

*Conceptual Framework for
Follow-up Study of Thimerosal-
containing Vaccines and
Neurologic Developmental
Disorders (NDDs)*

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Background and History

- FDA Modernization Act of 1997 called for review of use of mercury-containing biologics
- FDA, EPA, WHO, ATSDR reviews raised concerns about organic mercury exposure from Thimerosal in vaccines
- June 1999, PHS and AAP recommended postponing hepatitis B vaccine until 2nd month of life as a precaution
- August 1999, NIH workshop concluded there was no significant public health problem from Thimerosal-containing vaccines, despite theoretical risks; recommended further research
- Late 1999-early 2000, CDC conducted analyses using VSD (NCK & GHC) data [Phase I Study]

Initial Findings of NCK and GHC Analyses (Phase I Study)

Statistically significant associations between:

- cumulative exposure to Thimerosal-containing vaccines at 2 months of age and unspecified developmental delays;
- cumulative exposure at 3 months of age and tics;
- cumulative exposure at 6 months of age and attention deficit/hyperactivity disorder (ADHD);
- cumulative exposure at 1, 3, and 6 months of age and language and speech delay; and
- cumulative exposure at 1, 3, and 6 months of age and neurodevelopmental delays, in general.

Concerns of Simpsonwood Panel Members Regarding Phase I Study

- Possibility of a health care-seeking bias
- Inexactness of the diagnoses of neurodevelopmental outcomes and inconsistency of these diagnoses across clinicians, clinics, and HMOs
- Unclear meaning and significance of the exposure estimates:
 - minimal biologic data for ethylmercury
 - uncertain relevance of extrapolating from studies of methylmercury
 - levels of ethylmercury exposures in VSD cohort appear to be below methylmercury levels that produced no adverse neurobehavioral effects attributable to postnatal exposures among Seychelles and Faroe Islanders
- Lack of data reflecting familial/genetic predispositions to neurobehavioral outcomes
- Limited ability to distinguish excess risks attributable to other vaccine components or other vaccine-related associations

Simpsonwood Panel's Conclusions Regarding Phase I Study Results

- On a scale from 1 (very weak evidence) to 6 (very strong evidence), the panel's mean rating of the evidence for a causal relationship was 1.8 (all but one consultant assigned a rating ≤ 2)
- **CONCLUSION:** "...the VSD screening analyses were insufficient to support a causal relationship between exposure to Thimerosal-containing vaccines and selected NDDs, ...[but] these questions [should] be vigorously pursued along several lines of scientific investigation."

Simpsonwood Panel's Recommendations for Future Studies

- Reanalysis of NCK and GHC data
- Analysis of similar data sets
- Pharmacokinetic studies of ethylmercury in humans
- Toxicological and neurodevelopmental studies of ethylmercury in experimental animals
- Epidemiologic studies to examine Phase I results that obviate/control for potential biases and other inadequacies in Phase I study data

Initial Findings of Harvard Pilgrim Analyses (Phase II Study)

- Conducted in mid-2000 to verify Phase I Study results
- Smaller study cohort, but no statistically significant excess risks of NDDs associated with receipt of Thimerosal-containing vaccines

Purpose of Possible Phase III Follow-up Study(ies)

If Phase III follow-up epidemiologic study(ies) are performed, the purpose would be to examine more closely the risk of the NDDs identified in the Phase I Study results that may be attributable to Thimerosal-containing vaccines.

Development of Conceptual Framework for Phase III Follow-up Study

- Developed draft protocol based on extant literature, initial Phase I and II study results, and advice of CDC/ATSDR experts
- Convened external consultation group
- Revised protocol based on consultants' and public meeting attendees' comments
- Convened advisory panel to recommend battery of neuropsychological tests and confirmatory exams

Phase III Follow-up Study Conceptual Framework

Overall Study Design: Two-part, retrospective cohort study in which participants would be enrolled based on exposure to Thimerosal-containing vaccines at some specified point in the past, then tested with a battery of neuropsychological tests and confirmatory exams at the time of the study.

Phase III Follow-up Study, Proposed Entry Criteria

Exposure Group Definitions: Focus on

exposures occurring at the earliest ages:

- at birth (receipt of hepatitis B vaccine in the first week of life) and
- during the first 3 months of life (cumulative exposure to all Thimerosal-containing vaccines during the first three months of life).

➔ BUT COULD ALSO assess cumulative exposures at later ages, using body weight-/vaccination timing-adjusted measures

Phase III Follow-up Study, Proposed Outcomes

Psychological Domains (based on studies of exposure to methylmercury):

- Verbal ability
- Visual/spatial ability
- Executive functioning and attention
- Short-term memory
- Fine manual motor task
- Achievement

Phase III Follow-up Study, Proposed Outcomes

Primary Diagnostic Outcomes (based on initial Phase I study results):

- ADHD
- Language deficits
- Speech deficits
- Tics

➔ **OF NOTE:** Autism is not included as a diagnostic outcome; consider separate study

Phase III Follow-up, Proposed Outcome Measures

Part 1--Administer standardized set of neuropsychological tests:

- identify children with indications of selected NDDs;
- compare mean differences among exposure groups on neuropsychological test results.

➔ Part 1 tests would be highly *sensitive* for identifying participants with possible NDDs

Phase III Follow-up, Proposed Outcome Measures

Part 2--Evaluate children to confirm diagnosis of selected NDDs:

- administer confirmatory neuropsychological tests and interviews to diagnose “impairment”;
 - compare exposure groups on the prevalence of selected neuropsychological deficits.
- ➔ Part 2 tests would be highly *specific* for confirming true cases of selected NDDs

Phase III Follow-up Study, Proposed Measurement of Other Exposures

- Proxy measures for exposure to organic mercury, lead, polychlorinated biphenyls, and alcohol and other drugs would be obtained from questionnaires and/or chart reviews;
- Measures of vaccine antigens and other vaccine components would be obtained from vaccination histories;
- ➔ **OF NOTE**, other potential neurotoxic exposures would NOT be measured: e.g., cadmium, arsenic, organophosphate pesticides, and vinyl chloride.

Phase III Follow-up Study, Proposed Measurement of Confounders

Measurement of possible confounders (e.g., SES, participant's and family medical history, etc.) would be obtained through systematic abstraction of medical records (where available) and through participants' (and their parents'/caregivers') responses to questionnaires.

Thimerosal Research Agenda, Next Steps

- Prioritize future research
- Finalize study protocol(s)
 - exposure/selection criteria
 - diagnostic outcomes and test measures
 - study site(s)
- Develop detailed budgets and identify funding sources
- Award/amend contract(s)
- Conduct study(ies), analyze data, prepare reports

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THANK YOU.....

PROPOSED PHASE III STUDY
DESIGN DETAILS

Phase III Follow-up Study, Proposed Entry Criteria

Selection of Study Participants:

- Exposure groups will be equal size
- Children 7-9 years old at the time of the study
- Participants in each exposure group randomly chosen from 3 cohorts, stratified by age
 - $<25 \mu\text{g}$ ethyl mercury from cumulative Thimerosal exposure by 3 months of age
 - $\geq 25 \mu\text{g}$, but $< 62.5 \mu\text{g}$ ethyl mercury
 - $\geq 62.5 \mu\text{g}$ ethyl mercury
- Approximately half in each exposure group will have received hepatitis B vaccine at birth

Phase III Follow-up Study, Proposed Entry Criteria

Selection of Study Participants (continued):

Exclusion criteria:

- selected congenital disorders,
- selected severe perinatal disorders,
- receipt of hepatitis B immunoglobulins,
- low birth weight (< 2,500 grams), or
- gestational age less than 38 completed weeks.

Phase III Follow-up Study, Proposed Outcome Measures

Criteria for Neuropsychological Tests:

- Must have reasonable, population-based normative standards for the 7-9 year old age group;
- Must have a clear track-record of use and usefulness by practicing psychologists, developmental specialists, and educators;
- Should assess abilities that have been shown to be susceptible to exposures to organic mercury;
- Total testing time must be tolerable for participants and acceptable to parents (~ 4 hours).

Phase III Follow-up Study, Required Sample Size

Sample Size Estimates:

- 80% power ($\alpha=0.05$)
- Sample size required under differing assumptions:

Prevalence of NDD of interest

<u>No/Low Exp.</u>	<u>Medium Exp.</u>	<u>High Exp.</u>	<u>Group Sample Size</u>
2.5%	3.75%	5.0%	1,113
2.5%	5.0%	6.5%	525
2.5%	5.0%	7.5%	367
2.5%	5.0%	10.0%	182

- N=3,339 (1,113 in each group) to detect doubling in risk between lowest and highest exposure

Phase III Follow-up Study, Proposed Study Setting

Criteria for Study Site(s):

- Sufficient overall sample size and by exposure groups
- Up-to-date locating information available
- High-quality vaccination records available
- Available records of manufacturers and lots for vaccines used
- High-quality medical records available
- Culturally appropriate neuropsychological tests available
- Means of controlling for bias and confounding

➡ Proposed sites: up to 4 VSD-affiliated HMOs