

## **Vaccines and Autism**

### **National Institute of Environmental Health Sciences Report to Congress Thimerosal Exposure in Pediatric Vaccines: Feasibility of Studies Using the Vaccine Safety Datalink**

#### **Background**

In 2006, Congress requested the National Institute of Environmental Health Sciences, part of the National Institutes of Health, to convene a panel of independent, non-government scientists to determine whether data from the Centers for Disease Control and Prevention's (CDC) Vaccine Safety Datalink (VSD) Project could be used to identify or rule out any association between thimerosal exposure in pediatric vaccines and increased autism rates.

A panel of independent researchers not associated with the U.S. government met in May 2006. Panel members included scientists with expertise in epidemiology, neurotoxicology, mercury toxicity, autism and related neurodevelopmental disorders, biostatistics, risk assessment and clinical research.

The panel reviewed the merits of an "ecologic" study design that would use VSD Project data to compare autism rates before and after the removal of thimerosal from most pediatric vaccines used in the United States. The panel identified several information gaps in this data that would make such a study "uninformative and potentially misleading." Other study designs using VSD Project data also were considered; however, panel members recommended that the identified information gaps be addressed before considering further thimerosal and autism studies using VSD data.

**Q: What is the Vaccine Safety Datalink Project, and what role does it play in evaluating the safety of vaccines?**

**A:** The Vaccine Safety Datalink (VSD) Project is a collaboration among CDC, eight large managed care organizations (MCOs) and America's Health Insurance Plans (AHIP). The VSD Project was established in 1990 to monitor immunization safety and address the gaps in scientific knowledge about serious side effects following immunization.

The VSD Project investigates vaccine safety issues in the United States through analyses of data collected from large administrative databases maintained by the individual MCOs as providers of routine health services. The databases contain detailed records of vaccine administration; medical data from inpatient and outpatient procedures and visits; and birth and census data on more than 5.5 million children and adults, which accounts for nearly 2 percent of the U.S. population. The VSD Project allows for planned immunization safety studies as well as timely

investigations of vaccine safety questions that arise from reports to the Vaccine Adverse Event Reporting System (VAERS), changes in immunization schedules or the introduction of new vaccines.

VSD currently has contracts with the following MCO sites:

- Group Health Cooperative of Puget Sound, Seattle, WA,
- Kaiser Permanente Northwest, Portland, OR,
- Kaiser Permanente Medical Care Program of Northern California, Oakland, CA
- Southern California Kaiser Permanente Health Care Program, Los Angeles, CA
- HealthPartners Research Foundation, Minneapolis, MN
- Marshfield Clinic Research Foundation, Marshfield, WI
- Kaiser Permanente Colorado, Denver, CO
- Harvard Pilgrim Health Care, Boston, MA

**Q. What VSD strengths did the panel identify?**

- A.** The panel recognized the VSD Project’s overall value in detecting infrequent, vaccine-related adverse events of modest size. Another important strength noted is VSD Project’s ability to supplement the administrative data collected by the MCOs through more detailed reviews of hardcopy medical records, standardized interviews with parents and children and additional diagnostic assessments. Investigators also benefit from the demographic information available in the VSD Project on the MCO members.

**Q. What information gaps did the panel identify that would limit the usefulness of the VSD data in an ecologic study of thimerosal and autism rates?**

- A.** The panel concluded that the administrative data routinely collected by the VSD Project do not provide sufficient information to identify autism cases accurately for research. As a result, 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. In many cases, however, CDC researchers also conduct medical chart reviews in its VSD Project studies to supplement the administrative data.

The following are other limitations the panel noted that would limit the use of VSD data in an ecologic study of autism rates:

- Differences in business practices among the MCOs, including different screening and diagnostic practices, specialist referral guidelines and patient tracking methods. These variations affect the comparability of autism data across the sites.

- Changes over time in the way that the MCOs create medical records, including a transition from paper to electronic medical records and changes in the way medical diagnoses are classified and recorded. According to the experts, these changes would distort trends in autism rates over time, regardless of whether autism cases are truly rising, falling or staying constant.
- 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. While these linkages might be helpful in identifying relevant prenatal and genetic factors, it is not clear whether such studies would have enough statistical power to provide answers regarding the potential association between thimerosal and rare diseases like autism.
- An inability to estimate accurately total cumulative mercury exposure from sources other than vaccines, such as diet, air and water.

**Q. What major recommendations did the expert panel make?**

- A.** The expert panel found that an ecologic study using VSD Project data to compare autism rates before, during and after the removal of thimerosal from pediatric vaccines would be “uninformative and potentially misleading” due to the limitations noted earlier.

The panel suggested alternative study designs for future research into thimerosal exposure and autism, including a study of a high-risk population defined as siblings of individuals diagnosed with autism. The panel recommended that the identified gaps in VSD Project data be addressed before considering this or other future thimerosal and autism studies using this data.

In addition, the panel recommended that members of the autism advocacy community participate in all aspects of any future VSD Project studies into thimerosal and autism, including study design, analyses and interpretation of findings. In fact, prior to the NIEHS expert panel review, CDC had taken steps to involve representatives of the autism advocacy community in its two current thimerosal studies. However, to protect patient confidentiality, access to VSD Project data is limited; data are not available for review by members of the autism community or the general public.

**Q: What is an ecologic study? Has CDC conducted ecologic studies in the past to evaluate the association between thimerosal and autism?**

- A:** Ecologic studies are based on data representing groups rather than data collected on each individual separately. VSD Project studies rely on various epidemiologic

study designs, but few have been ecologic studies. For example, a comparison review of changes in autism rates over a period of time along with a review of changes in the median age of mothers at pregnancy over time would be an ecologic study looking at whether older age during pregnancy carries a higher risk of having an autistic child. However, trends through time may coincidentally appear to be related even if there is no real cause-and-effect relationship. A more credible study would be to evaluate for each individual mother her age at pregnancy and whether or not her child developed autism.

VSD Project studies evaluating the association between thimerosal and autism, including the 2003 thimerosal screening study, have not been ecologic studies. The National Immunization Program published in 2003 the results of an ecologic study addressing autism and thimerosal-containing vaccines. That study, which analyzed data from the United States, Sweden and Denmark, including immunization coverage surveys, vaccination coverage levels, inpatient data and autism registries, found no consistent evidence of an association between thimerosal and autism.<sup>1</sup>

The VSD Project currently has eight priority studies underway to address a range of important immunization safety questions, none of which are ecologic studies. Instead, these current studies, including two studies evaluating associations between thimerosal-containing vaccines and neurological development disorders, all require 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 normally provide better scientific evidence.

**Q. What steps is CDC taking to address the potential association between thimerosal exposure in pediatric vaccines and autism?**

- A.** CDC currently is reviewing in detail the recommendations made by the panel of experts convened by the National Institute of Environmental Health Sciences (NIEHS) and will discuss the panel's findings with NIEHS and other agencies involved in addressing this issue.

Several studies conducted by CDC researchers and others have looked at whether there is a relationship between vaccines and autism. The weight of the current scientific evidence indicates that vaccines are not associated with autism. However, CDC is committed to maintaining the safest, most effective vaccine supply in history, and we are continuing to explore if vaccines are linked to autism.

**Q. Are there any current CDC studies underway that address the potential association between thimerosal exposure in pediatric vaccines and neurological developmental disorders, including autism?**

- A. Yes. CDC is completing significant research to address this critical issue. In fact, earlier studies, including the thimerosal screening study published in 2003<sup>2</sup>, have guided the development of more rigorous studies currently underway. In the 2003 CDC thimerosal screening study, which was not an ecologic study, an analysis of computerized data from three different managed care organizations (MCOs) found no consistent, significant associations between thimerosal-containing vaccines and neurological developmental disorders. However, conflicting results were found at different MCOs for certain outcomes, and researchers at the time acknowledged there were weaknesses in the study – similar to the data limitations noted by the NIEHS panel of experts. The researchers recommended additional studies be conducted, including neuropsychological testing of children with different thimerosal exposures. This type of study, according to researchers, would address one of the main limitations of the CDC screening study: the reliance on existing administrative medical records for outcomes assessment, rather than performing medical assessments designed to address specific research questions.

Following are highlights of the current studies.

- **Thimerosal and Autism Study**

This study has been designed to address the issues raised by the 2003 thimerosal screening study, including a reliance on administrative medical records for outcomes assessment. The study design also addresses some of the same issues noted by the NIEHS panel. In this study, which began in June 2001, VSD Project researchers are examining potential associations between thimerosal exposure in infancy or during pregnancy and the development of autism.

Researchers will compare children with autism to those without autism. In-person neurological development examinations, telephone interviews, medical chart reviews and immunization tracking systems will be used to collect information on vaccine history and other possible health factors related to autism. Independent, external expert consultants, including a member of the autism advocacy community, are providing input into every aspect of this study, which is expected to be completed in late 2008.

- **Thimerosal and Neurological Developmental Disorders Study**

In this follow-up study to the 2003 thimerosal screening study, VSD Project researchers assessed the potential relationship between thimerosal and neurological developmental disorders. This study involves neuropsychological testing of children between the ages of 7 and 10 years whose vaccinations in

the first year of life could have contained thimerosal. Detailed vaccination records were used to assess accurately the amount of thimerosal exposure. Developmental milestones assessed include speech and language skills, fine motor coordination and academic and intellectual functioning. This study compares the neuropsychological performance among children exposed to different quantities of thimerosal from vaccines administered and other exposures during the first year of life.

This study does **not** assess autism as a possible outcome of thimerosal exposure through vaccination; autism occurs too infrequently to be assessed with this study design. Thirteen external experts representing a broad spectrum of expertise in fields related to autism, child development, immunization and immunization safety, including a member from the autism advocacy community, provided consultation on every aspect of this study. The resulting study is better informed by this broad expertise. Data collection and analysis have been completed, and a manuscript, "Early Life Exposure to Thimerosal and Neuropsychological Test Performance at 7 to 10 Years of Age," has been submitted for publication to a peer-reviewed journal.

- **Italy Thimerosal Neurological Developmental Disorders Study**  
CDC is collaborating with 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 is expected to be completed in late 2007.

## References

1. Paul Stehr-Green, DrPH, MPH, Peet Tull, Michael Stellfeld, MD, Preben-Bo Mortenson, DrMedSC, Diane Simpson, MD, PhD. Autism and thimerosal-containing vaccines: lack of consistent evidence for an association. *Am J Prev Med.* 2003 Aug;25 (2):101-6.
2. Verstraeten T, Davis RL, DeStefano F, Lieu TA, Rhodes PH, Black SB, Shinefield H, and Chen RT. Safety of Thimerosal-Containing Vaccines: A Two-Phased Study of Computerized Health Maintenance Organization Databases. [Journal: Article] *Pediatrics.* Vol. 112(5) (pp 1039-1048), 2003.