REPORT OF THE EXPERT PANEL

TO THE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Thimerosal Exposure in Pediatric Vaccines:

Feasibility of Studies Using the Vaccine Safety Datalink

August 24, 2006

Thimerosal Exposure in Pediatric Vaccines: Feasibility of Studies Using the Vaccine Safety Datalink

Executive Summary

The Vaccine Safety Datalink (VSD) is a resource that was developed by the National Immunization Program of the US Centers for Disease Control and Prevention through collaborative arrangements established with several managed care organizations (MCOs). It has been proposed that the VSD could be used to look at the association between autistic disorder (AD) or autism spectrum disorders (ASD) by means of an ecologic analysis that would compare rates before and after the removal of thimerosal from most childhood vaccinations. To determine the feasibility and potential contribution and/or drawbacks of such a study, and to consider alternative study designs that could be conducted using the VSD database, the NIEHS convened a panel of experts on May 4th, 2006 in Research Triangle Park, NC.

The panel identified several serious problems that were judged to reduce the usefulness of an ecologic study design using the VSD to address the potential association between thimerosal and the risk of AD/ASD. These included uncertainties in case ascertainment, heterogeneity of business practices within and across MCOs and their systematic changes over time, misclassification of exposure status using comparisons of before vs. after removal of thimerosal from most childhood vaccines, and the inability to control for temporal changes in awareness, diagnostic practices and potential confounding factors. In light of the cumulative effect of these limitations, the panel reached consensus that an analysis comparing the rates of AD/ASD in the VSD over the time period before, during and after the removal of thimerosal from most childhood vaccines would be uninformative and potentially misleading.

An alternate future study design that was viewed positively among panel members was a study of a high risk population, defined, in this instance, as siblings of individuals diagnosed with AD/ASD. A sibling cohort from the VSD would allow comparison of AD/ASD risk in siblings as a function of their thimerosal exposure through vaccination and the sample size would lend itself to supplemental data collection. A related study design based on sib-pairs or sets could be used to address discordant ASD/AD status in relation to thimerosal exposures. Another possibility that generated support by the panel was an expansion of the VSD study published by Verstraten et al (2004). The availability of several additional years of VSD data was seen as an opportunity to provide a more powerful test of any potential association between thimerosal and AD/ASD and would enable reconsideration of some aspects of the original study design (e.g., exclusion criteria). A related idea was to conduct a VSD retrospective cohort study using California-based MCOs linked with the California DDS, which would improve the diagnostic data and provide more complete ascertainment. For each of these designs, the ability to link medical records from mothers with those of their children was deemed critical.

A number of gaps were identified in the information available at the meeting. These involved business and medical practices at the MCOs that might impact data quality and interpretation of study results, and more generally, the completeness and validity of exposure and diagnostic data in the VSD and the ability to link across family members. The panel recommended that these gaps be addressed prior to consideration of further studies of AD/ASD and thimerosal using the VSD.

The panel recognized the sensitivity of the questions regarding AD/ASD and thimerosal, and the perception by some members of the public and the advocacy community that previous VSD analyses have not been conducted in an open manner. The panel recommended that the AD/ASD advocacy community participate meaningfully in all aspects of any future VSD study of AD/ASD, including design, analysis and interpretation. The proposal that VSD studies be conducted entirely by independent investigators external to the CDC and the VSD MCOs was not considered to be feasible given the complexity of the data sources and the many limitations that may not be apparent to someone without intimate familiarity with the VSD.

Background

Description of VSD

The Vaccine Safety Datalink (VSD) is a resource that was developed by the National Immunization Program of the US Centers for Disease Control and Prevention through collaborative arrangements established with several managed care organizations (MCOs). Approximately 3% of the US population of children (2.3 million children) is enrolled in the eight participating MCOs, and 92,000 annual births occur. Large administrative databases maintained at the individual MCOs form the backbone of the VSD. These databases allow linkage of detailed records of vaccine administration (e.g., lot number and manufacturer) with diagnostic data from inpatient and outpatient procedures and visits. The overall coordination of member health care services at MCOs enables the VSD to capture all of the health care services provided to plan members.

Creation of an expert panel

It has been proposed that the VSD could be used to look at the association between autistic disorder (AD) or autism spectrum disorders (ASD) by means of analyses that compare rates before and after the removal of thimerosal from most childhood vaccinations. To determine the feasibility of such a study and to consider any alternate designs that could capitalize on the unique advantages of the VSD to address the association between thimerosal exposure and AD/ASD, the NIEHS convened a panel of non-government scientists on May 4th, 2006 in Research Triangle Park, NC. Panel members included experts in epidemiology, neurotoxicology, mercury toxicity, autism and related neurodevelopmental disorders, biostatistics, risk assessment and clinical research. VSD investigators and data managers from the CDC and the MCOs were present to provide the expert panel with information regarding the VSD and to answer questions. A number of public advocacy groups were in attendance and provided public comments to the panel.

Charge to panel

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/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 (an epidemiologic design where there is no linkage between individual-level data on exposure and health outcome)
- 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
- Dicuss the potential impact of possible VSD-based studies in the context of what is already known about autism and ASD

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Report of the Expert Panel

VSD strengths and weaknesses

The panel acknowledged the overall value of the VSD for detecting infrequent vaccine-related adverse events and/or effects of modest size. The possibility of supplementing the administrative data through medical chart review and/or the conduct of additional interviews and diagnostic assessments was recognized as an important strength. The availability of demographic characteristics for MCO enrollees was identified as another benefit for investigators, as this allows an assessment of whether the HMO population is representative of the larger population of interest.

Despite these overall strengths, the panel identified several areas of weakness. The cumulative effect of these weaknesses was judged to reduce the usefulness of the VSD for addressing the potential association between exposure to the vaccine preservative thimerosal and risk of AD/ASD. The weaknesses of primary importance are summarized below.

Case ascertainment. A VSD study that relies exclusively on administrative data to identify cases of ASD is subject to both false positives and missed cases. This stems in part from the original design of the MCO data systems that support the VSD; these systems were designed for administrative rather than research purposes. For example, diagnostic codes entered in the MCO administrative records for outpatient visits are intended only to indicate the initial reason for the visit. In cases where enrollees obtain services at MCO-affiliated outside clinics, the administrative record serves as the mechanism for billing and reimbursement. For these reasons, a diagnosis code for AD/ASD that appears in the administrative VSD records does not necessarily indicate its presence nor does it reflect onset or severity. For example, the administrative record created for an outpatient visit of a child with AD/ASD who is being treated for another medical condition will reflect that other condition rather than the presence of autism. Entries of this type would lead to under-ascertainment of cases. In other cases, an AD/ASD diagnostic code may be assigned to indicate the parental concern that prompted a visit. The medical evaluation that takes place during that visit, or subsequent visits, may rule out that that particular diagnosis, but this determination will not alter the original code assigned to the visit. This type of scenario would result in over-ascertainment, i.e., erroneous classification of unaffected persons who would be categorized as AD/ASD in any analysis. The degree of under and over-ascertainment of AD/ASD that would result from reliance solely on the administrative VSD records could not be

determined by the panel with the data available, but was noted as a potentially serious problem. 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.

Heterogeneity in business practices across and within MCOs. Eight MCOs currently participate in the VSD and each relies on data systems designed to meet the specific business requirements of the MCO. In addition to obvious differences among MCOs in enrollment size and geographic location of the populations served, many other aspects of service delivery and tracking vary (e.g., developmental screening practices and specialist referral guidelines). For example, differing diagnostic practices across MCOs may support entry of an ASD code at different points in the evaluation process. Differences across clinics and other service providers affiliated with an individual MCO occur as well. The panel noted that these variations within and among VSD sites would complicate interpretation of a VSD study that combined data across clinics and sites by introducing heterogeneity in the completeness and quality of case ascertainment. Moreover, membership in an MCO might be influenced by an AD/ASD diagnosis. This could occur, for example, if children presenting with problems predictive of the development of AD/ASD (e.g., speech delay) are more likely to leave a MCO-administered plan because the parents believed that another model of service delivery would be more beneficial for the medical management of developmental difficulties.

Systematic changes over time. The systems for creating medical records at the VSD sites are dynamic and change frequently in response to the evolution of the individual MCO business model. The panel noted that at least some of these changes would be expected to affect the observed rate of autism and could confound a trend analysis. One such change was the transition from paper to electronic medical records. This change occurred at different times for each of the participating MCOs. An ecologic analysis of AD/ASD rates in the time periods before and after thimerosal removal would have to rely on data spanning these transition periods. Other changes, such as an increase in the number of ICD codes that could be entered in the electronic medical record for a single outpatient visit, would distort trends in AD/ASD rates over time regardless whether true incidence were rising, falling, or staying constant.

Linking records of children and their mothers. The MCO systems that populate the VSD provide an efficient means for linking medical information from multiple administrative sources to a single individual. This efficiency derives from the unique identifier assigned to each individual who is enrolled in the MCO. In contrast, use of the VSD administrative data for discerning family relationships is more difficult. Complex algorithms that match enrolled individuals based on factors such as shared residence or phone number, or through designation by the primary subscriber of partner or dependent status, can be used to provide an initial basis for grouping individuals by family unit. This strategy will be uninformative in cases where only one member of a family is enrolled in the

MCO. It cannot discern biologic from non-biologic relationships between a parent and a child, or between two siblings. The panel considered this to be a serious problem for some of the study designs under consideration, as 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. Relevant prenatal exposures include maternal receipt of a thimerosal-preserved Rhogam injection, other vaccinations given during pregnancy, and potential confounding factors such as complications of pregnancy.

Estimation of mercury burden. Panel members expressed a concern that thimerosal dose, administered through a series of vaccinations, may provide a poor surrogate measure of the cumulative exposure of a child to organic mercurials. Exposures through diet or other environmental sources would not be documented reliably in either the VSD administrative data or medical charts. Although the panel acknowledged that some useful information could be elicited through interviews with family members, implementation of this on a large scale was considered unrealistic. Measurement of current blood levels of mercury was recognized as uninformative due to the relatively short half life of mercury. Analysis of mercury deposition in stored hair samples could be used to reconstruct exposure history under some circumstances, but obtaining a sufficient number of hair samples from mothers and children were judged to present a challenge with regard to feasibility.

Research designs considered by the panel

Population-based studies of AD/ASD rates from VSD data. In light of the limitations noted earlier in this report, the panel addressed the utility of an ecologic analysis of VSD data to compare the rates of autism/ASD in the time period before and after the removal of thimerosal from most childhood vaccines. The consensus was that such a design would have limited value and be potentially misleading. This conclusion was based on limitations inherent in the VSD noted above, as well as concerns regarding the inability to control for temporal factors that include heightened awareness, number of professionals trained to make ASD/AD diagnoses, changes in diagnostic criteria and practices, and trends in other exposures that might therefore confound the association between thimerosal and ASD/AD. Some of these factors might inflate apparent associations and others might deflate them, but the net impact would distort the relationship, null or otherwise, between thimerosal and ASD/AD. As the VSD does not lend itself to precise measurement of most of the biasing or confounding factors, a finding of a positive association could not be interpreted as nonconfounded evidence of a true relationship, and similarly, a negative or null association could not be interpreted as unconfounded evidence against a relationship. The panel expressed the view that efforts would be better spent implementing more rigorous study designs.

Studies of high risk populations from VSD enrollees. A study design that generated significant enthusiasm among panel members was a study of a

high risk population, defined as siblings of individuals diagnosed with autism. The recurrence risk for AD/ASD is estimated to be 5-20% within families. The strong genetic component of AD/ASD, together with the shared environment of family members, indicates that siblings of AD/ASD children can be considered a susceptible population. Thus, a study that focused on this enriched-risk sample may have improved ability to detect an association of thimerosal with AD/ASD risk. Another benefit of this design would be the reduction in sample size, relative to studies in unselected samples; this would increase the feasibility of collecting more extensive data from medical chart review, additional interviews and assessments of children in the cohort to confirm diagnoses. Within the cohort, the risk for AD/ASD in those with exposure to thimerosal-containing vaccines would be compared with the risk among those not exposed. Further analyses could examine the risk as a function of dose of thimerosal. Under this design, members of the cohort would be defined as those siblings (of children with AD/ASD) who were born during the time periods before, during and after the removal of thimerosal. Limiting the birth years to a narrow window could minimize confounding from unmeasured factors that are changing over time.

A variation of this design would be a study of concordant/discordant sib pairs. A similar sampling frame would be employed initially, by identifying cases with siblings, but the analysis would include the index child as well as all siblings in the relevant time period. Informative families would be those with at least one unaffected and one affected child. Panel members discussed whether this might represent a more efficient design than a study that used the full sibling cohort. With a recurrence risk of 5 to 20 percent, only a small proportion of the available discordant sib pairs would be required for matching to concordant sib pairs, and this would allow a more in-depth evaluation of the sample for purposes such as confirming the diagnosis, further defining the phenotype and collecting additional exposure information that can be considered in the analysis.

Association study of thimerosal exposure and risk of AD/ASD incorporating recent VSD data. Another study design considered by the panel was an expansion of the VSD study published by Verstraten et al (2004). This publication used a retrospective birth cohort design and was restricted to VSD administrative data from three MCOs. The retrospective cohort differs from an ecologic design in that individual-level data on thimerosal-containing vaccine exposures are used. In light of the overall low number of cases of AD/ASD expected from the populations at the three participating MCOs, the authors examined several neurological or developmental outcomes in addition to AD/ASD, including tics, language delay and attention deficit disorders. Birth cohorts from 1991 to 1998 were included with follow-up of exposure (immunization) and outcomes to 1998 or 2000, corresponding to an age range of one to eight years. Separate analyses were conducted for VSD data at the three MCOs. A few weak associations were reported for neurological outcomes other than AD/ASD, although no strong or consistent pattern of results was observed across the three MCO sites. The availability of several additional years of VSD

data was seen as an opportunity to provide a more powerful examination of any potential association between thimerosal and AD/ASD conditions.

The design of a new study would have the additional benefit of enabling a reconsideration of some aspects of the original study design and the opportunity to collect additional data to evaluate issues such as diagnostic reliability and sensitivity. Of particular interest to the panel was the large proportion, around 25%, of births excluded from the analyses in the Verstraten study. These exclusions were intended to decrease confounding. The panel noted that these children may represent a susceptible population whose removal from the analysis might have had the unintended consequence of reducing the ability to detect an effect of thimerosal. The panel recommended that further consideration be given to conducting an extension of the Verstraten study that would include additional years for follow up, would add more MCOs and reexamine the criteria for exclusion of births and/or take a sensitivity analyses approach to examining the impact of various exclusion criteria.

Collaborative study of VSD and the California Department of Developmental Services (DDS). A related approach considered by the panel was the possibility of conducting a VSD retrospective cohort study linked with the California DDS database. The records in this administrative database contain information on all persons eligible for state-funded services because of a diagnosis of autism, dating back to the late 1980s. These data would likely improve upon the diagnostic information in the VSD. Thus, if DDS records were linked with the California MCO records that are present in the VSD, diagnostic reliability could be improved even without the expense of examining the children.

Additional general recommendations for study designs and collection of exposure and outcome information

- Alternative approaches for estimation of thimerosal exposure, based on both thimerosal dose and timing, should be considered for future studies. The possible importance of information about the neurodevelopmental stage associated with each exposure was emphasized by the panel.\
- In light of the potentially heightened vulnerability during the prenatal period of development, restriction of the VSD study population to children where prenatal exposure information could be obtained should be considered.
- The ability to collect additional data regarding potential mercurial exposures other than through routine childhood immunizations was considered essential to provide accurate exposure information. Of particular interest was the ability to access prenatal records to determine exposure to thimerosal through administration of Rhogam to mothers. Data on prenatal exposure to methylmercury from maternal fish consumption during pregnancy remains inaccessible retrospectively and would remain an unmeasured covariate in studies employing the VSD database.

- The need for an accurate biomarker of exposure was identified; blood levels of mercury are not good indicators of past exposures. Analysis of baby hair, often saved from the first haircut, could provide more information, and should be considered.
- Supplementation of the VSD administrative data through medical chart review and/or the conduct of additional interviews and standardized diagnostic assessments should be considered for any future VSD study. In studies with very large populations, this may not be feasible for the entire sample, but could be considered for or a validation subset or for a subgroup of special interest.

Information needed to inform further discussions

The panel identified a number of gaps in the information available at the meeting and recommended that the following questions be addressed and that validation studies of diagnoses of ASD/AD and of thimerosal-containing vaccine exposure information be completed prior to launching any further VSD studies that examine the association of thimerosal with the risk of AD/ASD

- How does the prevalence of AD/ASD, as calculated from the VSD administrative data, agree with the current prevalence estimates established recently from population-based studies in the US? The panel suggested that the network of Regional Centers established by the Department of Developmental Services in California for the coordination of autism services may provide a suitable comparison to the prevalence estimates calculated from VSD data at the two California-based MCO sites.
- How many AD/ASD cases are identified at each MCO by year of diagnosis, and year of birth?
- How many siblings of children with AD/ASD are enrolled at each MCO?
- What proportion of the AD/ASD cases identified in the VSD administrative data were enrolled from birth? What is the drop out rate of children with AD/ASD from the MCO compared to healthy children and what is the distribution of durations of enrollment? Do children with AD/ASD differ from typically developing children in these enrollment characteristics?
- What developmental screening is done routinely within and across the MCOs?
- How are the electronic medical records coded? Do they allow string searches that would facilitate identification of children who should be evaluated further within a proposed study?
- What is the feasibility of linking prenatal and postnatal data for an enrolled child at each MCO? What algorithms have been used to link families and how accurate and complete are the methods used?
- How are referrals to outside specialists handled at each MCO and under what conditions would these be reflected in the VSD?

- What are the ICD-9 coding policies at each MCO and what is the extent of variation in these policies across sites?
- What kind of validation data could be assembled from the existing VSD database, and what kind of validation studies on diagnoses and vaccine exposures could be conducted?
- What are the demographics of MCO enrollees at each site and are they representative of the census data from the geographic area served?
- How much of this information is known currently by the MCOs and can these known elements be assembled in a form suitable for examination by a larger group? What is the willingness of the VSD participating sites to provide this information? What information could be obtained but would require significant additional work on the part of VSD sites?

Public participation in VSD studies

The panel recognized the sensitivity of the questions regarding AD/ASD and thimerosal, as well as, the perception by some members of the public and the advocacy community that previous VSD analyses have not been conducted in an open manner. The panel recommended that the AD/ASD advocacy community participate meaningfully in all aspects of any future VSD study of autism, including design, analysis and interpretation. The proposal that VSD studies be conducted entirely by independent investigators external to the CDC and the VSD MCOs was not considered to be feasible. The complexity of the data sources and the management systems that have evolved to handle the data require the involvement of individuals intimately familiar with the VSD. The panel acknowledged the real risk of misinterpretation or overt error without this involvement. Given that each study would require access to personal health data, requirements for maintaining patient privacy also dictates the need to coordinate efforts with CDC and the VSD MCOs. The recognition that any arrangements that would provide increased openness would need to accommodate MCO concerns regarding data sharing was acknowledged, although these were considered issues outside the scope of the current panel deliberations.

Appendices

Expert Panel Members

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[1] Invited and supported by the NIEHS to attend as representative of a national autism program

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Bobbi Manning
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Angela Medlin
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Final Agenda

MORNING		
8:30-8:40	**Welcome** Introductions and opening remarks	David Schwartz (NIEHS) Robert Davis (CDC)
8:40-9:00	Time Trends in Autism	Irva Hertz-Picciotto (UC-Davis)
9:00-9:30	Introduction to the VSD	*Lisa Jackson (Group Health Coop.)*
9:30-9:50	Technical aspects of the VSD	*James Baggs (CDC)*
9:50-10:25	Q & A about the VSD	
10:25-10:40	***Break***	
10:40-11:00	VSD Research Collaboration and Data Sharing Considerations	*Richard Platt (Harvard Pilgrim Health)*
11:00-11:40	***Q & A about VSD Data Sharing***	
11:40-12:00	Other ongoing CDC studies	*Frank DeStefano (CDC)*
12:00-12:30	**Public Comments**	
AFTERNOON		
12:30-1:15	**Lunch (NIEHS cafeteria)**	
1:15-3:15	Roundtable discussion	*Discussion leaders:* *Irva Hertz-Picciotto (UC-Davis)* *Craig Newschaffer (Johns Hopkins)*
	Feasibility of ecological analysis with VSD to compare pre vs. post thimerosal autism rates Strengths and Limitations Relation to existing data & ongoing studies Impact	
3:15-3:30	**Break**	
3:30-4:30	Other potential VSD studies/resources	*Discussion continues*
4:30-5:00	***Recommendations and next steps***	*Jean Harry (NIEHS)*
5:00-5:30	***Public comments***	

Meeting Description and Goals

Meeting description

In response to continued public concern regarding a potential association of autism with thimerosal exposure, the NIEHS has worked cooperatively with the CDC to convene an external expert panel to discuss new studies that could be conducted with the Vaccine Safety Datalink (VSD) to examine a possible association. The collective expertise of this panel includes clinical and epidemiologic research, biostatistics, neurotoxicology, and risk assessment. Representatives from the NIH institutes that support autism research, several major autism advocacy organizations and the US Environmental Protection Agency have been invited to attend this meeting.

Meeting Goals

- Identify the strengths and limitations of the VSD, particularly with regard to longitudinal data analysis.
- Determine the feasibility of conducting a new ecologic study to compare autism rates before and after thimerosal removal from most US vaccines.
- Make recommendations for design, conduct, analysis and oversight of the proposed ecologic study.
- Discuss the impact of the proposed ecologic study in the context of what is known about autism and autism spectrum disorders.
- Identify any additional uses of the VSD or other existing resources that might be employed to examine a potential association of autism and thimerosal.

Questions to guide discussion

The Vaccine Safety Datalink (VSD) was developed by CDC to enable continual monitoring of vaccine safety through record linkage of vaccine administration data with potential adverse events in several large populations served by HMOs. The VSD has been the subject of many recent discussions and reviews, most notably an IOM report in 2005 entitled “Vaccine Safety Research, Data Access, and Public Trust”.

1. It has been proposed that the VSD could be used to look at the association between autistic disorder (AD) or autism spectrum disorders (ASD) by means of a classic ecological analysis that compared rates before and after the removal of thimerosal from most childhood vaccinations.
    a. Given your understanding of the VSD, do you believe this is plausible?
    b. If yes, what will be the advantages and limitations to this type of analysis?
    c. In the broader context of what is already known about AD and ASD, what impact will an ecological analysis of this type have?
2. Can you think of other uses of the VSD that might provide additional insights into any possible linkages between vaccines and AD/ASD? If yes, please

specify the type of analysis/study design and describe its impact on our understanding.

3. As we look toward the future use of the VSD, we are interested in strengthening its utility. With respect to AD and ASD, can you recommend other data that could be collected through review of charts, interviews or examinations to supplement the data routinely available in the VSD computerized data sets?
4. Based on your experience with collaborative analyses and data sharing in other forums, can you suggest the most appropriate mechanism(s) that could be developed to foster inter-agency collaboration and external input on a VSD study of autism trends?