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ARTICLE

Neuropsychological Performance 10 Years After Immunization in Infancy With Thimerosal-Containing Vaccines

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What's Known on This Subject

The issue of thimerosal neurotoxicity and infant vaccines remains controversial, although many studies support the lack of association between thimerosal and neuropsychological development.

What This Study Adds

The weak and inconsistent associations found in this study suggest that the association between thimerosal exposure through vaccination in infancy and neuropsychological deficits is unlikely or clinically negligible.

ABSTRACT

OBJECTIVE. Thimerosal, a mercury compound used as a preservative in vaccines administered during infancy, has been suspected to affect neuropsychological development. We compared the neuropsychological performance, 10 years after vaccination, of 2 groups of children exposed randomly to different amounts of thimerosal through immunization.

METHODS. Children who were enrolled in an efficacy trial of pertussis vaccines in 1992–1993 were contacted in 2003. Two groups of children were identified, according to thimerosal content in vaccines assigned randomly in the first year of life (cumulative ethylmercury intake of 62.5 or 137.5 μg), and were compared with respect to neuropsychological outcomes. Eleven standardized neuropsychological tests, for a total of 24 outcomes, were administered to children during school hours. Mean scores of neuropsychological tests in the domains of memory and learning, attention, executive functions, visuospatial functions, language, and motor skills were compared according to thimerosal exposure and gender. Standard regression coefficients obtained through multivariate linear regression analyses were used as a measure of effect.

RESULTS. Nearly 70% of the invited subjects participated in the neuropsychological assessment (N = 1403). Among the 24 neuropsychological outcomes that were evaluated, only 2 were significantly associated with thimerosal exposure. Girls with higher thimerosal intake had lower mean scores in the finger-tapping test with the dominant hand and in the Boston Naming Test.

CONCLUSIONS. Given the large number of statistical comparisons performed, the few associations found between thimerosal exposure and neuropsychological development might be attributable to chance. The associations found, although statistically significant, were based on small differences in mean test scores, and their clinical relevance remains to be determined. *Pediatrics* 2009;123:475–482

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Key Words
thimerosal, ethylmercury compounds, developmental disabilities, immunization, child, randomized, controlled trial

Abbreviations
CI— confidence interval
DTaP— diphtheria-tetanus-acellular pertussis
SRC—standardized regression coefficient
WISC-R—Wechsler Intelligence Scale for Children-Revised
RR—risk ratio

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CONCERN HAS BEEN raised regarding the potential effect of thimerosal, a mercury compound used as a preservative in vaccines, on neuropsychological development in children.[1] Autism,[2] motor tics,[3,4] mental retardation, language disorders, and attention-deficit/hyperactivity disorder[5] have been alleged as adverse events attributable to thimerosal contained in vaccines. In contrast, the results of large, well-designed studies do not support such associations between thimerosal exposure and neuropsychological development.[6–12]

Several international agencies recommended different safe limits of exposure to ethylmercury (a metabolite of thimerosal), according to body weight, on the basis of the available pharmacokinetic data on methylmercury, a similar compound.[12,13] However, the blood half-life of ethylmercury from thimerosal contained in vaccines is shorter than that of methylmercury.[14] Moreover, none of the studies conducted to date has been able to demonstrate what amount of thimerosal administered with vaccines is associated with adverse neurotoxic events.[9,12,13] Nonetheless, since 1999, regulatory agencies in both the United States and Europe have recommended eliminating thimerosal from vaccines when possible, as a precautionary measure.[15–17]

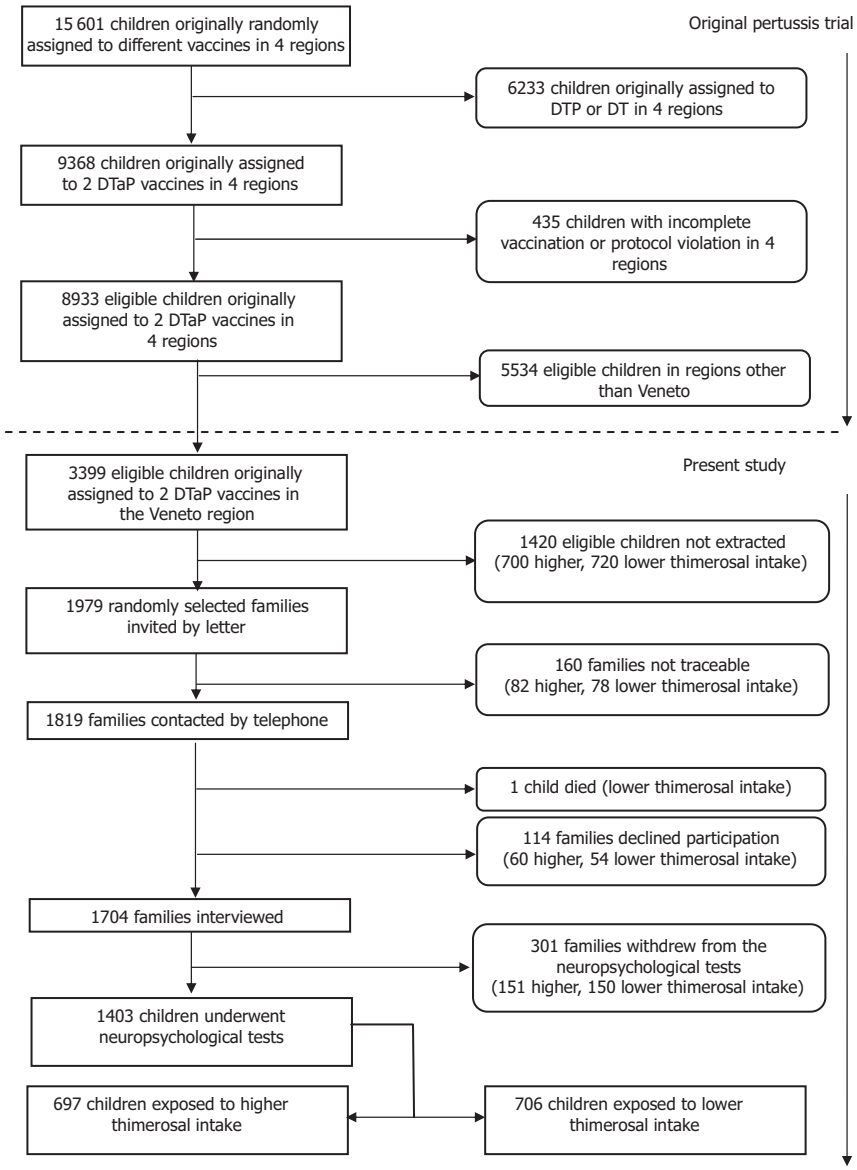

FIGURE 1
Selection process for the study population. DT indicates diphtheria-tetanus vaccine; DTP, whole cell diphtheria-tetanus-pertussis vaccine; DTaP, acellular diphtheria-tetanus-pertussis vaccine.

Assessing the effects of thimerosal in vaccines long after immunization is complicated by a variety of factors that potentially affect the quality of data on vaccine exposure and measures of neuropsychological development. Controlling for social and educational factors and some health conditions may be difficult in observational studies in the general population, in the absence of high-quality records including information on each of these factors.

A randomized, controlled, clinical trial on the efficacy of acellular pertussis vaccines started in Italy in 1992[18] and included a diphtheria-tetanus-acellular pertussis (DTaP) vaccine manufactured by Chiron Biocine that contained thimerosal and a DTaP vaccine manufactured by SmithKline Beecham that contained 2-polyphenoxyethanol (a compound with no known neurotoxicity) as a preservative. Because infants enrolled in this trial were assigned randomly to receive different vaccines, they also were exposed randomly to different cumulative quantities of thimerosal in their first year of life. Moreover, children were monitored actively, with monthly contacts up to the age of 6 years, and did not receive other vaccines containing thimerosal during this period. In the present study, we compared neuropsychological outcomes, 10 years after vaccination, for children who had been exposed to different amounts of thimerosal.

METHODS

Exposure to Thimerosal

In 1992–1993, 15 601 healthy, 2-month-old infants were enrolled in the Italian Trial on Pertussis Vaccines.[18–20] In this trial, infants were selected from the general population in 4 of Italy's 20 regions (Fig 1) and were assigned randomly to receive, under double-blind conditions, 3 doses of 1 of 4 vaccines, 2 of which were DTaP vaccines from 2 different manufacturers. One DTaP vaccine contained 50 μg of thimerosal (or 25 μg of

TABLE 1 Ethylmercury Exposure Through Thimerosal According to Group and Age

	Ethylmercury Exposure, μg							
	Lower Thimerosal Intake Group				Higher Thimerosal Intake Group			
	HBV	DTaP	DT	Total	HBV	DTaP	DT	Total
2 mo	12.5	0		12.5	12.5	25		37.5
4 mo	12.5	0		12.5	12.5	25		37.5
6 mo		0		0		25		25
11 mo	12.5		25	37.5	12.5		25	37.5
Cumulative total				62.5				137.5

HBV indicates hepatitis B virus vaccine; DT, diphtheria-tetanus vaccine.

ethylmercury) per dose, and the other was thimerosal-free (2-phenoxyethanol was used as preservative). The 3 doses of DTaP vaccine were administered at 2, 4, and 6 months of age. To comply with Italy's vaccination schedule, all children also received 3 doses of hepatitis B virus vaccine (child formulation), each of which contained 25 μg of thimerosal (or 12.5 μg of ethylmercury), at 2, 4, and 12 months of age, and a fourth dose of diphtheria-tetanus vaccine, which contained 50 μg of thimerosal (or 25 μg of ethylmercury), at 11 months of age. Table 1 reports the vaccination schedule and the cumulative amounts of ethylmercury, the mercury metabolite of thimerosal, administered to infants in the trial according to age. These children received no other doses of thimerosal-containing vaccines until they were 6 years of age, when they received a booster dose of either diphtheria-tetanus vaccine or DTaP vaccine, in accordance with Italy's vaccination schedule. Therefore, in the first 12 months of life, the cumulative intake of ethylmercury, the mercury metabolite of thimerosal, was 137.5 μg for the children who were assigned randomly to receive the DTaP vaccine that contained thimerosal ("higher intake group") and 62.5 μg for those who received the thimerosal-free DTaP vaccine ("lower intake group").

Enrollment and Neuropsychological Assessment

The study population for the present study included children living in the Veneto Region who were vaccinated with 3 doses of 1 of the 2 DTaP vaccines during the trial. A random sample from all 3399 subjects originally included in the trial in the region was extracted progressively until the desired sample size was met. Parents were sent a letter of invitation; once they provided written informed consent, they were interviewed by trained nurses over the telephone to update the information on the children's medical history and sociodemographic characteristics. An appointment was scheduled for administration of neuropsychological tests to the children. No economic incentive was provided to participants. The tests were administered during a single 2-hour session during regular school hours, by 1 of 10 trained psychologists (who were blinded to the vaccine received by each child).

A total of 11 neuropsychological tests, which had been selected on the basis of previous studies,[3,21] were administered to the enrolled children. The tests were used to explore areas of cognitive function allegedly affected by thimerosal exposure, were age-appropriate, and were standardized for the Italian population. The following domains were assessed: (1) memory and learning, with the California Verbal Learning Test-Children Version[22] and the Wechsler Intelligence Scale for Children-Revised (WISC-R) digit span test[23]; (2) attention, with the continuous performance test (Conners' version), a computer-assisted test that evaluates sustained attention, inhibition, and impulsivity[24]; (3) executive functions, with the WISC-R coding test[23] and the phonemic verbal fluency test, which assesses the ability to access a lexicon through phonemic cues and to set up adequate verbal search strategies[25]; (4) visuospatial functions, with the WISC-R block design test[23]; (5) language, with the WISC-R vocabulary and similarities tests,[23] the Boston Naming Test,[26] and the semantic verbal fluency test, which assesses the ability to access a lexicon according to semantic categories[25]; and (6) motor skills, with the finger-tapping test,[27] which provides an assessment of fine motor speed and coordination, and the writing praxia test,[28] which measures the writing speed of the child.

Autism was considered as a separate outcome of the study and was assessed through review of the medical history with the parents and the medical charts of family pediatricians, according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria.[29] The presence of any motor or phonic tics was screened by psychologists through direct observation of the children during the neuropsychological assessments. The psychologists were trained to recognize tic behaviors, and 2 binary variables were created to indicate the presence of motor and phonic tics.

Children were 10 to 12 years of age when the neuropsychological evaluations were conducted, between the end of 2003 and early 2005. The study was approved by the review boards of the Istituto Superiore di Sanità (Italy's National Health Institute) and the Veneto Region.

Abstraction of Other Information

Sociodemographic variables and health information at birth and in infancy were derived from the original trial database for all children included in the present study. Medical conditions identified during the telephone interviews and relevant therapies were verified with the family pediatricians through review of local medical charts. For each child, the following information was collected: gender, birth weight, gestational age, mother's age at birth, Rh immunoglobulins during pregnancy, hepatitis B immunization at birth, type of delivery, breastfeeding duration, family composition, parents' education, presence of diseases of the central nervous system or other chronic diseases, and current prescription of antihistamines or antiepileptic drugs.

Sample Size and Data Analysis

Comparison between the 2 groups of children (higher and lower intake groups) was performed for a total of 24

neuropsychological outcomes. With the assumption that children in the lower intake group had mean scores for neuropsychological tests equal to reference values, a sample size of 700 children in each group (for a total of 1400 children) would be sufficient to yield a statistical power of 90% for identifying differences of at least ±5%, at a 5% significance level with a 2-tailed test.

We assessed differences between groups by using Student's *t* test for continuous variables. The difference between the mean neuropsychological test scores, with 95% confidence intervals (CIs), was used as a measure of effect size. The Mann-Whitney *U* test was used to validate results in cases of violation of normality and homoscedasticity assumptions. The χ^2 test or Fisher's exact probability test were used for categorical variables. We also calculated risk ratios (RRs), with 95% CIs, to assess the association between thimerosal exposure and the presence of tics at the univariate level.

We performed separate, ordinary, least-squares, multivariate, linear regression analyses, using the raw score of each test as the dependent variable, to assess the association between thimerosal intake and the results of neuropsychological tests, with adjustment for the following potential confounders: age at test administration, gender, birth weight, gestational age, type of delivery, breastfeeding duration, family composition, mother's age at birth, parents' education, presence of diseases of the central nervous system or other chronic diseases, current prescription of antihistamines or antiepileptic drugs, Rh immunoglobulins during pregnancy, and hepatitis B immunization at birth. Standardized regression coefficients (SRCs) were used as a measure of effect size, with the SRC representing the quantitative difference in the outcome scores, expressed in SD units, for the lower versus higher thimerosal intake group. We also assessed the effect of thimerosal exposure in separate analyses according to gender. In secondary analyses, we performed logistic regression analyses using as the dependent variable the presence of motor and phonic tics. The adjusted RR was used as a measure of effect size. During statistical analyses, the 2 study groups were masked with respect to the amount of thimerosal exposure. We did not correct for multiple comparisons, to maintain the highest possible sensitivity during statistical analyses.

RESULTS

A total of 1979 families, of the total regional cohort of 3399, were sent an invitation letter (Fig 1). We were unable to contact 160 families (8.1%) by telephone; of the remaining 1819 families, 114 (6.3%) declined participation, and 1 child (0.05%) had died. Telephone interviews were conducted for the remaining 1704 families (87.9% of the eligible population). We detected, through the telephone interviews with parents and reviews of medical charts, 1 case of autism among the 856 children in the lower thimerosal intake group and no cases among the 848 children in the higher thimerosal intake group.

A total of 301 children from the 1704 interviewed families did not undergo the neuropsychological evaluation. Therefore, a total of 1403 children (70.9%) were included in the analysis, 697 in the higher intake group and 706 in the lower intake group.

The proportions of families whose child did not undergo the neuropsychological tests did not differ significantly between the 2 groups. Parents failed to have their children evaluated for the following reasons: lack of time to participate, fear that the child would feel uncomfortable during the evaluation, or failure to keep the appointment for the tests (higher intake group: $n = 150$; lower intake group: $n = 146$); in some cases, the child had a medical condition (lower intake group: epilepsy, $n = 1$; autism, $n = 1$; leukemia, $n = 1$; retinitis pigmentosa, $n = 1$; higher intake group: head injury, $n = 1$).

The characteristics of the 1403 children who underwent neuropsychological assessments are listed in Table 2. The 2 groups were similar in terms of sociodemographic characteristics, clinical characteristics, and parents' educational level, whereas birth weight was slightly lower for the higher intake group.

Mean scores and SDs for each neuropsychological test according to thimerosal exposure are reported in Table 3, for the entire population included in the study and according to gender. All mean scores were in the normal range according to reference standards,[22–28] and the study groups were similar with respect to almost all neuropsychological outcomes. Children in the higher intake group performed significantly worse than children in the lower intake group only in the finger-tapping test with the dominant hand, although the difference in mean scores was modest (difference: 1.01; 95% CI: 0.30–1.73; $P = .006$, Student's *t* test). Motor tics were observed for 2.56% of patients in the lower thimerosal intake group and 2.91% of patients in the higher intake group (RR: 1.13; 95% CI: 0.60–2.13; $P = .744$, Fisher's exact probability test). Phonic tics were detected for 0.43% of patients in the lower intake group and 0.87% of patients in the higher intake group (RR: 2.04; 95% CI: 0.51–8.13; $P = .338$, Fisher's exact probability test).

Girls in the higher intake group performed significantly worse than did those in the lower intake group in the finger-tapping test with the dominant hand (difference in scores: 1.08; 95% CI: 0.11–2.05; $P = .029$, Student's *t* test) (Table 3). In multivariate analyses, we did not find any statistically significant associations for the overall group of children and for boys (Table 4). We found worse performance in the higher intake group for the Boston Naming Test (SRC: −0.16; $P = .025$) and the finger-tapping test with the dominant hand (SRC: −0.16; $P = .029$) for girls. Finally, we did not find any significant association in the logistic regression analyses for phonic and motor tics, in the entire population or according to gender.

DISCUSSION

One of the major problems in assessing the effects of exposure to thimerosal during infancy on neuropsychological development is identifying groups of children who have good vaccination records, who received different amounts of thimerosal, and who, many years later, are still comparable with respect to the occurrence of factors that may affect neuropsychological develop-

TABLE 2 Characteristics of Children Who Underwent Neuropsychological Evaluations, According to Thimerosal Intake

	Lower Intake Group (*N* = 706)	Higher Intake Group (*N* = 697)	Total (*N* = 1403)	*P*
Age, mean ± SD (range), y	11.76 ± 0.47 (10.37–12.67)	11.76 ± 0.46 (10.29–12.69)	11.76 ± 0.47 (10.29–12.69)	.963[a]
Female, *n* (%)	348 (49.29)	345 (49.50)	693 (49.39)	.957[b]
Birth weight, mean ± SD (range), g	3375 ± 481 (1700–5050)	3323 ± 484 (1800–5050)	3349 ± 483 (1700–5050)	.041[a]
Gestational age, mean ± SD (range), wk	39.43 ± 1.48 (33–43)	39.47 ± 1.48 (32–43)	39.45 ± 1.48 (32–43)	.618[a]
Operative delivery, *n* (%)	148 (21.20)	159 (22.94)	307 (22.07)	.439[b]
Breastfeeding duration, mean ± SD (range), mo	2.97 ± 2.60 (0–15)	2.78 ± 2.57 (0–15)	2.88 ± 2.59 (0–15)	.164[a]
Order of birth, mean ± SD (range)	1.57 ± 0.79 (1–7)	1.54 ± 0.72 (1–6)	1.55 ± 0.76 (1–7)	.524[a]
No. of siblings, mean ± SD (range)	2.12 ± 0.84 (1–8)	2.06 ± 0.78 (1–6)	2.09 ± 0.81 (1–8)	.175[a]
Single parent, *n* (%)	62 (8.78)	57 (8.18)	119 (8.48)	.702[b]
School level, *n* (%)				.268[c]
Elementary, fourth year	4 (0.57)	0 (0.00)	4 (0.29)	
Elementary, fifth year	61 (8.66)	56 (8.05)	117 (8.36)	
Junior high, first year	444 (63.07)	443 (63.65)	887 (63.36)	
Junior high, second year	194 (27.56)	197 (28.30)	391 (27.93)	
Junior high, third year	1 (0.14)	0 (0.00)	1 (0.07)	
Mother's age at birth, mean ± SD (range), y	30.18 ± 4.58 (17–45)	30.12 ± 4.36 (17–44)	30.15 ± 4.47 (17–45)	.796[a]
Mother with college degree, *n* (%)	68 (9.63)	60 (8.62)	128 (9.13)	.518[b]
Father with college degree, *n* (%)	76 (10.81)	65 (9.42)	141 (10.12)	.424[b]
Central nervous system disease, *n* (%)	13 (1.84)	7 (1.00)	20 (1.43)	.260[b]
Other chronic diseases, *n* (%)	35 (4.96)	28 (4.02)	63 (4.49)	.440[b]
Antihistamines, *n* (%)	14 (1.98)	13 (1.87)	27 (1.92)	1.000[b]
Antiepileptic agents, *n* (%)	3 (0.42)	1 (0.14)	4 (0.29)	.624[b]
Rh immunoglobulins during pregnancy, *n* (%)	85 (12.27)	81 (11.84)	166 (12.06)	.869[b]
Hepatitis B immunization at birth, *n* (%)	3 (0.42)	7 (1.00)	10 (0.71)	.222[b]

[a] With Student's *t* test.
[b] With Fisher's exact test.
[c] With the χ^2 test.

ment. In this regard, our study population, as a subset of children who had participated in the Italian Trial on Pertussis Vaccines, had several advantages, particularly the following: (1) the children belonged to groups that had been assigned randomly to receive different thimerosal exposures through vaccines in the first year of life, (2) the children did not receive any other thimerosal-containing vaccines until they were 6 years of age, (3) vaccinations were administered under strict rules and were carefully monitored, (4) vaccination records were very accurate, being collected under rigorous clinical trial conditions, and (5) children were monitored actively for 6 years. Furthermore, Italy's population has low population mobility, which contributed to the high response rate 10 years after enrollment in the original study. Moreover, the school curriculum until 13 years of age is standardized throughout the country, and the children had similar learning experiences. Finally, the neuropsychological assessments and the statistical analyses were performed under blinded conditions with respect to exposure to thimerosal.

According to our results, greater thimerosal exposure through vaccines administered in the first year of life was significantly associated with lower scores for 2 neuropsychological outcomes, in the domains of motor function (finger-tapping test) and language (Boston Naming Test), among girls. However, the differences in the mean scores were very small and of doubtful clinical relevance. Neuropsychological deficits in the domains of language and, to a lesser extent, motor functions were also observed in a cohort of children exposed prenatally to methylmercury,[21] although a direct comparison may be inappropriate because ethylmercury, the metabolite of thimerosal, has different toxicokinetic features.[14,30] To date, studies on the effects of thimerosal contained in vaccines have not provided a clear pattern of associations, and many authors found even better neurodevelopmental outcomes for children exposed to thimerosal.[4,7,9] An association between thimerosal contained in vaccines and language delays was found in a study from the Vaccine Safety Datalink[3] and in a recent study in 4 US health maintenance organizations.[9] In the latter study, however, the Boston Naming Test outcome was not affected by thimerosal exposure. We failed to observe any association with tics, in contrast to the findings of some observational studies.[3,4,9]

Because we did not correct for multiple comparisons in the statistical analyses, we expected to find 4 significant associations among the 78 univariate statistical tests, at the 5% statistical significance level (Table 3), and 4 among the 72 multivariate analyses (Table 4) as effects of chance. Because we found only 2 significant associations between thimerosal exposure and neuropsychological outcomes, the observed associations might actually reflect the effects of chance. In addition, the associations were based on small differences in scores, they were detected only for girls, and they were not consistent with results from other studies.

Some limitations should be considered in the interpretation of our results. The cumulative intake of thimerosal was relatively low, compared with that in other countries including the United States, where vac-

TABLE 3 Neuropsychological Test Results for the Entire Population and According to Gender

Domain	Test	Item	Entire Group, Score, Mean ± SD		Female, Score, Mean ± SD		Male, Score, Mean ± SD	
			Lower Intake Group ($N = 704$)	Higher Intake Group ($N = 693$)	Lower Intake Group ($N = 346$)	Higher Intake Group ($N = 343$)	Lower Intake Group ($N = 358$)	Higher Intake Group ($N = 350$)
Memory and learning	California Verbal Learning	Total of 5 trials	51.47 ± 7.19	51.55 ± 7.06	52.24 ± 6.92	52.44 ± 6.94	50.73 ± 7.38	50.68 ± 7.08
		Interference list	6.54 ± 1.84	6.57 ± 1.74	6.69 ± 1.82	6.82 ± 1.82	6.39 ± 1.84	6.32 ± 1.62
		Short-term free recall	10.89 ± 2.13	10.85 ± 2.15	10.99 ± 2.04	11.05 ± 2.08	10.79 ± 2.20	10.66 ± 2.21
		Short-term cued recall	11.28 ± 1.88	11.36 ± 1.92	11.49 ± 1.71	11.65 ± 1.73	11.08 ± 2.00	11.07 ± 2.06
		Long-term free recall	11.48 ± 2.04	11.50 ± 1.97	11.63 ± 1.90	11.64 ± 1.76	11.33 ± 2.16	11.36 ± 2.14
		Long-term cued recall	11.64 ± 1.87	11.67 ± 1.90	11.86 ± 1.67	11.89 ± 1.72	11.43 ± 2.03	11.46 ± 2.04
		Total recognition	14.35 ± 0.98	14.32 ± 0.99	14.45 ± 0.86	14.43 ± 0.81	14.25 ± 1.08	14.22 ± 1.12
	Digit span	Forward	6.38 ± 1.67	6.26 ± 1.66	6.37 ± 1.70	6.26 ± 1.64	6.38 ± 1.65	6.26 ± 1.67
		Backward	5.40 ± 1.73	5.49 ± 1.73	5.48 ± 1.80	5.57 ± 1.72	5.33 ± 1.65	5.40 ± 1.74
Attention	Continuous performance	Omission errors	9.56 ± 10.27	9.42 ± 9.62	8.09 ± 8.65	7.49 ± 7.01	10.98 ± 11.46	11.33 ± 11.33
		Commission errors	22.27 ± 7.20	22.39 ± 7.28	20.42 ± 7.35	20.80 ± 7.07	24.06 ± 6.59	23.95 ± 7.16
		Hit reaction time	5.95 ± 0.15	5.95 ± 0.15	5.97 ± 0.15	5.97 ± 0.15	5.93 ± 0.15	5.93 ± 0.16
Executive functions	Coding		54.02 ± 9.85	54.09 ± 9.59	57.35 ± 9.61	57.00 ± 9.19	50.79 ± 8.97	51.23 ± 9.11
	Verbal fluency	Phonemic	29.45 ± 9.14	28.72 ± 8.29	31.53 ± 9.70	30.64 ± 8.10	27.44 ± 8.09	26.82 ± 8.04
Visuospatial functions	Block design		40.13 ± 10.05	39.60 ± 9.69	39.93 ± 10.01	39.24 ± 9.60	40.32 ± 10.10	39.95 ± 9.78
Language	Vocabulary		47.95 ± 6.74	47.64 ± 6.41	47.67 ± 6.31	47.17 ± 6.07	48.23 ± 7.13	48.09 ± 6.69
	Similarity		20.57 ± 3.51	20.43 ± 3.33	20.57 ± 3.59	20.24 ± 3.43	20.56 ± 3.44	20.61 ± 3.22
	Boston Naming		48.64 ± 4.97	48.41 ± 5.25	48.84 ± 4.78	48.14 ± 5.12	48.46 ± 5.15	48.67 ± 5.37
	Verbal fluency	Semantic	58.48 ± 10.84	58.11 ± 10.98	59.14 ± 10.81	58.31 ± 10.56	57.85 ± 10.85	57.92 ± 11.39
Motor skills	Finger tapping	Dominant hand	35.52 ± 6.81[a]	34.50 ± 6.79[a]	34.16 ± 6.50[a]	33.08 ± 6.47[a]	36.84 ± 6.86	35.91 ± 6.81
		Nondominant hand	31.98 ± 5.80	31.74 ± 5.95	30.81 ± 5.52	30.09 ± 5.61	33.12 ± 5.85	33.36 ± 5.84
	Writing praxia	Numbers	100.18 ± 21.73	99.91 ± 22.15	102.67 ± 20.03	103.10 ± 22.42	97.76 ± 23.02	96.78 ± 21.46
		Uno	92.84 ± 18.88	92.42 ± 18.76	96.60 ± 19.05	96.53 ± 19.48	89.21 ± 18.01	88.39 ± 17.13
		Le	81.92 ± 14.83	80.53 ± 14.39	84.50 ± 14.22	83.26 ± 13.24	79.41 ± 15.00	77.85 ± 14.97
	Tics, mean ± SE, %	Motor	2.56 ± 0.60	2.91 ± 0.64	0.87 ± 0.50	1.47 ± 0.65	4.20 ± 1.06	4.32 ± 1.09
		Phonic	0.43 ± 0.25	0.87 ± 0.36	0.29 ± 0.29	0.88 ± 0.51	0.56 ± 0.40	0.87 ± 0.50

Higher scores indicate better performance, except for the continuous performance test, for which lower scores indicate better performance.

[a] Significant differences between lower and higher intake groups in univariate comparisons ($P < .05$). Differences between continuous variables were assessed with Student's *t* test, whereas differences between categorical variables were assessed with Fisher's exact test.

TABLE 4 SRCs for Neuropsychological Tests From the Multivariate Linear Regression Model for the Entire Population and According to Gender

Domain	Test	Item	SRC (95% CI)		
			Entire Group ($N = 1344$)	Female ($N = 663$)	Male ($N = 681$)
Memory and learning	California Verbal Learning	Total of 5 trials	0.0012 (−0.1480 to 0.1504)	0.0138 (−0.1342 to 0.1617)	−0.0123 (−0.1653 to 0.1408)
		Interference list	−0.0559 (−0.2068 to 0.0950)	0.0526 (−0.1044 to 0.2095)	−0.0629 (−0.2104 to 0.0846)
		Short-term free recall	−0.0624 (−0.2113 to 0.0866)	0.0197 (−0.1261 to 0.1655)	−0.0650 (−0.2184 to 0.0885)
		Short-term cued recall	0.0009 (−0.1455 to 0.1473)	0.0822 (−0.0549 to 0.2192)	−0.0181 (−0.1755 to 0.1393)
		Long-term free recall	0.0309 (−0.1174 to 0.1792)	0.0000 (−0.1385 to 0.1385)	0.0127 (−0.1460 to 0.1714)
		Long-term cued recall	0.0068 (−0.1414 to 0.1550)	0.0203 (−0.1160 to 0.1565)	−0.0099 (−0.1708 to 0.1510)
		Total recognition	−0.0730 (−0.2223 to 0.0762)	−0.0004 (−0.1301 to 0.1294)	−0.0839 (−0.2505 to 0.0827)
	Digit span	Forward	−0.0666 (−0.2156 to 0.0825)	−0.0814 (−0.2315 to 0.0688)	−0.0749 (−0.2258 to 0.0760)
		Backward	0.0499 (−0.0992 to 0.1990)	0.0307 (−0.1235 to 0.1848)	0.0431 (−0.1037 to 0.1900)
Attention	Continuous performance	Omission errors	0.0516 (−0.0984 to 0.2016)	−0.0572 (−0.1772 to 0.0627)	0.0518 (−0.1250 to 0.2285)
		Commission errors	−0.0054 (−0.1536 to 0.1428)	0.0432 (−0.1112 to 0.1975)	−0.0045 (−0.1488 to 0.1397)
		Hit reaction time	−0.0176 (−0.1626 to 0.1274)	−0.0314 (−0.1771 to 0.1143)	−0.0092 (−0.1567 to 0.1384)
Executive functions	Coding		0.0550 (−0.0789 to 0.1890)	−0.0319 (−0.1721 to 0.1083)	0.0549 (−0.0757 to 0.1855)
	Verbal fluency	Phonemic	−0.0288 (−0.1718 to 0.1143)	−0.0890 (−0.2419 to 0.0639)	−0.0408 (−0.1764 to 0.0949)
Visuospatial functions	Block design		0.0250 (−0.1173 to 0.1673)	−0.0904 (−0.2359 to 0.0550)	0.0243 (−0.1174 to 0.1660)
Language	Vocabulary		0.0157 (−0.1237 to 0.1552)	−0.0799 (−0.2139 to 0.0541)	0.0075 (−0.1406 to 0.1556)
	Similarity		0.0641 (−0.0796 to 0.2078)	−0.1017 (−0.2522 to 0.0487)	0.0425 (−0.0960 to 0.1810)
	Boston Naming		0.0980 (−0.0425 to 0.2385)	−0.1567 (−0.2934 to −0.0201)[a]	0.0940 (−0.0531 to 0.2411)
	Verbal fluency	Semantic	0.0421 (−0.1025 to 0.1868)	−0.0888 (−0.2350 to 0.0575)	0.0269 (−0.1194 to 0.1732)
Motor skills	Finger tapping	Dominant hand	−0.1043 (−0.2508 to 0.0423)	−0.1631 (−0.3090 to −0.0172)[a]	−0.0985 (−0.2477 to 0.0507)
		Nondominant hand	0.0321 (−0.1104 to 0.1745)	−0.1232 (−0.2667 to 0.0204)	0.0210 (−0.1222 to 0.1643)
	Writing praxia	Numbers	−0.0551 (−0.1977 to 0.0875)	−0.0139 (−0.1552 to 0.1275)	−0.0437 (−0.1901 to 0.1027)
		Uno	−0.0426 (−0.1821 to 0.0969)	−0.0126 (−0.1587 to 0.1335)	−0.0450 (−0.1797 to 0.0897)
		Le	−0.1196 (−0.2655 to 0.0262)	−0.0915 (−0.2332 to 0.0502)	−0.1164 (−0.2674 to 0.0346)

A SRC of >0 indicates a higher (adjusted) mean value for the outcome variable in the higher intake group, compared with the lower intake group; a SRC of <0 indicates a lower (adjusted) mean value for the outcome variable in the higher intake group, compared with the lower intake group.

[a] Significant SRCs ($P < .05$).

cination schedules included more thimerosal-containing vaccines in the first year of life. Moreover, there was no comparison group with no exposure to thimerosal, although our setting was appropriate to identify a dose-response effect in the absence of any evidence suggesting a threshold dose for observation of an effect. Our analysis included only healthy children who were selected during enrollment in the original trial, and some families might have declined to participate in the present study because their children had cognitive developmental problems. This might have reduced the prevalence of adverse neuropsychological conditions and might have made potential differences hard to detect. The eligibility criteria of the original trial also limited the participation of low birth weight children, and only 55 children with birth weights of <2500 g underwent the neuropsychological evaluation (data not shown). Moreover, only 1% of children in this study received hepatitis B virus vaccine at birth. Although no effect of birth weight according to thimerosal intake was detected through multivariate analyses, our study was not powered to detect an association of thimerosal exposure and neuropsychological development in low birth weight infants.

CONCLUSIONS

No study conducted to date has been able to provide conclusive evidence of an effect of thimerosal on neuropsychological development. Final judgments regarding this association must rely on the entire body of results from studies conducted in different settings and with different levels of validity and on the coherence of results. The lack of consistency among the results of our study and other available studies suggests that an association between thimerosal exposure through vaccination in infancy and neuropsychological deficits is unlikely or clinically negligible. Additional data from populations with wider ranges of exposure to thimerosal and additional neuropsychological assessments at older ages may help to clarify the issue of potential associations between thimerosal and neurodevelopmental outcomes.

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