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

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## ABSTRACT

### BACKGROUND

It has been hypothesized that early exposure to thimerosal, a mercury-containing preservative used in vaccines and immune globulin preparations, is associated with neuropsychological deficits in children.

### METHODS

We enrolled 1047 children between the ages of 7 and 10 years and administered standardized tests assessing 42 neuropsychological outcomes. (We did not assess autism-spectrum disorders.) Exposure to mercury from thimerosal was determined from computerized immunization records, medical records, personal immunization records, and parent interviews. Information on potential confounding factors was obtained from the interviews and medical charts. We assessed the association between current neuropsychological performance and exposure to mercury during the prenatal period, the neonatal period (birth to 28 days), and the first 7 months of life.

### RESULTS

Among the 42 neuropsychological outcomes, we detected only a few significant associations with exposure to mercury from thimerosal. The detected associations were small and almost equally divided between positive and negative effects. Higher prenatal mercury exposure was associated with better performance on one measure of language and poorer performance on one measure of attention and executive functioning. Increasing levels of mercury exposure from birth to 7 months were associated with better performance on one measure of fine motor coordination and on one measure of attention and executive functioning. Increasing mercury exposure from birth to 28 days was associated with poorer performance on one measure of speech articulation and better performance on one measure of fine motor coordination.

### CONCLUSIONS

Our study does not support a causal association between early exposure to mercury from thimerosal-containing vaccines and immune globulins and deficits in neuropsychological functioning at the age of 7 to 10 years.

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Thimerosal has been used as a preservative in vaccines since the 1930s. It is 49.6% mercury by weight and is metabolized into ethyl mercury and thiosalicylate.[1] In 1999, the Food and Drug Administration (FDA) estimated that infants who were immunized according to the recommended schedule could receive amounts of mercury exceeding the limits set by the Environmental Protection Agency for exposure to methyl mercury.[2] As a precautionary measure, the Public Health Service and the American Academy of Pediatrics urged vaccine manufacturers to remove thimerosal from all infant vaccines as soon as was practical and recommended that studies be carried out to understand better the risks associated with mercury exposure from thimerosal-containing vaccines.[3] In response, the Centers for Disease Control and Prevention (CDC) performed an analysis using computerized databases from three large health maintenance organizations (HMOs).[4] Increasing exposure to mercury was associated with a greater likelihood of tics in one HMO population and language delay in another; in the third HMO, no significant associations were found.

Our study was designed to assess more rigorously the relationship between mercury exposure from thimerosal and neuropsychological functioning in a manner similar to that of previous studies of prenatal exposure to methyl mercury.[5,6] Our study improved on previous thimerosal studies by enrolling children on the basis of thimerosal exposure, independent of health status; prospectively assessing neuropsychological functioning independently of exposure and health care–seeking behavior; and collecting extensive information on potential confounders, including medical history and socioeconomic and educational factors that could influence a child's health and development.

## METHODS

### STUDY DESIGN

We performed a cohort study with extensive assessments of relevant exposures and neuropsychological functioning. The institutional review boards of all participating organizations approved the study. A panel of independent external consultants in the fields of toxicology, epidemiology, biostatistics, and vaccine safety approved the study protocol and planned analyses. Further details regarding the study design, analyses, and results can be found in two technical reports.[7,8]

### STUDY POPULATION

We enrolled children from four HMOs that participate in the CDC's Vaccine Safety Datalink.[9,10] Children from each HMO were eligible to participate if they were 7 to 10 years of age and had been enrolled in the HMO from birth through their first birthday. Birth dates ranged from January 1, 1993, to March 30, 1997; testing was conducted between June 1, 2003, and April 27, 2004. All parents provided written informed consent for their children to participate in the study. Children were excluded if they had certain conditions recorded in their medical records that could bias neuropsychological testing (e.g., encephalitis, meningitis, or hydrocephalus) or if their birth weight was less than 2500 g (Table A of the Supplementary Appendix, available with the full text of this article at www.nejm.org).

Thimerosal exposure in the first 7 months of life was estimated for the entire eligible population from HMO computerized records, and a sample was selected with the use of these data to include adequate numbers of children across a range of ages and estimated exposures.

### EXPOSURE TO MERCURY

We determined the mercury content of vaccines and immune globulins that the study children received when they were infants (1993–1998) from published data[11-13] and the FDA (Table B of the Supplementary Appendix). We identified vaccines and immune globulins that children had received from HMO computerized immunization records, paper medical records, personal immunization records, and maternal interviews. Prenatal exposure to mercury included all known exposures of the mother to thimerosal-containing vaccines and immune globulins during pregnancy. We defined postnatal exposure as micrograms of mercury divided by the weight of the child in kilograms at the time of administration of each vaccine or immune globulin. Individual exposures were summed during the period of interest: birth to 1 month and birth to 7 months (1 to 214 days). We did not assess periods of thimerosal exposure after 214 days of age because we hypothesized that the potential effect of such exposure would be small. (Since most vaccines that are administered after 214

days would typically be given at 12 to 18 months of age, the dose per kilogram would be substantially lower.)

### NEUROPSYCHOLOGICAL ASSESSMENT

Each child was assessed on 42 neuropsychological outcomes selected on the basis of findings from the CDC's screening study,[4] previous studies of methyl mercury,[5] and the recommendations of an external panel of independent consultants. Most of the measures were collected during a 3-hour neuropsychological assessment performed by trained evaluators. The outcome measures included speech and language indexes, verbal memory, achievement, fine motor coordination, visuospatial ability, attention and executive-functioning tasks, behavior regulation, tics, and general intellectual functioning (Table C of the Supplementary Appendix). Measures of attention, hyperactivity, and executive functioning were based on reports from parents and teachers. We evaluated motor tics, phonic tics, and stuttering on the basis of a combination of ratings by evaluators and reports by parents and teachers (Table D of the Supplementary Appendix). Personnel who were administering the neuropsychological battery were not aware of the children's exposure to mercury or medical history. Mothers were asked to refrain from giving children selected prescription medicines for attention deficit–hyperactivity disorder (ADHD) the day before testing. Since the CDC is conducting a separate case–control study of autism in relation to mercury exposure, a measure of autism was not included in the test battery.

### MATERNAL INTERVIEW AND MATERNAL IQ TEST

Mothers of all children were biologic mothers. During the maternal interview, a standardized questionnaire was administered, covering receipt of immune globulins (e.g., Rh immune globulin), influenza vaccine, and other vaccines during pregnancy; prenatal and postnatal exposures to potential environmental toxins, including mercury in the diet or from dental fillings; the Home Observation for Measurement of the Environment (HOME) inventory[14,15]; socioeconomic indicators; pregnancy and birth history; children's experience in infancy and early childhood; and children's experience with computers. The Kaufman Brief Intelligence Test was also administered to the mothers.

### MEDICAL-RECORD ABSTRACTION

Trained abstractors reviewed the medical records of mothers and children for maternal receipt of immune globulins and vaccines during pregnancy and children's prenatal and birth histories, including the receipt of immune globulins, the vaccination history until the age of 5 years, antibiotic use during the first 7 months, anemia or pica, and neurodevelopmental disabilities. Computerized pharmacy records were reviewed for the history of dispensing of ADHD medications (Table E of the Supplementary Appendix) and antibiotics.

### STATISTICAL ANALYSIS

We examined two primary exposure periods: the prenatal period and the period from birth to 7 months (1 to 214 days). We also evaluated exposures to mercury from hepatitis B vaccines and immune globulins in the first 28 days of life. Separate effects for boys and girls were estimated from models that included sex-by-exposure interaction terms. Furthermore, we tested two a priori interactions between prenatal and postnatal mercury exposures and between postnatal mercury exposure and antibiotic use.

We used ordinary least-squares regression and logistic regression to estimate measures of association. The effect size for least-squares regression used standardized regression coefficients,[16-18] which represents the change in the outcome, expressed in standard-deviation units (SD), given a change of 1 SD in the exposure variable. We measured tics and stuttering dichotomously, and we estimated odds ratios for a 2-SD increase in mercury exposure. All tests were two-tailed; statistical significance was set at $P<0.05$ without correction for the number of statistical tests performed. The study was designed to have a power of 90% to detect a standardized regression coefficient of 0.10.

We analyzed raw test scores adjusted for a priori confounders, including linear terms for age, family income, and score on the HOME scale[14,15] and dummy-coded variables for sex, HMO, maternal IQ, maternal education, single-parent status, and birth weight. Other covariates were included in the full model if the P value was less than 0.20 or if their inclusion resulted in a change of 10% or more in the estimate of the main effect of mercury exposure[19,20] (Table F of the Supplementary Appendix).

## RESULTS

### CHARACTERISTICS OF THE CHILDREN

Of 3648 children selected for recruitment, 1107 (30.3%) were tested. Among children who were not tested, 512 did not meet one or more of the eligibility criteria, 1026 could not be located, and 44 had scheduling difficulties; in addition, the mothers of 959 children declined to participate. Most of the mothers (68%) who declined to participate in the study and provided reasons for nonparticipation cited a lack of time; 13% reported distrust of or ambivalence toward research. Of the 1107 children who were tested, 60 were excluded from the final analysis for the following reasons: missing vaccination records, 1 child; missing prenatal records, 5; missing data regarding weight, 7; and discovery of an exclusionary medical condition during record abstraction, 47. Thus, 1047 children were included in the final analyses. The exposure distribution of the final sample was similar to the exposure distribution of the initial 3648 children selected for recruitment in the study.

The median cumulative exposure to mercury from thimerosal from birth to 7 months was 112.5 μg (range, 0 to 187.5); 8.9% of the children had cumulative exposures of 62.5 μg or less of mercury, and 25.1% had cumulative exposures of 150 μg or more (Table 1). Sixteen children (1.5%) had no documented exposure to any thimerosal-containing vaccine or immune globulin during their first 7 months of life. In the first 28 days of life, 30% of children had no thimerosal exposure, and 1.6% received more than 12.5 μg of mercury from hepatitis B vaccine and immune globulins.

Less than 11% of children were exposed to thimerosal prenatally through maternal vaccination or receipt of immune globulins. The sources of exposure included the following: influenza vaccine, 9 children; tetanus toxoid, 3; diphtheria and tetanus toxoid, 8; hepatitis B vaccine, 1; and thimerosal-containing Rh immune globulins, 103.

Children who had been exposed to higher levels of thimerosal were more likely to have mothers with higher IQ scores and levels of education and to be from two-parent households where English was the primary language spoken.

**Table 1. Cumulative Exposure to Ethyl Mercury, According to Age Range.**

| Quantity of Ethyl Mercury* | Birth to 1 Month | Birth to 7 Months |
|---|---|---|
| μg | *no. of subjects* | |
| 0.0 | 312 | 16 |
| 12.5 | 718 | 3 |
| 25.0 | 10 | 2 |
| 37.5 | 7 | 12 |
| 50.0 | | 37 |
| 62.5 | | 23 |
| 75.0 | | 146 |
| 87.5 | | 27 |
| 100.0 | | 116 |
| 112.5 | | 164 |
| 125.0 | | 115 |
| 137.5 | | 123 |
| 150.0 | | 52 |
| 162.5 | | 19 |
| 175.0 | | 130 |
| 187.5 | | 62 |
| Total | 1047 | 1047 |

* Documented sources of exposure to mercury were vaccines and immune globulins containing thimerosal.

### NEUROPSYCHOLOGICAL PERFORMANCE

Among the 42 neuropsychological outcomes that we assessed, we found few significant associations between performance on a neuropsychological test and exposure to mercury from vaccines and immune globulins administered prenatally or during the first 7 months of life. Significant findings are discussed below.

#### *Prenatal Exposure*

Increasing prenatal exposure to mercury was associated with significantly better performance on the Developmental Neuropsychological Assessment (NEPSY) speeded naming test and poorer performance on the digit-span test of backward recall on the Wechsler Intelligence Scale for Children, third edition (WISC-III) (Table 2). Among boys, higher prenatal exposure to mercury was associated with significantly better performance on the Stanford–Binet copying test and poorer performance on the WISC-III digit-span test of backward recall. Among girls, there were no significant associations.

#### *Exposure from Birth to 7 Months*

Increasing mercury exposure from birth to 7 months was associated with significantly better perfor-

mance on the Grooved Pegboard Test of the nondominant hand and the WISC-III digit-span test (Table 3). Among boys, higher exposure to mercury from birth to 7 months was associated with significantly better performance on letter and word identification on the Woodcock–Johnson test, third edition (WJ-III), poorer performance on the parental rating of behavioral regulation on the Behavior Rating Inventory of Executive Function, and a higher likelihood of motor and phonic tics, as reported by the children's evaluators. Among girls, higher exposure to mercury from birth to 7 months was associated with significantly better performance on the Grooved Pegboard Test of the nondominant hand and the WISC-III digit-span test of backward recall.

*Exposure from Birth to 28 Days*

Higher mercury exposure during the first 28 days of life was associated with significantly poorer performance on the Goldman–Fristoe Test of Articulation, second edition (GFTA-2), and better performance on the Finger Tapping Dominant Hand test (Table 3). Among boys, higher neonatal mercury exposure was associated with significantly better performance on the Finger Tapping Dominant Hand test, the Finger Tapping Non-dominant Hand test, and performance IQ on the Wechsler Abbreviated Scale of Intelligence (WASI). Among girls, increased neonatal mercury exposure was associated with significantly lower scores in verbal IQ on the WASI and a lower likelihood of motor tics on the basis of ratings by parents.

Tests of the interactions of mercury exposure with antibiotic use in the first 7 months of life did not show any consistent pattern of results. The tests of an interaction between prenatal and postnatal mercury exposure revealed no important differences from the above-mentioned main results.

## DISCUSSION

We assessed children on 42 neuropsychological outcomes and found few significant associations with exposure to mercury from vaccines and immune globulins administered prenatally or during the first 7 months of life. The associations that we detected were small, almost equally divided between positive and negative effects, and mostly sex-specific.

We found no consistent pattern between increasing mercury exposure from birth to 7 months and performance on neuropsychological tests. Among girls, the only significant findings were two associations with better test performance. Among boys, there was a beneficial association between mercury exposure and identification of letters and words on the WJ-III and a detrimental association with behavioral regulation and motor and phonic tics according to the ratings of evaluators. An association with tics was also found in one HMO in the screening analysis of the CDC's Vaccine Safety Datalink[4] and an analysis of the General Practice Research Database.[21] The replication of the findings regarding tics suggests the potential need for further studies.

Increasing exposure to mercury during the neonatal period (birth to 28 days) was related to significantly poorer performance on the GFTA-2 measure of speech articulation, one of nine tests that measured speech and language performance. An increase of 2 SD in mercury exposure resulted in an average increase of 0.29 articulation error. Among children overall, we found no association between neonatal exposure to mercury from thimerosal and total IQ. Among boys, there was a significant positive association with performance IQ, and among girls there was a significant negative association with verbal IQ. An increase of 2 SD in mercury exposure was associated with an average of a 3-point increase in performance IQ among boys and a 3-point decrease in verbal IQ among girls.

Although the effect sizes were very small, the speech-articulation findings among all children and the lower verbal IQ findings among girls suggest a possible adverse association between neonatal exposure to mercury and language development. In the previous Vaccine Safety Datalink analysis, an increased risk of language delays at one HMO was associated with postneonatal exposure to thimerosal-containing vaccines.[4] Conversely, the finding of higher scores on the performance IQ tests in boys makes it difficult to draw general conclusions about possible effects of neonatal mercury exposure from vaccines and immune globulins on intellectual abilities.

Previous studies have reported negative effects of thimerosal exposure on neuronal cells, biochemical pathways, and animal behavior.[22-31] One study showed persistently low levels of inorganic mercury in the brains of monkeys exposed to ethyl mercury, but the implication of these findings for humans is not known.[24] In contrast to some laboratory studies and studies in animals,

**Table 2. Association between Prenatal Thimerosal Exposure and Neuropsychological Outcomes.***

| Evaluation Category and Instrument | Estimate (95% CI) | | |
|---|---|---|---|
| | Full Model | Boys | Girls |
| **Speech and language** | | | |
| Boston Naming Test | 0.03 (–0.01 to 0.08) | 0.04 (–0.02 to 0.09) | 0.03 (–0.04 to 0.10) |
| NEPSY | | | |
| Speeded naming | 0.06 (0.00 to 0.11)† | 0.07 (0.00 to 0.13) | 0.05 (–0.04 to 0.14) |
| Comprehension of instructions | –0.01 (–0.06 to 0.05) | –0.01 (–0.08 to 0.06) | 0.01 (–0.08 to 0.10) |
| Clinical Evaluation of Language Fundamentals | | | |
| Formulated sentences | 0.03 (–0.03 to 0.08) | 0.02 (–0.04 to 0.09) | 0.03 (–0.05 to 0.12) |
| Recalling sentences | 0.03 (–0.02 to 0.08) | 0.03 (–0.03 to 0.10) | 0.03 (–0.05 to 0.12) |
| Goldman–Fristoe Test of Articulation 2 (lower = better) | –0.01 (–0.07 to 0.05) | 0.00 (–0.07 to 0.07) | –0.02 (–0.12 to 0.08) |
| Stuttering (lower = better)‡ | | | |
| Rating by evaluator | 0.96 (0.48 to 1.93) | 0.00 (0.00 to ∞)§ | 1.85 (0.85 to 4.00) |
| Rating by parent | 0.67 (0.14 to 3.24) | 0.92 (0.23 to 3.73) | 0.00 (0.00 to ∞)§ |
| Rating by teacher | 0.50 (0.19 to 1.31) | 0.52 (0.16 to 1.71) | 0.47 (0.10 to 2.29) |
| **Verbal memory** | | | |
| California Verbal Learning Test for Children | | | |
| Free recall | | | |
| No delay | 0.02 (–0.03 to 0.08) | 0.02 (–0.05 to 0.09) | 0.03 (–0.06 to 0.12) |
| Short delay | 0.00 (–0.06 to 0.05) | 0.00 (–0.07 to 0.07) | 0.00 (–0.10 to 0.09) |
| Long delay | 0.00 (–0.05 to 0.06) | 0.02 (–0.05 to 0.09) | –0.03 (–0.12 to 0.06) |
| Cued recall | | | |
| Short delay | 0.00 (–0.06 to 0.05) | 0.01 (–0.06 to 0.08) | –0.03 (–0.12 to 0.06) |
| Long delay | 0.02 (–0.04 to 0.07) | 0.04 (–0.03 to 0.11) | –0.03 (–0.12 to 0.06) |
| Children's Memory Scale | | | |
| Immediate recall | 0.01 (–0.03 to 0.06) | 0.03 (–0.03 to 0.08) | –0.01 (–0.08 to 0.06) |
| Delayed recall | –0.01 (–0.05 to 0.04) | 0.01 (–0.04 to 0.07) | –0.03 (–0.11 to 0.04) |
| **Achievement** | | | |
| Woodcock–Johnson III (letter and word identification) | 0.01 (–0.04 to 0.06) | 0.03 (–0.03 to 0.08) | –0.02 (–0.10 to 0.05) |
| **Fine motor coordination** | | | |
| Grooved pegboard (lower = better) | | | |
| Dominant hand | –0.03 (–0.07 to 0.01) | –0.04 (–0.09 to 0.00) | –0.01 (–0.08 to 0.05) |
| Nondominant hand | –0.02 (–0.06 to 0.02) | –0.03 (–0.08 to 0.02) | –0.01 (–0.07 to 0.06) |
| Finger tapping | | | |
| Dominant hand | –0.02 (–0.07 to 0.03) | –0.03 (–0.10 to 0.04) | 0.00 (–0.08 to 0.09) |
| Nondominant hand | –0.02 (–0.07 to 0.03) | –0.05 (–0.12 to 0.01) | 0.03 (–0.05 to 0.12) |
| **Visuospatial ability** | | | |
| Stanford–Binet copying test | 0.01 (–0.04 to 0.07) | 0.08 (0.01 to 0.15)† | –0.09 (–0.19 to 0.00) |
| **Attention and executive function** | | | |
| Gordon Diagnostic System (vigilance task) | | | |
| Correct responses | –0.02 (–0.08 to 0.04) | –0.02 (–0.09 to 0.05) | –0.02 (–0.12 to 0.07) |
| Errors (lower = better) | 0.02 (–0.04 to 0.08) | 0.02 (–0.06 to 0.09) | 0.03 (–0.07 to 0.12) |

**Table 2. (Continued.)**

| Evaluation Category and Instrument | Estimate (95% CI) | | |
|---|---|---|---|
| | Full Model | Boys | Girls |
| Wechsler Intelligence Scale for Children (digit span) | | | |
| Forward recall | 0.00 (–0.06 to 0.06) | 0.05 (–0.03 to 0.12) | –0.08 (–0.17 to 0.02) |
| Backward recall | –0.07 (–0.12 to –0.01)¶ | –0.09 (–0.16 to –0.02)¶ | –0.02 (–0.12 to 0.07) |
| Combined | –0.03 (–0.09 to 0.02) | –0.02 (–0.09 to 0.05) | –0.06 (–0.15 to 0.03) |
| Behavior Rating Inventory of Executive Function (metacognition index) (lower = better) | | | |
| Rating by parent | 0.01 (–0.05 to 0.07) | 0.06 (–0.02 to 0.13) | –0.07 (–0.17 to 0.02) |
| Rating by teacher | 0.01 (–0.05 to 0.07) | 0.02 (–0.06 to 0.11) | –0.02 (–0.12 to 0.09) |
| **Behavior regulation (lower = better)** | | | |
| Connors' Rating Scales (revised) | | | |
| Hyperactive or impulsive | | | |
| Rating by parent | 0.01 (–0.05 to 0.07) | 0.03 (–0.04 to 0.11) | –0.03 (–0.13 to 0.07) |
| Rating by teacher | 0.03 (–0.03 to 0.10) | 0.04 (–0.04 to 0.12) | 0.02 (–0.09 to 0.12) |
| Inattentive | | | |
| Rating by parent | 0.02 (–0.04 to 0.07) | 0.06 (–0.01 to 0.14) | –0.07 (–0.16 to 0.03) |
| Rating by teacher | 0.00 (–0.06 to 0.07) | 0.00 (–0.08 to 0.08) | 0.00 (–0.10 to 0.11) |
| Behavior Rating Inventory of Executive Function (behavioral regulation index) | | | |
| Rating by parent | –0.02 (–0.08 to 0.04) | 0.00 (–0.08 to 0.07) | –0.05 (–0.14 to 0.05) |
| Rating by teacher | 0.02 (–0.04 to 0.09) | 0.03 (–0.05 to 0.11) | 0.01 (–0.10 to 0.11) |
| **Tics (lower = better)‡‖** | | | |
| Rating by evaluator | | | |
| Motor tics | 1.34 (0.94 to 1.89) | 1.21 (0.80 to 1.84) | 1.73 (0.89 to 3.36) |
| Phonic tics | 0.84 (0.46 to 1.51) | 0.89 (0.48 to 1.65) | 0.62 (0.14 to 2.75) |
| Rating by parent | | | |
| Motor tics | 1.04 (0.70 to 1.55) | 1.14 (0.76 to 1.70) | 0.42 (0.07 to 2.43) |
| Phonic tics | 0.80 (0.47 to 1.36) | 0.97 (0.58 to 1.64) | 0.32 (0.06 to 1.71) |
| **General intellectual functioning** | | | |
| Wechsler Abbreviated Scale of Intelligence | | | |
| Verbal IQ | 0.03 (–0.02 to 0.08) | 0.03 (–0.03 to 0.10) | 0.02 (–0.06 to 0.11) |
| Performance IQ | 0.00 (–0.06 to 0.05) | 0.00 (–0.07 to 0.07) | –0.02 (–0.12 to 0.08) |
| Full-scale IQ | 0.01 (–0.04 to 0.07) | 0.02 (–0.04 to 0.09) | 0.00 (–0.09 to 0.09) |

* Unless otherwise noted, all estimates are given as standardized coefficients, which represent the change in the outcome, expressed in standard-deviation units, given a change of 1 SD in exposure to thimerosal. Higher scores on scales indicate better outcomes, except where indicated. Independent variables in the full model were as follows: measures of cumulative exposure prenatally, from birth to 1 month, and from 1 to 7 months; age; sex; HMO; maternal IQ; family income (expressed as a percentage of the poverty line); maternal education level; single-parent status; score on the Home Observation for Measurement of the Environment scale; and other covariates if they met criteria for inclusion in the full model. Effects of sex were estimated from a full model with sex-by-exposure interaction terms. Postnatal exposure was defined as micrograms of mercury divided by the weight of the child in kilograms at the time of the administration of each vaccine or immune globulin. Individual exposures were summed over the 7-month period.

† P<0.05 for the association between a higher exposure to mercury and a better outcome.

‡ Estimates in this category are given as odds ratios. We estimated odds ratios for a 2-SD increase in mercury exposure. A lower odds ratio is associated with a better outcome.

§ None of the subjects in this category had prenatal exposure to mercury.

¶ P<0.05 for the association between a higher exposure to mercury and a worse outcome.

‖ Evaluators observed tics during the outcomes assessment, and parents reported tics within 7 days before the assessment.

**Table 3. Association between Thimerosal Exposure and Neuropsychological Outcome, According to Age Range.***

| Evaluation Category and Instrument | Estimate (95% Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|
| | Birth to 7 Months | | | Birth to 1 Month | | |
| | Full Model | Boys | Girls | Full Model | Boys | Girls |
| **Speech and language** | | | | | | |
| Boston Naming Test | 0.05 (–0.01 to 0.10) | 0.04 (–0.03 to 0.11) | 0.05 (–0.02 to 0.12) | –0.01 (–0.06 to 0.04) | 0.01 (–0.05 to 0.08) | –0.04 (–0.10 to 0.03) |
| NEPSY | | | | | | |
| Speeded naming | 0.01 (–0.06 to 0.08) | –0.01 (–0.09 to 0.08) | 0.02 (–0.06 to 0.11) | –0.01 (–0.07 to 0.04) | –0.02 (–0.10 to 0.06) | –0.01 (–0.09 to 0.08) |
| Comprehension of instructions | –0.03 (–0.10 to 0.03) | –0.05 (–0.14 to 0.04) | –0.02 (–0.11 to 0.07) | –0.02 (–0.08 to 0.04) | 0.04 (–0.05 to 0.12) | –0.08 (–0.16 to 0.01) |
| Clinical Evaluation of Language Fundamentals | | | | | | |
| Formulated sentences | –0.04 (–0.10 to 0.02) | –0.03 (–0.11 to 0.05) | –0.05 (–0.13 to 0.03) | –0.02 (–0.08 to 0.03) | 0.00 (–0.08 to 0.07) | –0.04 (–0.12 to 0.04) |
| Recalling sentences | 0.00 (–0.06 to 0.06) | –0.01 (–0.09 to 0.07) | 0.01 (–0.07 to 0.08) | –0.01 (–0.06 to 0.04) | 0.00 (–0.07 to 0.08) | –0.02 (–0.10 to 0.05) |
| Goldman–Fristoe Test of Articulation 2 (lower = better)† | 0.04 (–0.03 to 0.11) | 0.05 (–0.04 to 0.15) | 0.03 (–0.06 to 0.12) | 0.08 (0.01 to 0.14)† | 0.08 (–0.01 to 0.17) | 0.07 (–0.01 to 0.16) |
| Stuttering (lower = better)‡ | | | | | | |
| Rating by evaluator | 1.44 (0.58 to 3.62) | 1.42 (0.46 to 4.35) | 1.44 (0.41 to 5.08) | 1.23 (0.57 to 2.65) | 1.34 (0.51 to 3.52) | 1.00 (0.31 to 3.18) |
| Rating by parent | 1.33 (0.40 to 4.40) | 1.13 (0.26 to 4.82) | 1.73 (0.31 to 9.73) | 0.64 (0.25 to 1.62) | 0.68 (0.21 to 2.27) | 0.58 (0.14 to 2.50) |
| Rating by teacher | 1.16 (0.58 to 2.35) | 1.21 (0.53 to 2.78) | 1.07 (0.37 to 3.14) | 1.12 (0.64 to 1.95) | 1.44 (0.74 to 2.80) | 0.70 (0.28 to 1.75) |
| **Verbal memory** | | | | | | |
| California Verbal Learning Test for Children | | | | | | |
| Free recall | | | | | | |
| No delay | 0.00 (–0.07 to 0.07) | 0.00 (–0.08 to 0.09) | 0.00 (–0.09 to 0.08) | 0.00 (–0.06 to 0.06) | 0.04 (–0.04 to 0.13) | –0.04 (–0.12 to 0.04) |
| Short delay | –0.06 (–0.13 to 0.00) | –0.05 (–0.14 to 0.03) | –0.07 (–0.16 to 0.02) | –0.01 (–0.07 to 0.05) | 0.02 (–0.06 to 0.10) | –0.05 (–0.13 to 0.03) |
| Long delay | –0.05 (–0.12 to 0.01) | –0.06 (–0.15 to 0.02) | –0.04 (–0.13 to 0.04) | –0.02 (–0.08 to 0.04) | 0.02 (–0.06 to 0.10) | –0.05 (–0.14 to 0.03) |
| Cued recall | | | | | | |
| Short delay | –0.02 (–0.08 to 0.05) | 0.00 (–0.09 to 0.08) | –0.03 (–0.12 to 0.06) | 0.02 (–0.04 to 0.08) | 0.07 (–0.01 to 0.16) | –0.03 (–0.12 to 0.05) |
| Long delay | 0.00 (–0.06 to 0.07) | 0.01 (–0.08 to 0.10) | –0.01 (–0.09 to 0.08) | 0.01 (–0.05 to 0.07) | 0.07 (–0.02 to 0.15) | –0.05 (–0.14 to 0.03) |
| Children's Memory Scale | | | | | | |
| Immediate recall | –0.01 (–0.07 to 0.04) | –0.04 (–0.11 to 0.03) | 0.01 (–0.06 to 0.08) | –0.01 (–0.06 to 0.04) | 0.00 (–0.07 to 0.06) | –0.01 (–0.08 to 0.05) |
| Delayed recall | 0.00 (–0.05 to 0.06) | –0.01 (–0.08 to 0.06) | 0.02 (–0.05 to 0.09) | –0.01 (–0.06 to 0.04) | 0.01 (–0.06 to 0.08) | –0.03 (–0.09 to 0.04) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Achievement** | | | | | | |
| Woodcock–Johnson III (letter and word identification) | 0.05 (−0.01 to 0.10) | 0.09 (0.01 to 0.16)§ | 0.01 (−0.07 to 0.08) | −0.02 (−0.07 to 0.03) | 0.00 (−0.06 to 0.07) | −0.04 (−0.11 to 0.03) |
| **Fine motor coordination** | | | | | | |
| Grooved pegboard (lower = better) | | | | | | |
| Dominant hand | −0.02 (−0.07 to 0.02) | −0.03 (−0.09 to 0.03) | −0.01 (−0.07 to 0.05) | −0.02 (−0.06 to 0.02) | −0.03 (−0.09 to 0.03) | −0.01 (−0.07 to 0.05) |
| Nondominant hand | −0.06 (−0.11 to −0.01)§ | −0.05 (−0.11 to 0.02) | −0.08 (−0.14 to −0.01)§ | −0.01 (−0.06 to 0.03) | −0.01 (−0.07 to 0.05) | −0.02 (−0.08 to 0.04) |
| Finger tapping | | | | | | |
| Dominant hand | 0.04 (−0.03 to 0.10) | 0.06 (−0.02 to 0.15) | 0.01 (−0.08 to 0.09) | 0.06 (0.01 to 0.12)§ | 0.12 (0.04 to 0.19)¶ | 0.01 (−0.07 to 0.09) |
| Nondominant hand | 0.02 (−0.04 to 0.08) | 0.05 (−0.03 to 0.13) | −0.01 (−0.09 to 0.08) | 0.01 (−0.04 to 0.07) | 0.08 (0 to 0.16)§ | −0.06 (−0.14 to 0.02) |
| **Visuospatial ability** | | | | | | |
| Stanford–Binet copying test | 0.02 (−0.06 to 0.09) | −0.04 (−0.13 to 0.06) | 0.07 (−0.03 to 0.16) | −0.01 (−0.08 to 0.05) | 0.00 (−0.09 to 0.08) | −0.02 (−0.11 to 0.07) |
| **Attention and executive function** | | | | | | |
| Gordon Diagnostic System (vigilance task) | | | | | | |
| Correct responses | 0.04 (−0.03 to 0.11) | 0.04 (−0.05 to 0.13) | 0.05 (−0.04 to 0.14) | 0.00 (−0.07 to 0.06) | 0.03 (−0.05 to 0.12) | −0.04 (−0.13 to 0.05) |
| Errors (lower = better) | −0.01 (−0.08 to 0.06) | 0.04 (−0.06 to 0.13) | −0.06 (−0.15 to 0.03) | 0.00 (−0.06 to 0.06) | 0.00 (−0.09 to 0.08) | 0.00 (−0.09 to 0.09) |
| Wechsler Intelligence Scale for Children (digit span) | | | | | | |
| Forward recall | −0.01 (−0.08 to 0.06) | 0.00 (−0.10 to 0.09) | −0.01 (−0.11 to 0.08) | −0.02 (−0.08 to 0.05) | −0.04 (−0.12 to 0.05) | 0.00 (−0.08 to 0.09) |
| Backward recall | 0.08 (0.01 to 0.15)§ | 0.05 (−0.04 to 0.14) | 0.11 (0.02 to 0.20)§ | 0.04 (−0.02 to 0.11) | 0.06 (−0.02 to 0.15) | 0.02 (−0.07 to 0.11) |
| Combined | 0.04 (−0.03 to 0.11) | 0.03 (−0.06 to 0.12) | 0.05 (−0.04 to 0.14) | 0.01 (−0.05 to 0.07) | 0.01 (−0.08 to 0.09) | 0.01 (−0.07 to 0.10) |
| Behavior Rating Inventory of Executive Function (metacognition index) (lower = better) | | | | | | |
| Rating by parent | −0.02 (−0.09 to 0.05) | −0.01 (−0.10 to 0.08) | −0.03 (−0.12 to 0.06) | 0.00 (−0.06 to 0.06) | 0.04 (−0.05 to 0.13) | −0.04 (−0.13 to 0.05) |
| Rating by teacher | −0.05 (−0.13 to 0.04) | −0.04 (−0.15 to 0.07) | −0.06 (−0.16 to 0.05) | 0.00 (−0.07 to 0.07) | 0.08 (−0.02 to 0.18) | −0.07 (−0.17 to 0.03) |
| **Behavior regulation (lower = better)** | | | | | | |
| Connors' Rating Scales (revised) | | | | | | |
| Hyperactive or impulsive | | | | | | |
| Rating by parent | 0.03 (−0.04 to 0.10) | 0.05 (−0.04 to 0.15) | 0.00 (−0.10 to 0.09) | 0.03 (−0.04 to 0.09) | 0.06 (−0.03 to 0.15) | 0.00 (−0.09 to 0.09) |
| Rating by teacher | −0.06 (−0.14 to 0.02) | −0.05 (−0.16 to 0.05) | −0.07 (−0.18 to 0.04) | −0.01 (−0.08 to 0.07) | 0.05 (−0.05 to 0.15) | −0.06 (−0.16 to 0.04) |
| Inattentive | | | | | | |
| Rating by parent | −0.03 (−0.10 to 0.04) | −0.04 (−0.13 to 0.06) | −0.02 (−0.12 to 0.07) | 0.01 (−0.06 to 0.07) | 0.04 (−0.05 to 0.12) | −0.02 (−0.11 to 0.07) |
| Rating by teacher | −0.03 (−0.12 to 0.05) | 0.00 (−0.11 to 0.11) | −0.07 (−0.18 to 0.04) | 0.00 (−0.07 to 0.08) | 0.09 (−0.01 to 0.19) | −0.08 (−0.18 to 0.02) |

**Table 3. (Continued.)**

| Evaluation Category and Instrument | Estimate (95% Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|
| | | Birth to 7 Months | | | Birth to 1 Month | |
| | Full Model | Boys | Girls | Full Model | Boys | Girls |
| Behavior Rating Inventory of Executive Function (behavioral regulation index) | | | | | | |
| Rating by parent | 0.05 (–0.02 to 0.12) | 0.10 (0.01 to 0.20)† | –0.01 (–0.10 to 0.09) | –0.01 (–0.08 to 0.05) | 0.02 (–0.07 to 0.11) | –0.05 (–0.14 to 0.04) |
| Rating by teacher | –0.03 (–0.11 to 0.06) | 0.00 (–0.11 to 0.10) | –0.05 (–0.16 to 0.06) | 0.03 (–0.04 to 0.10) | 0.07 (–0.03 to 0.18) | –0.02 (–0.12 to 0.08) |
| **Tics (lower = better)‡‖** | | | | | | |
| Motor tics | | | | | | |
| Rating by evaluator | 1.59 (0.86 to 2.93) | 2.19 (1.02 to 4.67)† | 1.04 (0.45 to 2.39) | 0.90 (0.54 to 1.50) | 1.27 (0.68 to 2.35) | 0.52 (0.23 to 1.16) |
| Rating by parent | 0.99 (0.55 to 1.75) | 1.05 (0.53 to 2.08) | 0.89 (0.38 to 2.08) | 0.66 (0.40 to 1.12) | 0.89 (0.47 to 1.67) | 0.41 (0.18 to 0.92)§ |
| Phonic tics | | | | | | |
| Rating by evaluator | 1.70 (0.90 to 3.22) | 2.44 (1.12 to 5.35)† | 0.97 (0.39 to 2.41) | 1.17 (0.68 to 2.01) | 1.51 (0.78 to 2.92) | 0.74 (0.31 to 1.75) |
| Rating by parent | 1.11 (0.66 to 1.87) | 1.78 (0.92 to 3.45) | 0.58 (0.28 to 1.21) | 1.11 (0.69 to 1.80) | 1.11 (0.60 to 2.05) | 1.12 (0.53 to 2.39) |
| **General intellectual functioning** | | | | | | |
| Wechsler Abbreviated Scale of Intelligence | | | | | | |
| Verbal IQ | –0.02 (–0.08 to 0.04) | 0.00 (–0.08 to 0.09) | –0.05 (–0.13 to 0.04) | –0.05 (–0.11 to 0) | –0.01 (–0.09 to 0.07) | –0.10 (–0.18 to –0.02)† |
| Performance IQ | 0.06 (–0.01 to 0.13) | 0.07 (–0.02 to 0.16) | 0.05 (–0.04 to 0.14) | 0.04 (–0.02 to 0.10) | 0.11 (0.02 to 0.20)§ | –0.03 (–0.11 to 0.06) |
| Full-scale IQ | 0.03 (–0.04 to 0.09) | 0.04 (–0.05 to 0.12) | 0.02 (–0.06 to 0.11) | –0.01 (–0.07 to 0.05) | 0.05 (–0.03 to 0.13) | –0.07 (–0.15 to 0.01) |

* Unless otherwise noted, all estimates are given as standardized coefficients, which represent the change in the outcome, expressed in standard-deviation units, given a change of 1 SD in exposure to thimerosal. Higher scores on scales indicate better outcomes, except where indicated.
† P<0.05 for the association between a higher exposure to mercury and a worse outcome.
‡ Estimates in this category are given as odds ratios. We estimated odds ratios for a 2-SD increase in mercury exposure.
§ P<0.05 for the association between a higher exposure to mercury and a better outcome.
¶ P<0.01 for the association between a higher exposure to mercury and a better outcome.
‖ Evaluators observed tics during the outcomes assessment, and parents reported tics within 7 days before the assessment.

epidemiologic studies have shown few associations between exposure to thimerosal-containing vaccines in infancy and subsequent neurodevelopmental disorders, and these findings include similar frequencies of better and poorer performance. Andrews and colleagues[21] studied 103,043 British children and found more protective associations than harmful associations with mercury exposure from vaccines administered in the first year of life. The one deleterious association involved an increased risk of tics, a finding similar to that in our study. Heron and Golding[32] studied 12,956 British children who typically had been exposed to mercury from vaccination at 3, 4, and 6 months of age. Among 69 outcomes, the only adverse association was poorer prosocial behavior, and there were several beneficial associations.

Several studies of the effects of prenatal exposure to methyl mercury from fish consumption on neuropsychological performance have shown negative associations with speech and verbal abilities, dexterity, attention, and visuospatial abilities,[5,33] whereas other studies have shown no effects.[34] Summaries of these studies by the National Research Council and other groups have concluded that there were significant negative effects.[17,35] However, the appropriateness of methyl mercury as a referent for assessment of exposure to ethyl mercury from thimerosal is questionable, since the half-life of ethyl mercury in blood (<10 days) is much shorter than the half-life of methyl mercury (>20 days).[24,36]

Our study had several limitations. A majority of the selected families declined to participate or could not be located, and we were able to enroll only 30% of the subjects included for recruitment. Therefore, our findings may have been influenced by selection bias. In addition, we were not able to control for interventions, such as speech therapy, that may have ameliorated the potential negative effects of thimerosal exposure and could have biased the results toward the null hypothesis. Given that parents were not trained to assess tics, the parental ratings of tics may have been less reliable than the ratings by trained evaluators. We did not assess exposure to thimerosal beyond 214 days. Finally, the information available for some potential confounding factors, such as family income, which may have resulted in unmeasured residual confounding, was imprecise. Our study did not examine the possible association between autism and exposure to mercury from vaccines and immune globulins.

Our study had several strengths. We performed a comprehensive neuropsychological assessment that was similar to the assessment used in the landmark studies of prenatal exposure to methyl mercury.[5,6] Potential biases were reduced by enrolling children on the basis of receipt of vaccination, without regard to the seeking of health care or documented neurodevelopmental diagnoses. We collected exposure information from many different sources and controlled for confounding by adjusting our analyses for a wide range of characteristics and exposures for both mothers and children.

The weight of the evidence in this study does not support a causal association between early exposure to mercury from thimerosal-containing vaccines and immune globulins administered prenatally or during infancy and neuropsychological functioning at the age of 7 to 10 years. The overall pattern of results suggests that the significant associations may have been chance findings stemming from the large number of statistical tests that we performed.

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