

# Early Thimerosal Exposure and Neuropsychological Outcomes at 7 to 10 Years

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# Background

- Thimerosal
  - Preservative used previously in many childhood in vaccines during the 1990's
  - Metabolized into ethylmercury and thiosalicylate
  - 50% mercury by weight
- Little known about potential harmful effects of low dose ethylmercury exposure from vaccines and immunoglobulins
- More known about prenatal methylmercury exposure from fish consumption



# Background

- Study was designed with significant input from independent, external experts
- The analysis plan was written and approved in 2002 prior to the start of data collection
- Statistical analyses were executed as specified in the analysis plan
- Additional analyses were conducted based on input from independent, external experts



# Methods Overview

- Retrospective cohort study of children from 4 Vaccine Safety Datalink (VSD) sites
- Children who could have received thimerosal-containing vaccines (born 1993-1997)
- Children aged 7 to 10 years at time of the neuropsychological testing
- Stratified by thimerosal exposure during first 7 months of life using automated VSD vaccine records



# Neuropsychological Test Battery

## 42 Different Outcomes

- Speech and Language Measures (9 outcomes)
- Verbal Memory (7 outcomes)
- Attention/Executive Functioning (7 outcomes)
- Behavior Regulation (6 outcomes)
- Fine Motor Coordination (4 outcomes)
- Tics (4 outcomes)
- General Intellectual Functioning (3 outcomes)
- Achievement (1) & Visual Spatial Abilities (1)



# Methods

## Thimerosal Exposure

- Four sources of information on thimerosal exposure from vaccines and immune globulins
  - VSD Automated Data - postnatal vaccine exposures
  - Chart Reviews – prenatal and postnatal exposures
  - Parent Vaccine Records – postnatal exposures
  - Maternal Interview - prenatal exposures
- Discrepancies in vaccine records needed to be resolved across four sources of data



# Methods

## Statistical Analyses

### Primary Model

$$Y = B0 + B1 (\text{Prenatal Thimerosal}) \\ + B2 (\text{Thimerosal 0-7 months}) \\ + B3 (\text{Site Dummy Codes}) \\ + B4 (\text{Child and Family Characteristics}) \\ + B5 (\text{Other Exposures and Confounders}) \\ + e$$



# Methods

## Statistical Analyses

### Expanded Model

$$Y = B0 + B1 \text{ (Prenatal Thimerosal)} \\ + B2 \text{ (Thimerosal 0-28 Days)} \\ + B3 \text{ (Thimerosal 1-7 months)} \\ + B4 \text{ (Site Dummy Codes)} \\ + B5 \text{ (Child and Family Characteristics)} \\ + B6 \text{ (Other Exposures and Confounders)} \\ + e$$





# Methods

## Statistical Analyses

- A total of 378 statistical tests were presented in the manuscript:
  - 42 neuropsychological outcomes
  - 3 exposure periods
    - Prenatal
    - 0-7 months
    - 0-28 days
  - Full model plus gender specific analyses



# Methods

## Sample Tested

- Tested 1,107 children in the clinics
  - 30% response rate
- Final Analysis Sample Size = 1,047
- Power = 90% to detect .10 of a standardized regression coefficient



# Results

- The majority of outcomes have NO association with thimerosal exposure
- Among the 378 statistical tests conducted, the following significant effects were found:
  - 12 better outcomes
  - 7 poorer outcomes
- This represents significant findings for 5.0% of the statistical tests conducted



# Results

## Thimerosal Prenatal Exposure

- Better Outcome
  - NEPSY Speeded Naming Test
- Poorer Outcome
  - WISC III Digit Span Backward Recall



# Results

## Thimerosal Exposure Birth – 7 Months

- Better Outcome
  - Grooved Peg-Board Non-Dominant Hand
  - WISC III Digit Span Backward Recall
- Poorer outcome – no significant effects



# Results

## Thimerosal Exposure Birth – 28 Days

- Better Outcome
  - Finger Tapping Dominant Hand
- Poorer Outcome
  - Goldman-Fristoe Test of Articulation 2 (GFTA-2)



# Results

## Thimerosal Prenatal Exposure

### Sex Effects

- Males
  - Better Outcome
    - Stanford Binet Copying
  - Poorer Outcome
    - WISC III Digit Span Backward Recall
- Females – no significant effects



# Results

## Thimerosal Exposure Birth – 7 Months

### Sex Effects

- Males
  - Better Outcome
    - WJ-III: Letter-Word Identification
  - Poorer Outcome
    - BRIEF Parent Rating of Behavior Regulation
    - Motor and phonic tics as reported by the child assessor
- Females
  - Better Outcome
    - Grooved Peg Board Non-Dominant Hand
    - WISC III Digit Span Backward Recall





# Results

## Thimerosal Exposure Birth – 28 Days

### Sex Effects

- Males
  - Better Outcome
    - Finger Tapping Dominant Hand
    - Finger-Tapping-Non-Dominant-Hand
    - WASI Performance IQ
- Females
  - Better Outcome
    - Motor tics based on the parent rating
  - Poorer Outcome
    - WASI Verbal IQ



# Discussion

- Among 42 outcomes, few significant associations with thimerosal exposure prenatally or during the first 7 months of life were found
- These associations were few, equally divided among better and poorer outcomes, and mostly sex-specific



# Discussion

- Poorer outcomes for boys
  - BRIEF behavior regulation and Tics
  - Tic finding also found in 2 previous vaccine safety studies
    - Verstraeten (2003) VSD Screening Study ~140,000 children
    - Andrews (2004) study in the UK ~ 100,000 children
  - Suggests potential need for further study



# Discussion

- Poorer outcome with Verbal IQ among girls and GFTA-2 among all children suggests a possible association with language development
  - Association with language delay found in one HMO in the Verstraeten VSD screening study
- Better outcome with Performance IQ for boys suggests findings could not be generalized



# Conclusions

- The weight of the evidence in this study does not support a causal association between early ethyl mercury exposure from thimerosal-containing vaccines and immunoglobulins and neuropsychological functioning at ages 7 to 10 years.



# Additional Information

- Public Use Data Set
  - [http://www.cdc.gov/od/science/iso/research\\_activities/thimerosal\\_outcomes.htm](http://www.cdc.gov/od/science/iso/research_activities/thimerosal_outcomes.htm)
- Reference
  - N Engl J Med 2007;357:1281-92.



# Collaborative Effort

- Cristofer Price
- Barbara Goodson
- David Shay
- Patti Benson
- Virginia Hinrichsen
- Edwin Lewis
- Eileen Eriksen
- John Dunn
- Lisa A. Jackson
- Tracy Lieu
- Paula Ray
- Steve Black
- Michael Marcy
- Gerrie Stewart
- Eric S. Weintraub
- Robert Davis
- Frank Destefano



# Methods - Exclusions

- Birth weight < 2500 grams
- ICD-9 coded conditions recorded in the first year of life that were likely to affect neuropsychological test performance
  - included encephalitis, meningitis, or hydrocephalus
- Lived further than 50 miles from test site
- Lived with mother < 4 days per week
- Lived with non-biological mother





# Neuropsychological Test Battery

## 42 Different Outcomes

- Autism was not assessed in this study.
- A separate case-control study is in progress that will assess the potential relationship between thimerosal exposure and autism



# Methods

## Statistical Analyses

- Ordinary least squares regression for continuous outcomes – majority of the outcomes
- Logistic regression for dichotomous outcomes
  - Stuttering
  - Tics



# Methods

## Statistical Analyses

- A priori confounders
  - HMO
  - Child age
  - Child sex
  - Child birth weight
  - Maternal IQ
  - Maternal education
  - Single parent
  - Percent of poverty line
  - HOME total index



# Methods

## Statistical Analyses

- Other confounders entered analyses if:
  - P-value < .20 or
  - Change in estimate greater than 10%
- Examples of other confounders
  - Maternal age
  - English spoken in the home
  - Siblings (older, younger)
  - Day care experience
  - Duration of breast feeding



# Methods

## Statistical Analyses

- Interactions defined a priori in protocol
  - Thimerosal Exposure by Sex Interactions
  - Thimerosal Exposure by Antibiotic Use Interactions
- Interactions proposed after 1st round of statistical analyses
  - Joint test of prenatal and postnatal effect
  - Prenatal by postnatal interactions



# Ethylmercury Distribution for Sample

Ethylmercury	Freq	Percent
0 – 37.5 ug	33	3%
50 – 87.5 ug	233	22%
100 – 137.5 ug	518	49%
150 – 175 ug	201	19%
187.5 ug	62	6%
Total	1,047	100%

