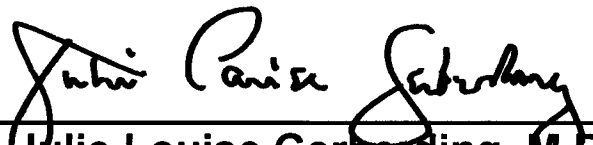
DEPARTMENT OF HEALTH AND HUMAN SERVICES

CENTERS FOR DISEASE CONTROL AND PREVENTION

REPORT TO CONGRESS ON VACCINE SAFETY DATALINK

House Appropriations Committee



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Executive Summary

In its report on the Fiscal Year 2008 budget for the Department of Health and Human Services, the House Appropriations Committee stated:

"Vaccine safety datalink - In fiscal year 2006, the Committee requested that the National Institute of Environmental Health Sciences (NIEHS) convene a panel of expert, independent researchers for the purpose of exploring the possibility of using the CDC's vaccine safety datalink (VSD) to conduct a study that could identify or rule out any association between thimerosal exposure in pediatric vaccines and increased rates of autism. The expert panel convened in May 2006 and issued a report, which recommended that gaps and uncertainties in the VSD be addressed prior to the consideration of further studies of autism and thimerosal using the VSD. Given that the VSD ten-year contract totals more than $120,000,000, the Committee urges CDC to report to the House Committee on Appropriations no later than March 1, 2008 on its response to the NIEHS recommendations. This report should include information about current and ongoing CDC studies that address the potential association between thimerosal exposure in pediatric vaccines and neurodevelopmental disorders including autism." (Appropriations Committee House Report No. 110-231, July 13, 2007)

BACKGROUND

The Vaccine Safety Datalink (VSD) is a collaborative research project among CDC and eight managed care organizations (MCOs) that was created in 1991. The VSD provides comprehensive medical and immunization histories for more than 5.5 million people annually, which are used to answer vaccine safety questions.

The National Institutes of Health's National Institute of Environmental Health Sciences (NIEHS) convened an expert panel in May 2006 to determine the feasibility of using the VSD data in an ecological study to compare rates of autistic disorder (AD) or autism spectrum disorders (ASD) before and after the removal of thimerosal from most childhood vaccinations.

REPORT OF THE EXPERT PANEL

In October 2006, NIEHS released its report from the expert panel, *Thimerosal Exposure in Pediatric Vaccines: Feasibility of Studies Using the Vaccine Safety Datalink.* The report summarizes the expert panel's findings and recommendations and CDC's response.

CDC'S CURRENT RESEARCH

The VSD currently has a number of priority studies underway to address a range of important immunization safety questions, none of which utilize an ecologic study design. Instead, these current studies, including one study evaluating associations between thimerosal-containing vaccines and autism, all evaluate individual-level data. This typically involves the review of individual medical charts to confirm the vaccines each individual received as well as the outcomes being studied. Studies using individual rather than group data provide stronger scientific evidence.

BACKGROUND

The Vaccine Safety Datalink (VSD) is a collaborative research project among CDC and eight managed care organizations (MCOs) that was created in 1991. It was established to benefit from the advantages offered by MCOs for efficient population-based health research. The VSD provides comprehensive medical and immunization histories for more than 5.5 million people annually, which are used to answer vaccine safety questions. The VSD sites include: Group Health Cooperative Center (Seattle, Washington), Harvard Pilgrim Health Care (Boston, Massachusetts), Healthpartners Research Foundation (Minneapolis, Minnesota), Kaiser Permanente Colorado (Denver, Colorado), Kaiser Permanente Northwest (Portland, Oregon), Marshfield Clinic Research Foundation (Marshfield, Wisconsin), Northern California Kaiser Permanente (Oakland, California), and Southern California Kaiser Permanente Health Care Plan (Los Angeles, California).

The VSD is used to test vaccine safety hypotheses. These hypotheses may arise from medical literature, passive surveillance systems such as the Vaccine Adverse Event Reporting System, and changes in immunizations schedules and/or the introduction of new vaccines. For example, VSD has been used to demonstrate associations between intussusception following Rotasheild vaccination and the risk of seizures following Measles, Mumps, Rubella (MMR) or whole-cell pertussis vaccine. Another valuable contribution of VSD is that it provides a rapid cycle analysis mechanism that can make preliminary assessments of vaccine safety concerns much more rapidly than formal studies. This sequential monitoring method is being used to study vaccine safety concerns about RotaTeq vaccine and intussusception, Menactra (meningococcal conjugate vaccine) and Guillain-Barre syndrome, and the safety of Gardasil (HPV).

The National Institutes of Health's National Institute of Environmental Health Sciences (NIEHS) convened an expert panel in May 2006 to determine the feasibility of using the VSD data in an ecological study to compare rates of autistic disorder (AD) or autism spectrum disorders (ASD) before and after the removal of thimerosal from most childhood vaccinations. The panelists included external scientists with expertise in autism clinical and epidemiologic research, biostatistics, toxicology and risk assessment. It also included representatives from major autism advocacy organizations.

Ecological studies are based on aggregate group-level data collected over time, rather than individual-level data. There are many limitations of an ecologic analysis, such as differences of exposure levels and covariate levels within the study group, challenges in controlling for confounders, and within-group misclassifications that lead to potentially severe biases in the interpretation of the results[1]. These problems severely limit the interpretation of causality, particularly biologic causality, from a study that relies solely on ecologic analysis. For example, trends over time may coincidentally appear to be related even if there is no cause-and-effect relationship.

The VSD currently has a number of priority studies underway to address a range of important immunization safety questions, none of which utilize an ecologic study design. Instead, these

[1] Rothman K J & Greenland S. (1998). *Modern Epidemiology – 2nd ed.* Philadelphia PA: Lippincott – Raven Publishers.

current studies, including one study evaluating associations between thimerosal-containing vaccines and autism, all evaluate individual-level data. This typically involves the review of individual medical charts to confirm the vaccines each individual received as well as the outcomes being studied. Studies using individual rather than group data provide stronger scientific evidence.

The panel was tasked with the following:

- Identify the strengths and weaknesses of the VSD for evaluating the possible association between exposures to thimerosal-containing vaccines and AD or ASD;
- Advise NIEHS and CDC on the feasibility of a new VSD study to compare autism rates before and after removal of thimerosal from most US childhood vaccines, using an ecologic study;
- Identify any other uses of the VSD or other existing resources that might be used to examine an association between thimerosal and AD/ASD;
- Develop recommendations for design, conduct, analysis and oversight of any proposed study; and
- Discuss the potential impact of possible VSD-based studies in the context of what is already known about autism and ASD.

REPORT OF THE EXPERT PANEL

In October 2006, NIEHS released its report from the expert panel, *Thimerosal Exposure in Pediatric Vaccines: Feasibility of Studies Using the Vaccine Safety Datalink.* The following summarizes the expert panel's findings and recommendations and CDC's response.

VSD Strengths and Weaknesses

NIEHS Finding: Strengths
The panel identified the major strengths of the VSD to be: its ability to detect infrequent, vaccine-related adverse events of modest size; the possibility to supplement the MCO administrative data with reviews of medical records, interviews with parents and children, and additional diagnostic assessments; and the availability of demographic information about the MCO members.

CDC Response: CDC agrees with the panel's assessment of the strengths of the VSD Project to evaluate vaccine safety concerns. The VSD is a unique public-private collaboration that provides a model for the study of patient safety concerns by using individual-level data. In addition, CDC recognizes the tremendous value of the VSD as a national resource of expertise in vaccine safety research.

NIEHS Finding: Weaknesses
The panel identified several areas of weakness that when taken together reduce the usefulness of the VSD Project for conducting an ecologic study design to address the potential association between exposure to thimerosal and the risk of AD/ASD.

CDC Response: CDC concurs with this conclusion and does not plan to use VSD for ecological studies.

The weaknesses of primary importance identified by the NIEHS panel are summarized below:

- **NIEHS Finding: Case ascertainment.** The MCO data systems supporting the VSD Project are designed for administrative rather than research purposes. Research studies relying solely on these data would not be able to identify cases of autism reliably, and therefore might under- or overestimate rates of autism. The panel recommended that the feasibility of including a broader list of ICD-9 codes (e.g., mental retardation, speech delay) in the initial administrative case finding, and of re-diagnosis of potential cases to confirm case status, should be addressed.

  CDC Response: CDC concurs with the recommendation that broader ICD-9 codes should be considered. This weakness further emphasizes why an ecological design is not appropriate for studying this vaccine safety topic using the VSD. The VSD data are intended for administrative purposes and may not be predictive of the outcome studied. Because the outcomes have not been validated and considering the sensitivity of this issue, any VSD study of vaccines and autism, including a broader list of ICD-9 codes, would require chart review.

- **NIEHS Finding: Variations in business practices.** Differences in business practices among the MCOs include different screening and diagnostic practices, specialist referral guidelines and patient tracking methods. These variations affect the comparability and interpretation of autism data across the sites.

  CDC Response: CDC acknowledges that differences in business practices among participating MCOs are an inherent limitation of utilizing VSD data for an ecologic analysis related to vaccines and AD/ASD. CDC does not have the ability to require that participating MCOs implement uniform business practices. However, the difference among vaccine practices can also be considered a strength of the VSD for conducting some vaccine safety research, as it allows the study of contrasts in vaccine safety experience, such as the use of combination versus individual antigen vaccines, or the timing of vaccinations[2].

- **NIEHS Finding: Systemic changes over time.** The systems for creating medical records at the individual VSD sites are dynamic and change frequently to accommodate the individual MCO business models. For example, the transition from paper to electronic records occurred at different times for each of the VSD-participating MCOs. An ecologic analysis of AD/ASD rates before and after the removal of thimerosal from pediatric vaccines would rely on data spanning these transition periods. The panel noted that such changes could affect the observed rate of autism and could confound or distort trends in autism rates over time, regardless of whether autism cases are truly rising, falling or staying constant.

[2] Chen R T et al. Vaccine Safety Datalink Project: A new tool for improving vaccine safety monitoring in the United States. *Pediatrics*. 1997 June; 99 (6);765-73.

CDC Response: CDC acknowledges this limitation and concurs that conducting an ecologic analysis using VSD administrative data to address potential associations between thimerosal exposure and risk of AD/ASD is not useful.

VSD studies evaluating the association between thimerosal and autism have utilized stronger study designs such as case control and cohort studies and have not been ecologic studies. Instead, these studies utilize individual-level data, including medical chart reviews, neurological assessments, and parent interviews. However, such data collection methods are significantly more time and resource-intensive. In addition to the changes in MCO systems identified by the panel, the definitions and concepts for diagnosing AD/ASD have also changed significantly over the time period of concern about thimerosal exposure from pediatric vaccines. These diagnostic changes could also confound or distort trends in autism rates over time.[3]

- **NIEHS Finding: Difficulties linking medical records of children and their mothers and other family relationships, including biologic and nonbiologic relationships between parents and children and between siblings.** The panel noted that while MCO systems provide an efficient means for linking medical information from multiple administrative sources to a single individual and may be helpful in identifying prenatal and genetic factors, it is not easy to use these systems for linking family relationships. The panel considered this to be a serious problem for some of the study designs under consideration because it would hamper identification of prenatal factors that should be considered in the analysis of the potential association of thimerosal with increased AD/ASD risk.

  CDC Response: CDC acknowledges this limitation of relying on the automated administrative data for linking medical records of biologic and nonbiologic family relationships. In its research using the VSD to assess possible associations between thimerosal-containing vaccines and autism, CDC has utilized individual-level data such as medical charts and parent interviews. These data are more reliable and useful in establishing biologic and nonbiologic family relationships.

- **NIEHS Finding: Difficulty in estimating cumulative exposure of a child to organic mercury.** The panel expressed concern that VSD administrative data or medical charts would not be accurate in recording or estimating a child's total cumulative mercury exposure from sources other than vaccines, such as diet, air and water.

  CDC Response: CDC acknowledges this concern and recognizes this limitation. In addition to administrative data and medical chart review, CDC has employed parent interviews to identify total cumulative mercury exposure from sources other than vaccines, such as diet. However, parent recall, often for events several years in the past, poses limitations as well.

[3] Frombonne E. Epidemiology of autistic disorder and other pervasive developmental disorders. Journal of Clinical Psychiatry. 2005; 66 Supplement 10: 3-8.

Research Designs Considered by the Panel

- **NIEHS Finding: Population-based studies of AD/ASD rates from VSD data**

Considering the weaknesses described above as well as the inability to control for temporal factors, the panel concluded that an ecologic analysis of VSD data comparing the rates of AD/ASD over the time period before, during and after the removal of thimerosal from most childhood vaccines would have limited value and be potentially misleading. The panel expressed the view that efforts would be better spent implementing a more rigorous study design.

CDC response: CDC agrees with the conclusion that such an ecologic analysis of VSD data to evaluate potential associations between thimerosal and AD/ASD would be uninformative and potentially misleading. Current and published VSD studies evaluating the potential association between thimerosal and risk of neurodevelopmental disorders have not used an ecologic study design. Rather, they have employed more rigorous study designs such as cohort and case control designs that have allowed for individual-level data to be collected and evaluated.

- **NIEHS Finding: Studies of high risk populations from VSD enrollees**

The panel recommended a study of siblings of individuals diagnosed with AD/ASD, which would allow for comparison of AD/ASD risk in siblings as a function of their thimerosal exposure through vaccination. A variation considered is a study of concordant/discordant sibling pairs. This variation may provide a more efficient study design than using the entire sibling cohort.

CDC response: CDC concurs that these study designs are appropriate for the research question posed. CDC does not currently have plans to conduct such a study on thimerosal exposure and AD/ASD. However, a study is being planned at one VSD site that will create a database of siblings and birth mothers to evaluate whether children with a personal or family history of atopic or autoimmune disease are at an increased risk of adverse events following vaccination. The creation of this family database for this study will serve as a pilot to determine the feasibility of a larger family database for the VSD. Currently, using only the existing automated VSD data for identifying biological relationships is not possible because the appropriate information is not uniformly captured or contained in the data files. Additional data sources would need to be accessed by the MCOs to further identify biological relationships.

- **NIEHS Finding: Association study of thimerosal exposure and risk of AD/ASD incorporating recent VSD data**

The panel recommended further consideration of a study extending upon the 2003 thimerosal screening study[4]. This study design would include additional years for follow up, would add more MCOs, and should reexamine the criteria for exclusion of births and/or take sensitivity analyses approach to examining the impact of various exclusion criteria.

CDC response: The thimerosal screening study published in 2003 used the automated VSD data to screen for possible associations between exposure to thimerosal-containing vaccines and a variety of renal, neurologic and developmental disorders. In the first phase of this study, CDC

[4] Verstraeten T et al. Safety of thimerosal-containing vaccines: A two-phased study of computerized health maintenance organization databases. *Pediatrics* 2003;112;1039-1048.

used data from two VSD sites with automated outpatient data (where more subtle effects of mercury toxicity might be seen). The researchers found statistically significant associations between thimerosal and two neurodevelopmental disorders: language delays and tics. However, the associations were weak and were not consistent between the two MCOs. No association was shown with autism. In the second phase of the investigation, CDC researchers examined similar data from a third MCO using the same methods to see if these findings could be replicated. The analyses from the second phase did not confirm the results seen in the first phase of this study.

In a 2001 report entitled "Thimerosal-Containing Vaccines and Neurodevelopmental Disorders", the Institute of Medicine (IOM) recommended public health research related to thimerosal-containing vaccines and neurodevelopmental disorders be done in four areas.[5] One area of epidemiologic research recommended included the study of rates of specific neurodevelopmental diagnoses of children exposed to varying levels of thimerosal.

In response to this 2001 IOM recommendation and in follow up to the 2003 thimerosal screening study, CDC conducted a study designed to more rigorously assess the relationship between ethyl mercury exposure from thimerosal and neuropsychological functioning[6]. This study, published in September 2007, evaluated 1,047 children between the ages of 7 to 10 years who received vaccines during the 1990s when thimerosal was used as a preservative in many childhood vaccines. The study used a retrospective cohort design. Computerized medical records were used to select a sample of children with a wide range of exposures from thimerosal-containing vaccines and immunoglobulins during infancy. Each child's level of exposure to ethyl mercury was determined through maternal interviews (prenatal exposures), chart reviews (prenatal and postnatal exposures), VSD automated data (postnatal vaccine exposures), and parent vaccine records (postnatal exposures). Each child was then administered a series of standardized neuropsychological tests in a clinical setting at ages 7 to 10 years.

This study employed a number of improvements upon previous studies of thimerosal-containing vaccines and neuropsychological functioning:

- To reduce potential selection and health care seeking biases, children were selected independent of their health status and each child was assessed independent of thimerosal exposure and health care seeking behaviors.
- A comprehensive and objective assessment of each child's neuropsychological functioning was conducted using a battery of standardized neuropsychological tests. Most of these tests were administered in a clinical setting by trained professionals.
- Extensive information was collected about each child's medical history, maternal prenatal fish consumption (a source of methyl mercury) and socioeconomic and educational factors that could have influence on the child's health and development.

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[5]Institute of Medicine (IOM)(2001). Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders. Washington DC: National Academy Press.

[6] Thompson W et al. Early Thimerosal Exposure and Neuropsychological Outcomes at 7 to 10 Years. *New England Journal of Medicine* 2007 September; 357(13): 128-92.

The study concluded that the weight of the evidence does not support a causal association between ethyl mercury exposure from thimerosal-containing vaccines and immunoglobulins administered in the prenatal period through the first seven months of life and neuropsychological functioning at ages 7 to 10 years. This study did find a similar result to one found in the 2003 thimerosal screening study: an association between mercury exposure and tics. However, the current study only found the association among boys.

Another VSD study that builds upon the 2003 thimerosal screening study and was recommended by the IOM in 2001 is the VSD thimerosal and autism study. This case-control study is being conducted at three MCOs in which children with autism are being evaluated by certified specialists using standardized diagnostic assessments. Medical records and interviews with the parents of both the cases and their matched controls will be used to verify vaccination histories and information on other potential confounding factors. This study is in progress and the expected date of publication is September 2008.

- **NIEHS Finding: Collaborative study of VSD and the California Department of Developmental Services (DDS)**

Another approach considered by the panel was a VSD retrospective cohort study that links with the California DDS database. The California DDS database contains administrative information on all persons eligible for state-funded services because of an autism diagnosis, dating back to the late 1980s. This approach would improve the diagnostic reliability without the expense of examining the individual children.

CDC response: The California DDS database provides a rich source of statewide data regarding autism, and could be a potential resource of additional information on services rendered outside the MCO for those diagnosed with autism. However, there are several limitations with a study design that links the VSD data with the California DDS database. For example, the California DDS database only includes information for children who qualify for developmental services; it does not record any information on those children who did not meet eligibility criteria to qualify for services.[7,8] The counts of autism in the California DDS database reflect only persons who were referred to and/or voluntarily entered the DDS; therefore, autism counts may be underestimated for California. Because of the limitations with the California DDS data, a VSD study linking with the California DDS would still require chart reviews for confirming diagnosis. Furthermore the California DDS only includes information about California residents and is therefore limited in its applicability to the VSD.

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[7] Croen LA, Grether JK, Hoogstrate J, Selvin S. The Changing Prevalence of Autism in California. *Journal of Autism and Developmental Disorders*. 2002; 32(3): 207-215.

[8] M.I.N.D. Institute. (2002) Report to the Legislature on the Principle Findings from the Epidemiology of Autism in California. Sacramento, CA: University of California

Additional Recommendations

NIEHS Finding: Additional general recommendations for study designs and collection of exposure and outcome information
The panel made several general recommendations for consideration in the design and implementation of any future VSD studies of thimerosal-containing vaccines and neurodevelopmental disorders.

CDC Response: The current VSD studies of thimerosal-containing vaccines and neurodevelopment were already in progress collecting data at the time the NIEHS report was released. In the future, VSD studies on this vaccine safety topic will take into consideration the additional general recommendations for study designs and collection of exposure and outcome information in this report.

NIEHS Finding: Information needed to inform further discussions
The panel identified a number of gaps in the information made available to it for this review. The panel recommended that these gaps be considered fully before any further VSD studies examining the relationship between thimerosal and AD/ASD are conducted.

CDC Response: CDC concurs with this recommendation. If further research into this vaccine safety question is conducted using the VSD, CDC will review and carefully consider each of the information gaps identified.

NIEHS Finding: Public Participation in VSD Studies
The panel recommended that the AD/ASD community participate in all aspects of future VSD studies of autism, including design, analysis and interpretation. However, the proposal that VSD studies be conducted entirely by independent investigators external to the CDC and the VSD MCOs was not considered feasible for a number of reasons, including the complexity of the data, patient privacy concerns, and MCO concerns about data sharing.

CDC Response: CDC recognizes the value of external input into its vaccine safety research.

CDC has made significant efforts to include the AD/ASD community in all aspects of its two major VSD studies related to thimerosal and neurodevelopmental disorders: *Early Thimerosal Exposure and Neuropsychological Outcomes at 7 to 10 Years*[9]; and the *VSD Thimerosal and Autism Study* (in progress). For both studies, CDC engaged independent external consultants representing a broad spectrum of expertise in fields related to child development, immunization, and immunization safety, as well as one representative from the autism advocacy community. The consultants have been involved in every aspect of each study, including input into the development and revision of the study protocols and analysis plans, and providing comments on the results and the final manuscripts. The resulting studies are better informed by this broad expertise, and potentially more credible to the larger public because of the external input.

[9] Thompson W et al. Early Thimerosal Exposure and Neuropsychological Outcomes at 7 to 10 Years. *New England Journal of Medicine* 2007 357(13): 1281-92.

CDC'S CURRENT RESEARCH

In addition to providing a response to the recommendations in the NIEHS Report, Congress also requested that CDC provide information about its current and ongoing studies that address the potential association between thimerosal exposure in pediatric vaccines and neurodevelopmental disorders including autism.

CDC Response: In 2001, CDC and the National Institutes of Health requested the IOM conduct a scientific review of evidence related to thimerosal-containing vaccines and neurodevelopmental disorders[10]. This review resulted in the recommendation that epidemiologic research be undertaken in four areas: 1) case-control studies examining the potential link between neurodevelopmental disorders and thimerosal-containing vaccines; 2) further analysis of neurodevelopmental outcomes in DTaP clinical trial populations; 3) conduct epidemiologic studies that compare the incidence and prevalence of neurodevelopmental disorders before and after removal of thimerosal from vaccines; and 4) identify the primary sources and levels of prenatal and postnatal exposure to thimerosal and other forms of mercury in infants, children and pregnant women.

Since 2001, CDC has initiated vaccine safety research into each of these areas. These vaccine safety studies employ individual data collection methods and have required a significant investment of resources. These studies are investigating this issue to the fullest extent possible, using the best scientific methods available. None of these studies utilize an ecologic study design. Instead, these current studies all evaluate individual-level data. Studies using individual rather than group data provide stronger scientific evidence.

1) Case-control studies examining the potential link between neurodevelopmental disorders and thimerosal-containing vaccines.

> CDC is conducting a VSD thimerosal and autism study to rigorously examine the potential association between thimerosal exposure and autism. The study is comparing children with autism with those without autism in an effort to determine whether thimerosal exposure in infancy or in-utero is related to the development of autism. The study also will evaluate whether thimerosal exposure in infancy is related to development of autism predominately associated with regression. Children with autism will be evaluated by certified specialists using state of the art, standardized diagnostic assessments. Vaccination histories and information on other potential confounding factors will be ascertained for both cases and matched controls by review of medical records and standardized interviews of the children's parents. The findings from this study should provide the best available scientific information about a possible causal association between thimerosal exposure and the development of autism. This study is expected to be completed and submitted to a peer-reviewed journal for publication in September 2008.

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[10] IOM (2001). Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders. Washington DC: National Academy Press.

2) Further analysis of neurodevelopmental outcomes in DTaP clinical trial populations

CDC is funding a study conducted by researchers in Italy to evaluate children who were randomly exposed to differing amounts of thimerosal during infancy as part of a clinical trial of acellular pertussis (whooping cough) vaccines. The vaccines studied in the Italian clinical trial included thimerosal-containing and thimerosal-free preparations. Although thimerosal exposure was not studied at the time, researchers now are comparing the occurrence of neurological developmental disorders among the clinical trial participants related to level of thimerosal exposure. The study evaluates the children using a standardized battery of neuropsychological tests. This study is currently being submitted for publication.

3) Conduct epidemiologic studies that compare the incidence and prevalence of neurodevelopmental disorders before and after removal of thimerosal from vaccines

With data from the Healthcare Cost and Utilization Project (HCUP), CDC conducted descriptive analyses of secular trends of diagnosed psychiatric disorders between 1989 and 2000. The HCUP Nationwide Inpatient Sample (NIS) approximates a 20% sample of community hospitals in the United States as defined by the American Hospital Association (AHA). The AHA defines community hospitals as "all nonfederal, short-term, general and other specialty hospitals, excluding hospital units of hospital institutions." Psychiatric disorders were coded using ICD-9 codes. Disorders were associated with a hospital discharge if they were coded as the primary or secondary diagnosis for that discharge. For each disorder or set of disorders, three sets of rates were calculated. The rate of hospital discharges associated with each disorder was calculated for each calendar year as a function of the total number of hospital discharges for that year. Average rates were calculated across all years of the study period by year of age. Differences in trends in diagnosis were examined for each period. The results of this study, *Trends in diagnosis rates for autism and ADHD at hospital discharge in the context of other psychiatric diagnoses*, were published in January 2005[11].

4) Identify the primary sources and levels of prenatal and postnatal exposure to thimerosal and other forms of mercury in infants, children and pregnant women

[11] Mandell DS, Thompson WW, Weintraub ES, DeStefano F, Blank MB. et al. Trends in diagnosis rates for autism and ADHD at hospital discharge in the context of other psychiatric diagnoses. *Psychiatr Serv* 2005 January; 56(1): 56-62

In addition to the VSD thimerosal and autism study described above, CDC conducted the study, *Early Thimerosal Exposure and Neuropsychological Outcomes at 7 to 10 Years*, to more rigorously examine the hypotheses that increasing exposure to thimerosal is associated with neurodevelopmental disorders. In contrast to the 2003 thimerosal screening study, which utilized ICD-9 codes, this study objectively measures the neurodevelopmental disorders of interest through a three-hour objective assessment of children aged 7 to 9 years. The assessments were administered by staff trained to administer neuropsychological test batteries in a health care setting. The results of the study are significantly less vulnerable to the introduction of health care seeking bias and assist in the interpretation of the results obtained in the 2003 thimerosal screening study.

The study found associations that were both positive and negative between exposure from thimerosal and neuropsychological functioning, however, only a few were statistically significant associations. The weight of the evidence from this study does not support an association between early ethyl mercury exposure from thimerosal-containing vaccines and/or immunoglobulins and neuropsychological functioning at ages 7 to 10 years. The results were published in September 2007[12].

Additional CDC Research

In 2004, the IOM performed a comprehensive review of the scientific evidence regarding thimerosal-containing vaccines and autism newly available since its initial review in 2001[13]. In its 2004 report, the IOM concluded that "the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism," and further stated

> While the [IOM Immunization Safety Review] committee strongly supports targeted research that focuses on better understanding the disease of autism, from a public health perspective the committee does not consider a significant investment in studies of the theoretical vaccine-autism connection to be useful at this time. (p.11)

Although CDC concurs with the 2004 IOM findings, CDC is committed to completing its research undertaken in this area. CDC is currently completing the vaccine safety studies it undertook in response to the 2001 IOM report.

CDC recognizes that autism is an urgent health concern and is supporting comprehensive research as our best hope for understanding the causes of autism and other developmental disorders. Through collaborations with partners in government, research centers, and the public, CDC is focusing on three areas: 1) understanding the frequency and trends of autism spectrum disorders, 2) advancing research in the search for causes and effective treatments and 3) improving early detection and diagnosis so that affected children get treatments as soon as possible. These research efforts include the following:

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[12] Thompson W et al. Early Thimerosal Exposure and Neuropsychological Outcomes at 7 to 10 Years. *New England Journal of Medicine* 2007 September; 357(13):1281-92

[13] IOM. 2004. Immunization Safety Review: Vaccines and Autism. Washington DC: The National Academies Press.

- CDC is one of six sites across the country participating in a Centers of Excellence for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) study investigating risk factors and causes of autism in 2- to 5-year-olds. The study is targeting approximately 2,700 children among three groups: ASD cases, a neurodevelopmental comparison group and a typically developing comparison group. Data collection began in spring 2007.

CDC is conducting a study looking at all mercury exposures and working with the National Health and Nutrition Examination Survey (NHANES). NHANES 4 will collect samples of blood, hair and urine from women of reproductive age and children under five in order to assess mercury levels in the body from all sources of environmental exposure. Results of a study conducted using NHANES 3 data to check blood and hair mercury levels suggest that the mercury levels in young children and in women of childbearing age are generally below the level considered hazardous.