenza season of 2002/2003, CDC encouraged the vaccination of healthy children aged 6 to 23 months for the first time ever. The decision to encourage vaccination of children against influenza was largely based on the increased risk for hospitalization due to influenza that was seen among children in this age group. The decision was also based on new evidence that universal vaccination of school children may prevent influenza in the population of adults over 65 years of age through "herd immunity." In October 2003, the Advisory Committee on Immunization Practices (ACIP) voted to formally recommend vaccination against influenza for all healthy children ages 6-23 months. In deciding on this recommendation, national policy groups based their decision partly on existing data on the safety of the Trivalent Influenza Vaccine (TIV) in young children. However, they have also requested ongoing surveillance for possible rare adverse events due to this vaccine.

VSD RESPONSE

VSD researchers are currently working on a study that will provide the data needed to accurately assess the safety of the Trivalent Influenza Vaccine (TIV). Researchers will study a large cohort of young children who received the Trivalent Influenza Vaccine (TIV) over a period of 10 years (1993 - 2003) for evidence of any increased risk of adverse events requiring medical attention following vaccination. The study will include all children aged 6 to 23 months of age who received at least one TIV vaccination between 1993 and 2003, and who were continuously enrolled in the Vaccine Safety Datalink participating site at least 42 days prior to and 70 days following vaccination. Approximately 25,000 children are expected to be included in the study. All inpatient, outpatient, and emergency department visits will be used to identify patterns of medically attended events (MAEs) occurring within three "risk windows" following influenza vaccination (i.e., 0-2 days, 1-14 days, 15-42 days).

The specific objectives of this VSD priority study are to:

- Investigate whether or not receipt of the Trivalent Influenza Vaccine (TIV) in young children increases the risk for medically attended events (MAEs) in the post-vaccination period;
- Classify MAEs following TIV as either immediate (day 0 to 2), acute (day 1 to 14), or delayed (day 15 to 42);
- Assess the risk of MAEs after the second seasonal influenza vaccination, and in the subset of children who are at high risk for complications from influenza infection.

The preliminary results from this VSD priority study will be presented to the ACIP in February and June of 2004. Final study results are likely to have a strong influence on future vaccine policies and ACIP recommendations.

"The influenza vaccine will prevent an enormous amount of illness and suffering in infants and young children. All studies to date show the vaccine to be safe and effective in this population. Our study aims to further examine the safety of the influenza vaccine in very young children by looking for rare events that might occur after vaccination."

Simon J. Hambidge, MD, PhD, Co-Investigator, Kaiser Permanente Colorado

Measles–Mumps–Rubella: An Overview

MEASLES

Measles is a very contagious disease caused by a virus that usually begins with a cough, runny nose, fever, and "pink eye." A rash then appears on the face, spreads to the rest of the body, and lasts for about five days. Many children develop severe dehydration from the infection. About five percent of children infected with the measles virus develop pneumonia. In older children, measles can cause encephalitis, which can lead to brain damage. Although only about one out of every thousand children infected with measles develops encephalitis, permanent brain damage will occur in about 25 percent of those children.

The measles vaccine was first administered in the United States in 1963 and hundreds of millions of doses have been administered since that time. Due to the measles vaccine, measles infections are now uncommon in the United States. Yet, in the late 1980's and early 1990's, an outbreak of measles swept across the United States. More than 11,000 children were hospitalized and 120 died from measles during that outbreak. The outbreak of the 1980's and 1990's served as a reminder of the devastating effect that measles can have on children and communities.

MUMPS

Mumps is a virus that typically infects children and causes a painful swelling of the salivary or parotid glands (located just below the ears). Mumps can also infect the brain (encephalitis) and lining of the brain (meningitis). In addition, mumps can infect an unborn child during the first trimester of pregnancy and cause fetal death. Before the mumps vaccine, the mumps virus was the most common cause of viral meningitis and deafness.

Since the mumps vaccine, only about 500 cases of mumps virus are reported in the United States each year (down from 200,000 cases prior to the vaccine). The mumps vaccine is not known to cause any serious reactions and is therefore considered a very safe vaccine.

RUBELLA

Rubella, like measles and mumps, is a virus that typically infects children. Rubella, also known as German measles, begins with fever, swollen glands, and a light rash on the face. Although usually harmless, the rubella virus occasionally causes encephalitis and can cause a decrease in platelets. The rubella virus is most harmful in pregnant women. Up to 85% of infants whose mothers are infected with rubella in the first trimester of pregnancy will have blindness, deafness, heart defects, or mental retardation.

Between 1964 and 1965 there were about 12 million cases of rubella in the United States, resulting in birth defects in about 20,000 children. Since the rubella vaccine has been available in the United States, the number of birth defects due to rubella has decreased to about five per year. There are no known serious side effects from the rubella vaccine.

Idiopathic Thrombocytopenia Purpura (ITP) and MMR Vaccination: Is there an Increased Risk of ITP Following MMR Vaccination?

ISSUE

Idiopathic thrombocytopenia purpura (ITP) is an acquired disease that is caused by the destruction or impaired production of platelets. In children who are otherwise healthy, the acute onset of thrombocytopenia is commonly characterized as ITP. Over the last several years, there has been growing concern that the live virus measles-mumps-rubella (MMR) vaccination is associated with an increased incidence of idiopathic thrombocytopenia purpura (ITP). Two studies published in 2001 and in 2003 demonstrated a significant risk of ITP following the receipt of MMR vaccination. These studies, however, were based on only 28 and 23 cases, respectively.

VSD RESPONSE

To better quantify the relationship between MMR vaccination and ITP, VSD researchers are currently investigating the association in a large cohort of children. Researchers will use inpatient, outpatient and laboratory data to identify children with a diagnosis of ITP during a specified period of time. Medical charts will then be reviewed to verify cases of ITP and collect information on vaccination history. Analyses will be performed to assess the risk of ITP following MMR vaccination.

The specific objectives of this VSD priority study are to:

- Evaluate the risk of ITP following recent MMR vaccination in children between the ages of 1 to 2, 4 to 6, and 11 to 13 years of age;
- Identify periods of greatest risk for ITP within a six-week window after MMR vaccination;
- Explore the level of increased risk of ITP following the second dose of MMR;
- Assess the risk of recurrence of ITP following MMR vaccination.

The results of this VSD priority study will provide the most accurate assessment of the association between MMR vaccination and ITP. Thus, the study will have a significant impact on MMR vaccine recommendations, policies, and clinical practice.

VSD Priority Study Research Team:

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"We believe this study will prove to be the most definitive investigation to examine the relationship between MMR vaccination and the onset of ITP to date".

Eric K. France, MD, MSPH, Principal Investigator, Kaiser Permanente Colorado

VSD Priority Study Research Team:

IMMUNIZATION SAFETY BRANCH CENTERS FOR DISEASE CONTROL AND PREVENTION

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ABT ASSOCIATES, INC.

Vaccine Non-Specific Studies

Four of the VSD priority studies are non-vaccine specific in that the research questions pertain to multiple vaccines or the overall process of evaluating vaccine safety. Two of these studies are designed to assess the effect of thimerosal on child health and development. Thimerosal, a mercury-containing preservative, has been the focus of intense scrutiny by the U.S. Congress and the news media following its removal from all routinely recommended childhood vaccines in 2001. Prior to that time, thimerosal was added to multidose vials of vaccines such as diphtheria-tetanus-acellular pertussis (DtaP), hepatitis B, and Haemophilus influenzae type B (Hib) to prevent bacterial or fungal contamination. There continues to be concern that thimerosal contained in vaccines administered prior to 2001 might have harmed children.

The remaining two vaccine non-specific priority studies are aimed at improving the overall process associated with evaluating vaccine safety. One is a feasibility study to assess the extent to which VSD data can be used to provide real-time data and evidence to the CDC and other organizations (e.g., the FDA) about the presence and rate of adverse events following vaccination. The other study is concerned with evaluating sex-based differences in reporting of adverse effects associated with administration of vaccines.

Infant Environmental Exposures and Neurodevelopmental Outcomes: A Thimerosal Follow-up Study

ISSUE

In 2001, the Immunization Safety Review Committee of the Institute of Medicine (IOM) concluded that although a relationship between thimerosal-containing vaccines and neurodevelopmental disorders was biologically plausible, the evidence was insufficient to either accept or reject a causal relationship. The IOM report recommended follow-up studies of children who had participated in randomized trials of acellular pertussis trials to further investigate the possible relationship between the amount of thimerosal received in different trial study arms and subsequent neurodevelopmental disorders.

VSD RESPONSE

VSD researchers are currently collaborating on a retrospective cohort study that will provide additional data needed to assess the relationship between thimerosal and neurodevelopmental disorders. As part of this VSD priority study, researchers will administer a neuropsychological test to a cohort of children aged 7 to 10 years whose vaccinations in the first year of life could have contained thimerosal. Outcomes will include speech and language skills, fine motor coordination, motor tics, academic and intellectual functioning, and ADHD symptomology. Results will be stratified by level of thimerosal exposure.

The specific objectives of this VSD priority study are to:

- Investigate the possible relationship between the amount of thimerosal received in different trial study arms and subsequent neurodevelopmental disorders;
- Compare the neuropsychological performance of children exposed to different quantities of thimerosal from vaccines administered during the first year of life.

The results of this VSD priority study are likely to have important policy implications.

Vaccine Non-Specific Studies

VSD Priority Study Research Team:

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Thimerosal and Autism: A Case Control Study to Investigate the Relationship Between Exposure to Thimerosal and Onset of Autism

ISSUE

Over the past decade, autism prevalence rates have been rising. Although there is no evidence that any vaccine or vaccine additive increases the risk of developing autism, there has been considerable concern among parents and others regarding vaccines and autism. In 2001, the Institute of Medicine (IOM) established an independent expert committee to review the possible link between the MMR vaccine and autism. The committee concluded that the vast majority of cases of autism cannot be caused by MMR vaccine and therefore MMR vaccine cannot be used to explain the increasing trend in autism diagnoses.

VSD RESPONSE

Due to public concerns, VSD researchers have begun a case-control study to rigorously examine the association between thimerosal and autism. As part of the study, researchers will use automated data and registries to identify children with autism (cases) and without autism (controls). In-person examinations, telephone interviews, medical chart reviews, and immunization tracking systems will be used to collect information on vaccine history and other possible covariates.

The specific objectives of this VSD priority study are to:

- Determine whether exposure to thimerosal in infancy or in-utero is related to development of autism;
- Evaluate whether exposure to thimerosal in infancy is related to development of the subclass of autism predominantly associated with regression.

This IOM-recommended VSD study will be the first rigorous, epidemiological study conducted on the issue of thimerosal and autism. Data from this VSD priority study should provide the best available scientific information on whether or not there is a possible causal association between exposure to thimerosal and development of autism.

"The hypothesis that thimerosal exposure may be related to the development of autism has created considerable concern among parents, particularly the parents of autistic children. The VSD study of thimerosal and autism will provide critically needed objective scientific information to address these concerns and guide public policy."

Lisa Croen, PhD, Northern California Kaiser Permanente

Sex-Based Differences in Reporting of Potential Vaccine-Associated Adverse Events

ISSUE

Sex-based differences are well documented in many biologic systems, including immunology. In 2001, the Institute of Medicine (IOM) recommended that research analyses, including those concerned with vaccine safety, consider potential differences between men and women. Some of this interest was generated by anthrax vaccine trials in which females experienced a greater incidence of adverse events following vaccination. Sex-based differences in vaccine-related adverse events have also been noted in studies of measles, acellular pertussis, DTaP, and influenza vaccines. In these studies, women usually experience greater reactogenicity than men. Much of these data, however, are either uncontrolled, include small sample sizes, and/or do not evaluate a large spectrum of possible adverse outcomes. In addition, most large phase II and III studies do not report adverse events by sex. The VSD project provides a useful infrastructure to evaluate sex-specific vaccine safety in all age groups, using population-based data.

VSD RESPONSE

In response to the IOM recommendation, VSD researchers have been collaborating on a study to examine potential inequality in the sex distribution of local and/or systemic adverse events following vaccination. In this VSD priority study, researchers are using inpatient and outpatient data from health plans to conduct sex-specific analyses as follows: 1) for all routine and individual vaccines, by age and time interval post-vaccination; and 2) evaluation with adjustment for outcomes that are known to have a predilection for one or the other sex.

Preliminary results from this large study indicate that there may be sex-based differences in the incidence of adverse events related to vaccination. In general, females appear to be at higher risk than men and are more likely to be identified with one of several systemic conditions after vaccination including syncope, hematologic abnormalities, asthma and autoimmune conditions. Further work to clarify incidence rates, adjustment for various confounders including age and HMO, timing of the event after vaccination, and certainty of diagnosis is ongoing.

This priority VSD study will provide insight into the extent to which there are sex-based differences in the reporting of vaccine-related adverse events. We hope these data will assist the IOM in raising awareness in the scientific community of the potential for sex-based differences in adverse events following vaccination. This topic is not currently emphasized in preclinical and post-licensure trials of new vaccines.

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"A fuller understanding of potential differences between men and women regarding adverse responses to vaccination should lead to greater reporting and investigation of this issue in large pre and post-licensure trials of new vaccines. "

Ken Zangwill, MD, Principal Investigator, UCLA Center for Vaccine Research / Southern California Kaiser Permanente

Vaccine Non-Specific Studies

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Rapid Cycle Analysis of Vaccine Safety Data: Can VSD Data Be Used to Simulate a Rapid Cycle Analysis?

ISSUE

Recent events in the United States highlight the importance of setting up computerized reporting systems to detect adverse events in real time. The primary goal of such an adverse events reporting system would be to minimize lag time between the onset of vaccine adverse events and the proper evaluation, management and treatment of individuals experiencing such events. A secondary goal of such a system would be to provide real-time data to the Centers for Disease Control and Prevention (CDC) regarding rates of adverse events following vaccination, along with an assessment of the severity of the events. The need for such a system was highlighted when the newly licensed rotavirus vaccine was found to be associated with an increased risk of intussusception following vaccination.

VSD RESPONSE

VSD researchers have been collaborating on a study to assess the feasibility of using VSD data to develop computerized reporting systems that can detect adverse vaccine-related events in real time. As part of the study, researchers restructured the existing VSD cycle datasets into a format that would simulate how data would appear if received on a weekly basis in a rapid cycle analysis project. By doing so, researchers were able to evaluate the feasibility of the VSD to deal with three major challenges facing rapid cycle data analysis: outcome definition, rapid and routine creation of analytic datasets based on automated data, and statistical analysis of signal detection.

The specific objectives of this VSD priority study were to:

- Simulate a rapid cycle analysis framework within the VSD dataset;
- Evaluate VSD data "as if" analysis had been carried out on a weekly basis;
- Assess capability to find known or presumed signals for adverse events.

Early results from this study indicate that it is feasible to use VSD data to conduct rapid cycle analysis of routinely collected vaccine data. The VSD data could provide the basis for a population-based, non-biased surveillance system for vaccine safety.

"This study demonstrates that it is feasible to develop systems for rapid and routine assessment of new vaccine safety. Such systems can provide valuable population based estimates of vaccine adverse event rates in a more timely manner than is currently available."

Robert Davis, MD, MPH, Principal Investigator, Northern California Kaiser Permanente

VSD Sites

CENTERS FOR DISEASE CONTROL AND PREVENTION

National Immunization Program
Immunization Safety Branch
Atlanta, GA
Branch Chief: Robert Chen, MD

Site Description

The Immunization Safety Branch (ISB) is the funding organization for the Vaccine Safety Datalink (VSD) and the Clinical Immunization Safety Assessment (CISA) centers. The ISB provides scientific leadership and fully collaborates in all aspects of VSD and CISA activities. ISB scientists serve as principal or co-investigators on several VSD and CISA research studies. The ISB has the largest group of scientists worldwide to assess and minimize (whenever possible) the risks associated with immunization programs in the United States (and elsewhere upon request). Besides conducting epidemiologic activities related to surveillance and evaluation of the safety of routine vaccinations, ISB also develops new surveillance methodologies (e.g., data mining, syndromic surveillance), assists policy makers in rational vaccine use, and identifies optimal ways to communicate vaccine risks and benefits. Most recently, ISB has begun conducting surveillance for the safety of vaccinations used to protect against bioterrorism agents such as anthrax and smallpox.

Areas of VSD Research Activity

ISB scientists are involved in a wide array of immunization safety studies, including high-profile issues like intussusception after rotavirus vaccination and risks associated with thimerosal in vaccines. Other recent studies have included the occurrence of a newly identified oculorespiratory syndrome after influenza vaccine, identification of risk factors for serious reactions to the yellow fever vaccine, safety of acellular pertussis vaccines in managed care organizations, safety and effectiveness of influenza vaccine in asthmatic children, and whether hepatitis B vaccination is associated with multiple sclerosis.

Possibilities for new projects include: 1) assessing trends in prevalence of neurodevelopmental disabilities and risk factors in managed care populations; 2) assessing opportunities for using twins in vaccine safety studies; 3) investigating safety of new pediatric combination vaccines; 4) assessing safety of live intranasal influenza vaccines; 5) case control studies of risk factors for smallpox vaccine adverse events; 6) assessment of extensive limb swelling after DTaP vaccine boosters.

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VSD Sites

GROUP HEALTH COOPERATIVE

Center for Health Studies
Seattle, Washington
Principal Investigator: Lisa A. Jackson, MD, MPH

Site Description

Group Health Cooperative has been a VSD site since the project's inception in 1990 and Group Health investigators have played an active role in the design, conduct, analysis, interpretation, and reporting of VSD research. Sources of data for VSD studies at Group Health include administrative databases, chart abstraction, and patient interview. Group Health has long standing administrative databases recording information on immunizations, diagnoses assigned to outpatient and inpatient medical encounters, pharmacy prescriptions, and laboratory results. These databases record data for Group Health's population of 400,000 people over periods ranging from 12 to 30 years, depending on the data source, and provide millions of cumulative person-years of information for research purposes.

Group Health's VSD team includes epidemiologists, biostatisticians, project managers, programmers, and research assistants. The Group Health VSD study team is part of Group Health's Center for Health Studies, an internationally recognized academically-focused research organization that conducts primarily government funded clinical, epidemiologic, and health services research. The Center includes 21 MD and PhD investigators, over 200 staff members, and receives approximately $20 million in annual grant funding.

Areas of Research Activity

Group Health VSD researchers have led and participated in multiple VSD studies of vaccine safety and effectiveness. Recent VSD studies conducted at Group Health include a multi-site descriptive study of the risk of anaphylaxis in children and adolescents following vaccination, a multi-site case-control study of the risk of autoimmune thyroid disease following hepatitis B vaccination, an inception cohort study of the association between influenza vaccination and risk of recurrent cardiovascular events in adults, a comparison of DT rates of use and reasons for use during DTP and DTaP eras, and a cohort study of the effectiveness of pneumococcal polysaccharide vaccine in the elderly.

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HARVARD PILGRIM HEALTH CARE, HARVARD MEDICAL SCHOOL AND HARVARD VANGUARD

Department of Ambulatory Care and Prevention
Boston, Massachusetts
Principal Investigators: Tracy Lieu, MD, MPH, and Richard Platt, MD, MS

Site Description

The Harvard VSD site is located in the Department of Ambulatory Care and Prevention, a unique partnership between Harvard Pilgrim Health Care, Harvard Medical School and Harvard Vanguard. The core study population for the VSD Project at Harvard is patients of Harvard Vanguard Medical Associates, a multi-specialty physician group with 14 centers in the greater Boston area. The site has a fully computerized medical record that has been used with the core study population since 1969, ensuring maximally accurate vaccine administration data and access to full-text outpatient medical records.

The VSD's association with Harvard offers special opportunities to collaborate with colleagues in the Department of Epidemiology at the Harvard School of Public Health and adds to the geographic diversity to the VSD population. The Harvard site also contributes methodologic and technologic innovation through the expertise of its investigators in time-series analysis, health economics, and bioterrorism surveillance methods. The site also has close ties to Children's Hospital Boston, one of the nation's premier institutions in pediatric research and teaching.

Areas of VSD Research Activity

Each year, the Harvard VSD Team initiates several studies that focus on a broad range of topics related to vaccine safety. Recently completed studies include a smallpox study that identified vaccine safety as a key factor in hospital workers' projected decisions about acceptance or rejection of smallpox vaccination, and an influenza study that determined the incidence of outpatient visits associated with influenza among young children in the Harvard VSD cohort. Ongoing VSD studies include a Pneumococcal vaccination study evaluating the impact of the introduction of pneumococcal conjugate vaccine on immunization up-to-date status, a study of the association between thimerosal exposure from vaccines and neurodevelopmental outcomes in children, and an evaluation of the impact of shifts in practice for multiple immunizations on the risk of fever.

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HEALTHPARTNERS RESEARCH FOUNDATION

Minneapolis, Minnesota
Principal Investigator: Michael J. Goodman, PhD

Site Description

HealthPartners Research Foundation (HPRF) is a nonprofit research center that conducts public domain research as an independent part of the HealthPartners family of companies. HPRF joined the VSD project in March of 2001 and serves as a pediatric-only site that focuses on all areas of vaccine safety in children. HealthPartners is a mixed-model HMO with a large network of owned and contracted clinics, medical and dental centers. The VSD population is drawn from the two largest HealthPartners clinics serving more than 600,000 enrollees. HealthPartners serves a diverse population of urban, suburban, and rural residents, including low socioeconomic populations in the Minneapolis-St.Paul metropolitan area.

HPRF has a wealth of experience using administrative databases in vaccine-related, pharmacoepidemiology, pharmacoeconomic, and other large link database studies. HealthPartners' computerized information services system provides a fully integrated structure that captures inpatient and outpatient claims and encounters, electronic physician notes, and laboratory, pharmacy, emergency room, and urgent care data that can be accessed by the HPRF VSD staff. HPRF investigators also have access to electronic physician notes containing information not present in any other administrative data system. HealthPartners implemented an Epicare electronic medical record in the 2003 and has had an immunization registry since 1997.

Areas of VSD Research Activity

HPRF's multi-specialty VSD team consists of bio-statisticians, pediatricians, an economist, an epidemiologist, programmers, support staff and contracts with well-known vaccine researchers. The HPRF VSD team initiates and participates in several studies that focus on a wide range of vaccine safety topics. Some of our recent studies include a study of rotavirus vaccine and intussusception, an examination of the health consequences that result from exemption from immunization, an assessment of the safety of Yellow Fever vaccine in children and adults, and a feasibility study to enable real time surveillance using automated data to rapidly detect vaccine adverse events.

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KAISER PERMANENTE COLORADO

Clinical Research Unit
Denver, Colorado
Principal Investigator: Eric France, MD, MSPH

Site Description

Kaiser Permanente Colorado (KPC) has been a Vaccine Safety Datalink (VSD) site since 2000. The KPC site includes multi-disciplinary expertise in pediatrics, biostatistics, epidemiology, pharmacoepidemiology, prevention, and health economics. The VSD research team is located within the Clinical Research Unit of KPC, which has a high level of active grant support in a broad range of health services research areas, and clinical trials research. The KPC Clinical Research Unit is also involved with a wide range of pediatric studies including phase 3 and 4 trials, and prospective randomized studies of vaccine safety.

Areas of VSD Research Activity

KPC's areas of research interest include the impact of new vaccines or changing vaccine recommendations on vaccine coverage or vaccine policy, methodology research, and epidemiologic assessments. The KPC site first became involved with the VSD following Dr. France's work with the group that helped to delineate the relationship between vaccination against rotavirus and intussusception in young children.

Current research studies at the KPC site include assessing the safety of the trivalent inactivated influenza vaccine among the pediatric population, evaluating the possible association of idiopathic thrombocytopenic purpura with the measles, mumps, and rubella vaccination, the possible benefit of influenza vaccination in pregnancy on infant outcomes, and comparing four study designs used to examine the association between vaccination and acute adverse events. KPC is also interested in methodology research to develop analytic methods to minimize or assess bias in observational epidemiologic studies. Work includes comparing conditional models to longitudinal models used in vaccine safety studies, and evaluating the validity and stability of four types of study designs used to examine the association between vaccination and acute adverse events. Future plans include using HLA typing from cord bloods to look at adverse events and investigating the concept of the "healthy vaccinee effect".

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KAISER PERMANENTE NORTHWEST

Center for Health Research
Portland, Oregon
Principal Investigator: John Mullooly, PhD

Site Description

Kaiser Permanente Northwest (KPNW) has been a Vaccine Safety Datalink (VSD) site since the research program's inception in 1990, and conducts a wide range of pediatric and adult immunization studies. The multi-discipline VSD investigative team includes biostatistics, epidemiology, pediatrics and internal medicine, allergy/immunology, pharmaco-epidemiology, and health economics. The VSD research group exists within the larger Center for Health Research that is noted for epidemiologic and health services research in many areas.

Areas of VSD Research Activity

Areas of research activity include risk assessment of adverse events following vaccination, data quality assessment of automated immunization and diagnosis databases, statistical adjustments for misclassification, vaccine coverage and compliance, vaccine effectiveness, impacts of vaccination programs, medical care costs of infectious diseases, cost-effectiveness of vaccination programs, household transmission of infectious diseases, and infectious disease transmission modeling.

Current studies of adverse events following vaccination include wheezing in premature infants following hepatitis B vaccination, childhood asthma and atopy, and local and systemic adverse events following pediatric flu vaccination. Kaiser Permanente Northwest also leads the VSD data quality work group. Data quality studies include those related to assessing the completeness and accuracy of automated vaccination and vaccination exemption records, temperatures, fever codes, and inpatient and outpatient pneumonia codes.

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MARSHFIELD CLINIC RESEARCH FOUNDATION

Vaccine Safety Datalink Site
Marshfield, Wisconsin
Principal Investigator: Edward Belongia, MD

Site Description

Marshfield Clinic is the largest private group medical practice in Wisconsin and one of the largest in the United States. Although the primary service area includes northern, central, and western Wisconsin, and the Upper Peninsula of Michigan, patients from every county in Wisconsin, every state in the nation, and 24 foreign countries were seen within the Clinic system last fiscal year.

The Marshfield Clinic and the Marshfield Clinic Research Foundation, the nonprofit research division of the Marshfield Clinic, have participated in the VSD project since March 2001. Strengths of the Marshfield Clinic for vaccine safety research include access to a stable rural population, an electronic medical record with a sophisticated diagnosis coding system (with mapping to ICD codes), a real-time electronic immunization registry used by public and private providers, and an epidemiology research group with experience in vaccine safety research and infectious disease epidemiology.

Areas of VSD Research Activity

Current studies of adverse events following vaccination that are directed by investigators at the Marshfield Clinic include two investigations related to the small pox vaccination program. For one study, the main objectives are to determine the prevalence of diagnosed atopic dermatitis and eczema in a defined population, estimate the proportion of people who would be at increased risk of developing eczema vaccinatum if they or their household contacts were vaccinated, and determine if adults are able to accurately recall past diagnoses of atopic dermatitis for themselves, their children, or other members of their households. A second smallpox study will determine the sensitivity of a self-administered screening instrument to identify health care workers who should not receive smallpox vaccine, using the medical record as the gold standard.

MCRF is also leading a study to determine if immune-mediated hemolytic anemia (IMHA) in children is related to each of 3 different exposures: diphtheria-tetanus-pertussis (DTP) vaccination, hepatitis B vaccination, and parenteral ceftriaxone. The strength of the association between IMHA and the various exposures will be measured.

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NORTHERN CALIFORNIA KAISER PERMANENTE

Kaiser Permanente Vaccine Study Center
Oakland, California
Principal Investigators: Steven B. Black, MD and Henry Shinefield, MD

Site Description

Northern California Kaiser Permanente has been a VSD site since the program's inception in 1990. The Kaiser Permanente Vaccine Center conducts a wide range of pediatric and adult immunization studies, including phase 2, 3 and 4 trials, diverse prospective randomized studies, and observational studies of vaccine safety. The multi-disciplinary VSD investigative team has expertise in biostatistics, epidemiology, programming, pediatrics, internal medicine, rheumatology, health economics, and conduct of both chart review and telephone interview studies. The VSD research groups work extensively with the Kaiser Permanente Division of Research that is noted for both epidemiologic and health services research. The Center has access to one of the largest and most complete clinical automated databases in the country and a large group of clinicians, who cooperate in providing subspecialty expertise in vaccine safety studies.

Areas of VSD Research Activity

Areas of research interest include risk assessment of adverse events following vaccination, the use of large linked data bases to provide rapid epidemiologic and public health assessments, studies of genetic factors which might influence the nature and risk of vaccine adverse events, statistical adjustments for comparing populations with differing propensities to utilize care, the impact of new vaccines or changing vaccine recommendations on vaccine coverage, cost-benefit analyses and economic modeling.

Current studies evaluating adverse events following vaccination include an assessment of the risk of encephalopathy following DTP vaccines, evaluation of a possible association of alopecia with hepatitis B vaccination, the safety and benefit of influenza vaccination in pregnancy, and the risk of and possible genetic factors predicting arthritis following hepatitis B vaccination.

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UCLA CENTER FOR VACCINE RESEARCH/ SOUTHERN CALIFORNIA KAISER PERMANENTE HEALTH CARE PLAN

Los Angeles, California
Principal Investigators: Ken Zangwill, MD and Joel I. Ward, MD

Site Description

The southern California VSD site is based in Los Angeles at the UCLA Center for Vaccine Research and the Southern California Kaiser Permanente (SCKP) Health Care Plan, the largest HMO in southern California. UCLA/SCKP investigators have been active in vaccine research for more than 35 years, and have evaluated nearly all licensed vaccines and many experimental formulations. The VSD team at UCLA/SCKP includes several MDs, two PhD epidemiologists, a PhD biostatistician, a MPH project coordinator, several Master's level data management and computer programming staff, as well as staff involved with medical record review. Ongoing academic relationships are maintained with many collaborators nationally and internationally. In Los Angeles, these include the UCLA Schools of Medicine and Public Health, California State University at Dominquez Hills, and the Los Angeles County Department of Health Services.

Areas of VSD Research Activity

Ongoing VSD studies being led by UCLA/SCKP include evaluations of several potential vaccine-associate adverse events including aplastic anemia, acute flaccid paralysis (initially related to oral polio vaccine), and neonatal and infant mortality. UCLA/SCKP is also conducting studies of hepatitis A vaccine, the safety of vaccination in premature infants, and the impact on gender on vaccine safety. Lastly, UCLA/SCKP is currently piloting an innovative project that develops real time computer linkages between the Kaiser immunization tracking system and the national Vaccine Adverse Event Reporting system. Successful integration of these systems may serve as a model nationally. The UCLA/SCKP site also contributes to ongoing collaborative VSD projects including assessment of influenza vaccine safety in children, thimerosal-containing vaccines on infant neurodevelopment, and rapid surveillance for disease detection of bioterroristic importance.

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VSD Publications

2001, 2002 & 2003

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America's Health Insurance Plans