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## Post-publication Peer Reviews to:

## ARTICLE:

Thomas Verstraeten, Robert L. Davis, Frank DeStefano, Tracy A. Lieu, Philip H. Rhodes, Steven B. Black, Henry Shinefield, Robert T. Chen, and for the Vaccine Safety Datalink Team

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### **Safety of Thimerosal-Containing Vaccines: A Two-Phased Study of Computerized Health Maintenance Organization Databases**

Pediatrics 2003; 112: 1039-1048 [\[Abstract\]](#) [\[Full text\]](#)

## P<sup>3</sup>Rs published:

### ▼ **Comments on Verstraeten et al, Safety of Thimerosal-Containing Vaccines from Nov 5, 2003 Pediatrics**

Neal A. Halsey, Daniel A. Salmon and Lawrence H. Moulton (17 December 2003)

### ▼ **Safety of Thimerosal-Containing Vaccines: Response to Halsey et al**

Frank DeStefano, Philip H. Rhodes and Robert L. Davis (9 January 2004)

## Comments on Verstraeten et al, Safety of Thimerosal-Containing Vaccines from Nov 5, 2003 Pediatrics

17 December 2003



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To the editor,

Verstraeten et al. (1) are to be commended for trying to determine if there were adverse effects from administering multiple vaccines that contained thimerosal. However, we would like to point out a few aspects of the analyses and their interpretation that invite further elaboration of these data.

The results differ somewhat from those presented to the Institute of Medicine (IOM) in 2001 (2), where a statistically significant dose-response association was observed between thimerosal exposure by three months of age and neurodevelopmental delay assessed by

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[Email](#) Neal A. Halsey, et al.

combining several diagnostic categories. Such an analysis is reasonable since there is variability in coding of diagnoses for children with developmental delay and since a related compound, methylmercury, is known to be associated with multiple effects on neurological development. Analysis by separate diagnostic category may have substantially reduced the power to find important relationships. In addition, the selection criteria used in the published article appear to have been more lax than in the IOM presentation, as the latter was based on fewer outcomes.

Several important issues were not adequately described. Were all DTaP, Haemophilus influenzae type b, and hepatitis B vaccines assumed to contain the thimerosal preservative? Some vaccines were available that did not contain this preservative (3). Were diagnoses that were not made by a specialist (i.e. not validated) excluded from analyses? Primary care physicians are capable of diagnosing attention deficit disorder (ADD) without input from a subspecialist. Were analyses conducted to determine if there are differences in associations by gender? Males are more susceptible to the effects of methylmercury and elemental mercury than females (4).

The authors correctly hypothesize that concerned parents who obtained vaccines on time for their children may have been more likely to seek evaluations for delayed development and note the association between thimerosal exposure and increased visits for upper respiratory infections and well-child care in the second year of life. However, parents of children with mild developmental delay might have been more likely to seek evaluations for minor illnesses and well-child visits because of increased concern about their children's well-being.

The authors discount the positive association in HMO B between thimerosal exposure and language delays because no association was found in HMO C. The power to detect outcomes in HMO B was much greater than for HMOs A and C as the HMO B population was 8.3 and 6.6 times larger than HMOs A and C respectively. Also, HMO B had more variability in exposures to thimerosal, based on the information provided to the IOM. Discrepant findings could be due to differences in background exposure to mercury from other sources and coding of outcomes, and do not negate the statistically significant associations found. Some analyses for outcomes of interest were not conducted when there were fewer than 50 outcomes in HMOs A and C. These analyses should have been included with appropriate statistical analysis rather than excluded altogether.

The authors correctly suggest that detailed neurodevelopmental assessments of children who were randomized to receive vaccines with different amounts of thimerosal will provide useful data. However, such studies could have limitations. Few studies of sufficient size will have enough variability in thimerosal exposure to reflect the full range of exposures that have occurred. Also, intensive therapeutic intervention for young children with delayed

speech or language problems can result in significant improvements, and studies in rats suggest that some adverse effects of lead exposure early in life can be partially ameliorated by intensive retraining (5). Therefore, detailed histories of past problems should be included in comparison studies conducted at 5-7 years of age.

Public confidence in vaccines and the National Immunization Program could be enhanced if there was greater independence in vaccine safety assessments from the highly successful program to promote immunizations (6). We believe an independent organization, perhaps the IOM, should convene a panel with expertise in neurodevelopmental delay, effects of methylmercury exposure, and statistical methods to review the data and conduct additional analyses if indicated.

#### References

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## Safety of Thimerosal-Containing Vaccines: Response to Halsey et al

9 January  
2004



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To the editor:

Dr. Halsey and colleagues raise several important questions about

*Prevention, Atlanta, GA,*

Philip H. Rhodes and  
Robert L. Davis

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our study and we appreciate the opportunity to provide additional details. Several factors entered into our decision not to include the general category of "any neurodevelopmental disorder" in the results presented in the article, even though we had included such a category in a presentation of preliminary results to the Institute of Medicine (IOM). In the preliminary analysis, children with diagnoses of speech or language delay constituted a large proportion of the combined "any neurodevelopmental disorder" category. Thus, the combined category results were primarily a reflection of the speech and language delay results. Moreover, the combined category contained several heterogeneous conditions with variable age distributions and we were advised by some reviewers to delete this category.

In terms of the selection criteria, they were not more lax for the published report than for the IOM presentation. Actually, the criteria were more stringent for the published report. After the IOM presentation, we obtained more complete data on exclusionary conditions from HMO A. We also applied the exclusion criteria in a stricter fashion by excluding children who ever received one of the exclusionary codes rather than requiring that the code had to have been received in the first month of life as was done for the IOM presentation.

Contrary to the suggestion by Halsey et al, we did not make assumptions about the thimerosal contents of the vaccines. We used documented information on vaccine type and manufacturer to determine the thimerosal content of specific vaccines. For example, one of the DTaP vaccines did not contain thimerosal and was assigned a value of zero in calculating mercury exposure.

The diagnoses included in the analyses could have been made by any health care provider. We did not restrict to diagnoses made by a specialist. We also did not validate all the diagnoses by reviewing charts. We performed chart review validation for a sub-sample of speech delay, ADD, and autism diagnoses to gauge the validity of these diagnoses. The chart-review findings for these three conditions, however, were not used in the analysis. All the results for all conditions evaluated were based on the ICD-9 codes in the computerized files routinely maintained by the HMOs.

Although we did not present gender-specific results in the article, we have performed such analyses. We found no large or systematic differences in effects by gender.

We agree that parents of children with mild developmental delay might have been more likely to seek evaluations for minor illnesses and well child visits. This is another example of possible health-care seeking differences between different groups of children and reinforces the need to cautiously interpret the results of our study.

We did not mean to discount the positive association at HMO B between thimerosal exposure and language delays because no association was found at HMO C. We do not feel, however, that this

result by itself could be considered sufficient to establish a causal association. We are currently conducting a follow-up study that includes children from these same HMOs to more rigorously evaluate possible neurodevelopmental effects of thimerosal exposure. Children are selected according to different levels of thimerosal exposure and undergo an extensive standardized battery of neuropsychological tests that includes a thorough evaluation of speech and language function. The examiners are not aware of the children's thimerosal exposure level. We believe that the follow-up study will provide more reliable data for drawing causal inferences than the analysis based on limited computerized diagnostic codes.

The limitation to outcomes with 50 or more cases was an a priori decision at the time the protocol was written. The decision was based on preliminary power estimates.

We appreciate the suggestion to obtain detailed developmental and treatment histories. In the follow-up study that we are conducting, we are reviewing participants' medical charts and interviewing their parents regarding developmental and treatment histories for all outcomes that we are assessing. The study is powered to detect meaningful differences within the range of thimerosal exposures experienced by infants vaccinated in the 1990s.

We would welcome any additional review of our study, but we are uncertain about the value of such a review at this time. The study underwent extensive review internally at the Centers for Disease Control and Prevention, by external experts, by an IOM committee, and by peer reviewers for Pediatrics. Several helpful suggestions from throughout the review process were incorporated into the final analysis. Although other reviewers may be able to suggest improvements to the analysis, we do not think that any analysis would be able to fully overcome the inherent limitations of computerized health services data for evaluating causal associations with complex neurodevelopmental conditions. One of the initial reasons for our study was to provide guidance in selecting conditions to be evaluated in a more rigorous follow-up study that we are currently conducting. In the follow-up neuropsychological testing study, we are evaluating several neurodevelopmental outcomes, including any outcomes that showed any positive associations at any stage of our study from preliminary results to the final published manuscript. The follow-up study is scheduled to be completed in 2004. We suspect that it is unlikely that an independent re-analysis of the computerized HMO data could be completed much before when the more definitive results from the follow-up study are expected to be available.

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