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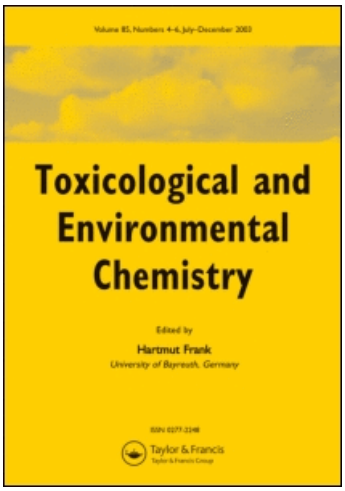

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Hepatitis B triple series vaccine and developmental disability in US children aged 1-9 years

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Hepatitis B triple series vaccine and developmental disability in US children aged 1–9 years

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This study investigated the association between vaccination with the Hepatitis B triple series vaccine prior to 2000 and developmental disability in children aged 1–9 years ($n = 1824$), proxied by parental report that their child receives early intervention or special education services (EIS). National Health and Nutrition Examination Survey 1999–2000 data were analyzed and adjusted for survey design by Taylor Linearization using SAS version 9.1 software, with SAS callable SUDAAN version 9.0.1. The odds of receiving EIS were approximately nine times as great for vaccinated boys ($n = 46$) as for unvaccinated boys ($n = 7$), after adjustment for confounders. This study found statistically significant evidence to suggest that boys in United States who were vaccinated with the triple series Hepatitis B vaccine, during the time period in which vaccines were manufactured with thimerosal, were more susceptible to developmental disability than were unvaccinated boys.

Keywords: early intervention; special education services; developmental disability; Hepatitis B vaccine triple series

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Introduction

Mercury (Hg) is a recognized neurodevelopmental toxicant (NRC 2000). Coal-fired power plants are a prime source of Hg emissions that aerosolize, travel through the atmosphere to waterways, are transformed by microorganisms into methyl Hg and consumed by fish, then magnify in the marine food chain (Trasande, Landrigan, and Schecter 2005). Pregnant women's consumption of seafood is the major route of *in utero* exposure to methyl Hg (Trasande, Landrigan, and Schecter 2005). Studies show an association between prenatal methyl Hg exposure and poor performance on cognitive tests (Grandjean et al. 1997). Researchers found that between 316,588 and 637,233 children each year have cord blood methyl Hg levels $>5.8\ \mu g\ L^{-1}$, a level associated with loss of IQ and a calculated corresponding loss of productivity equivalent to 8.7 billion dollars annually (Trasande, Landrigan, and Schecter 2005). Windam et al. (2006) reported an association between ambient air Hg levels and autism prevalence.

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Prior to March 2000, vaccines were preserved with thimerosal (CDC 2000), which consists of 49.6% Hg and breaks down in the body to ethyl Hg (Burbacher et al. 2005). In 1991, the Hepatitis B vaccine was first recommended for universal administration to US newborns, with two subsequent immunizations also administered during infancy (CDC 1991). While animal studies found that methyl Hg and ethyl Hg reacted differently in infant monkeys (Burbacher et al. 2005), studies have not been able to conclusively identify the health effects of ethyl Hg in human babies. However, based upon an analysis of the Vaccine Adverse Events Reporting System (VAERS), Geier and Geier (2006) reported significantly increased odds ratios for autism, speech disorders, mental retardation, infantile spasms, and thinking abnormalities reported to VAERS following vaccination with the thimerosal-containing diphtheria, tetanus, pertussis (DTP) and Hemophilus influenza type b (Hib) vaccines compared to children vaccinated with the diphtheria–tetanus–pertussis–Hemophilus influenza type b (DTPH) vaccine, which contained half the amount of thimerosal. Of note, the American Academy of Pediatrics (AAP) determined that this study was flawed due to its reliance on VAERS data, which, as a passive surveillance system, is not intended for hypothesis proving (AAP 2003). Based on a review of research literature, DeStefano (2007) concluded that the scientific evidence does not support a causal association between thimerosal-containing vaccines and autism. Moreover, Thompson and colleagues (2007) conducted a study of 1047 children between the ages of 7 and 10 years in which they administered standardized tests which assessed neuropsychological outcomes, and determined exposure to mercury from thimerosal using immunization records and parental interview. Their study findings do not support a causal association between thimerosal-containing vaccines and neuropsychological deficits in children aged 7–10 years.

This study investigated the association between the Hepatitis B triple series vaccination in children age 1–9 years and developmental disability, proxied by parental report of early intervention or special education services (EIS) in the 1999–2000 National Health and Nutrition Examination Survey (NHANES). Adams, Dey, and Vickers (2007) reported that about 6% of US children received early intervention or special education services in 2005, and Boyle, Decoufle and Yearginn Allsopp (1994) found that 17% of children were reported to have ever had a developmental disability. While this study uses EIS as a proxy for developmental disability in general, but not specifically autism, autism merits consideration because it is a developmental disorder with recent notable impacts on EIS. The number of children receiving special education services for autism increased 500% from 1991/92 to 1998/99 (CDC 2007b).

Vaccination with the Hepatitis B triple series vaccine during the time period vaccines were manufactured with thimerosal exposed newborns and infants to ethyl Hg (CDC 2000). By using NHANES 1999–2000 data for children age 1–9 years of age, children who were candidates for the thimerosal-containing triple series Hepatitis B vaccine were included in the study sample. The eldest children who received the triple series Hepatitis B vaccine would have been vaccinated during 1991, the first year that the thimerosal-containing vaccine was recommended for newborns (CDC 1991), while the youngest children would have been vaccinated during 1999, the last full year of known access to only thimerosal-containing vaccines (CDC 2000).

Methods

The study sample data set was obtained from the National Health and Nutrition Examination Survey (NHANES) 1999–2000 data set, which included a total of 9965

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participants – both adults and children. NHANES is a cross-sectional, random household survey of the civilian population based on a complex probability sampling design. The survey is a continuous program of the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC). NHANES provides information about the distribution of health problems and risk factors that contribute to poor health outcomes. In addition to conducting interviews of almost 10,000 persons per year, the survey examines a nationally representative sample of about 5000 persons each year. The sample for the survey is selected to represent the US population of all ages. African-Americans and Mexican-Americans are over-sampled to enable accurate estimates. Epidemiologists and health science researchers use NHANES data to generate findings that provide guidance for public health policy development and health program design. NHANES data provide researchers with important clues to the causes of disease (CDC 2004a).

Vaccination with the triple Hepatitis B vaccine was indicated by parental report during NHANES interview. The question about Hepatitis B vaccination was the only vaccination question asked of all ages included in this study's samples. The interview question and pertinent accompanying statement read, ''Has the survey participant ever received the 3-dose series of the hepatitis B vaccine? This vaccine is given in three separate doses and has been recommended for all newborn infants since 1991.'' Answer choices included the following: ''Yes, all 3 doses''; ''Less than 3 doses''; ''No doses''; ''Refused''; ''Don't know''. ''Less than 3 doses'' or ''No doses'' were coded ''0'' and ''Refused'' or ''Don't know'' were coded as missing data. Only the answer ''Yes, all 3 doses'' was coded ''1''.

A total of 1824 observations included (1) children aged 1–9 years of age, and (2) with parents who answered either ''yes'' or ''no'' to the survey question, ''Does your child receive Special Education or Early Intervention Services?'' (Responses of ''Refused'' or ''Don't know'' were coded as missing values). Statistical analysis was conducted using SAS version 9.1 software (© 2001/02). NHANES 2 year interview weights were used (except for *t*-test mean calculations for lab values, i.e., blood lead and Hg, where MEC weights were used). According to NHANES Analytic Guidelines, MEC weights should be used for any analyses that use one or more variables from the mobile examination component, which includes laboratory testing. Otherwise, interview weights should be used. The National Center for Health Statistics (NCHS) recommends the use of the Taylor Series Linearization methods for accurate estimates of sampling error. In accordance with the NCHS' and CDC's recommendations for complex survey methods (CDC 2007a), SAS callable SUDAAN was utilized to conduct Taylor Linearization procedures for calculation of the following statistical analyses, with the statistical adjustments for sampling error incorporated into the softwares' statistical procedures: *t*-tests and *p*-values for difference between means; adjusted Rao–Scott chi square test with *F*-adjusted *p*-values for difference between proportions. The NHANES web tutorial (CDC 2007a) explains that because NHANES data is characterized by small covariance, the assumption of small covariance has been incorporated into the statistical macro provided for download to conduct the *t*-test procedure. Logistic regression was also conducted using Taylor Linearization to quantify the association between Hepatitis B triple series vaccination and EIS. Sudaan (SAS callable version 9.0.1, © 2005) was utilized to calculate *p*-values for the Satterthwaite adjusted *F*-statistic generated by logistic regression. Logistic regression analysis was conducted utilizing a backwards selection procedure for significant covariates with maximum percent concordance between predicted probabilities and observed responses. Backwards selection entailed the input of all covariates for the first attempt at logistic regression, then omitting covariates with statistically insignificant coefficients on

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successive attempts. The SAS procedure, "Association of Predicted Probabilities and Observed Responses" is intended to provide a measurement of the explanatory power of the model. This procedure analyzes pairs of observations with different outcomes in order to determine whether the unit with a greater computed probability of the outcome is the one that actually experienced that outcome. Then, this pair is labeled "Concordant". Otherwise, the pair is labeled "Discordant". If both units share the same probability, the pair is labeled "Tied". The convergence criterion was satisfied for each model presented in this study, and global chi square statistics were significant, thus providing no indication to question the validity of model fit. In addition, the relative fit of alternative models was compared using the Akaike Information Criterion (AIC) and the Schwartz Criterion (SC) in order to select the better-fitting model.

Results

Findings, unadjusted for confounders

Table 1 describes the distribution of demographic characteristics, and Table 2 describes the distribution of environmental and health characteristics for the study population. Children who received early intervention or special education (EIS) comprised 5% of sample. This finding approximates the CDC's finding that about 6% of all US children received EIS in 2005 (Adams, Dey, and Vickers 2007).

Unadjusted statistically significant differences between EIS versus non-EIS total sample group means or proportions were found for these variables:

Age: The EIS mean = 5.8 years, and the non-EIS mean = 5 years (Table 1). Health status (1 = excellent to 5 = poor): The EIS mean = 2.19, and the non-EIS mean = 1.71 (Table 2). Percent with history of NICU (Neonatal Intensive Care Unit) stay: 28% of

Table 1. Demographic Characteristics, NHANES 1999/2000, children aged 1–9 years.

	Total Sample				Males only				Females only			
	EIS ($n=85$)		Non-EIS ($n=1739$)		EIS ($n=58$)		Non-EIS ($n=912$)		EIS ($n=27$)		Non-EIS ($n=827$)	
Variable	#	%	#	%	#	%	#	%	#	%	#	%
Male	58	68	912	52								
	{adj chi$^2=4.96$; F-adj $p=0.04$}											
Mean age (years)	5.8		5.0		5.6		4.9		6.4		5.1	
95% CI:	(5.2, 6.5)		(4.8, 5.2)		(5.0, 6.3)		(4.75, 5.1)		(5.51, 7.31)		(4.88, 5.39)	
	{$t=-3.2$; $p=0.0064$}				{$t=-2.25$; $p=0.04$}				{$t=-3.1$; $p=0.008$}			
White	24	28	431	25	16	28	223	24	8	30	208	25
Mean family Income Category 1 = \$0–4,999 6 = \$25,000–34,999 11 = \$75,000+)	6.1 ($n=79$)		6.6 ($n=1477$)		6.3 ($n=55$)		6.4 ($n=775$)		5.2 ($n=24$)		6.8 ($n=702$)	
Below poverty Index ratio	54 ($n=79$)	68	943 ($n=1477$)	64	41 ($n=55$)	75	479 ($n=755$)	62	13 ($n=24$)	54	464 ($n=702$)	66

Note: 95% CI's, t-statistics, adj chi^2, and p-values presented when significant at $\alpha=0.05$.

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Table 2. Health and environmental characteristics, NHANES 1999/2000, children age 1–9 years.

	Total sample				Males only				Females only			
	EIS ($n=85$)		Non-EIS ($n=1739$)		EIS ($n=58$)		Non-EIS ($n=912$)		EIS ($n=27$)		Non-EIS ($n=827$)	
Variable	#	%	#	%	#	%	#	%	#	%	#	%
Hepatitis B vaccinated, Triple series	58 ($n=78$)	74	1191 ($n=1616$)	74%	46 ($n=53$)	87	632 ($n=853$) {adj chi$^2=15.85$; F-adj $p=0.001$}	74	12 ($n=25$)	48	559 ($n=763$) {adj chi$^2=10.94$; F-adj $p=0.005$}	73
History of NICU stay	23 ($n=83$) {adj chi$^2=54.07$; F-adj $p<0.0001$}	28	185 ($n=1734$)	11	18 ($n=56$) {adj chi$^2=50.27$; F-adj $p<0.0001$}	32	89 ($n=908$)	10	5	19%	96 ($n=826$)	12
Ear infection 3 or more past year	12 ($n=84$)	14	228 ($n=1737$)	13	11 ($n=57$)	19	142 ($n=911$)	16	1	4	86 ($n=826$)	10
Crawl, walk, run, play limit (Devlimit)	12 {adj chi$^2=25.20$; F-adj $p=0.0002$}	14	19	1	7 {adj chi$^2=6.91$; F-adj $p=0.02$}	12	14	1.5	5 {adj chi$^2=50.86$; F-adj $p=0.001$}	19	5	0.6
Hospitalized over past Year	14 {adj chi$^2=11.71$; F-adj $p=.004$}	16	97 ($n=1736$)	6	9 {adj chi$^2=4.6$; F-adj $p=0.05$}	16	57 ($n=911$)	6	5 {adj chi$^2=5.13$; F-adj $p=0.04$}	19	40 ($n=825$)	5
Health status 1 = excellent 5 = poor 95% CI:	2.19 (1.84, 2.54) {$t=-3.41$; $p=0.004$}		1.71 (1.60, 1.81)		2.2 (1.82, 2.59) {$t=-2.82$; $p=0.01$}		1.77 (1.63, 1.91)		2.17 (1.76, 2.58) {$t=-2.81$; $p=0.01$}		1.64 (1.54, 1.74)	
Live with smoker	17	20	299 ($n=1704$)	18	13	22	152 ($n=897$)	17	4	15	147 ($n=807$)	18
Used pesticides last month	26	31	414 ($n=1689$)	25	18	31	212 ($n=889$)	24	8	30	202 ($n=800$)	25
Mean blood lead ($\mu g\,dL^{-1}$)	2.23 ($n=67$)		2.37 ($n=1242$)		2.03 ($n=49$)		2.3 ($n=661$)		2.84 ($n=18$)		2.45 ($n=581$)	

Note: 95% CI's, t-statistics, adj chi^2 and p-values presented when significant at $\alpha=0.05$.

Table 3. Age 1–9 years: Logistic regression on EIS, model for males only ($n = 900$*) – association of predicted probabilities and observed responses: percent concordant: 72.3; percent discordant: 26.3; percent tied: 1.4.

Variable	OR	Scatterthwaite Adj. F p-value	95% CI
HepB3	8.63	0.0003	{3.24, 22.98}
NICU	4.71	0.0005	{2.25, 9.87}
Age, years	1.19	0.0007	{1.09, 1.29}
Health status	1.50	0.0201	{1.08, 2.09}

Note: *A total of 70 observations were deleted due to missing values for one or more explanatory variables.

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the EIS group and 11% of the non-EIS group (Table 2). While this difference in proportions was statistically significant for the total sample and male subset, there was not a significant difference between the proportions of girls with a history of NICU stay in the EIS versus non-EIS group. Percent with developmental limitation in crawling, walking running or playing, per parents' report: The difference between proportions was significant (EIS = 14%; non-EIS = 1%) (Table 2). Gender: There were a greater proportion of males comprising the EIS group (68%; $n = 58$ of 85) compared to the proportion of males comprising the non-EIS group (52%; 912 of 1739), and this difference in proportions was statistically significant (Table 1). Hepatitis B triple series vaccination: Seven out of 228 (3%) boys who were not vaccinated were in EIS, whereas 46 of 678 (7%) vaccinated boys were in EIS (Table 2). On the other hand, among girls, 13 of 217 (6%) who were not vaccinated were in EIS, but only 12 out of 571 (2%) vaccinated girls were in EIS (Table 2). To take this divergent effect between boys and girls of vaccination upon EIS outcome into account, separate analyses were conducted for boys and girls.

Findings adjusted for confounders

Table 3 shows logistic regression model results for boys. The odds of receiving EIS were 8.63 times as great for vaccinated boys than unvaccinated boys. Thus, there is statistically significant evidence to suggest that the US male population aged 1–9 years who were vaccinated with the triple series Hepatitis B vaccine prior to the availability of thimerosal-free vaccines have significantly greater odds of receiving EIS, adjusting for history of NICU stay, age, and health status.

Table 4 shows logistic regression results for a separate model for girls aged 1–9 years. NICU stay was not a significant covariate in the model for girls as was the case in the model for boys. Vaccination was a significant covariate for girls aged 1–9, with an inverse relationship to EIS. In contrast to boys, girls who were vaccinated had 73% lower odds for EIS compared to unvaccinated girls. The ORs for age and health status for girls are similar to those for boys.

Discussion

This study found statistically significant evidence to suggest that boys vaccinated with the triple Hepatitis B vaccine, during the time period in which vaccines were manufactured with thimerosal, were at significantly greater odds to receive EIS than were

Table 4. Age 1–9 years: Logistic regression on EIS, model for females, only ($n = 788$*) – association of predicted probabilities and observed responses: percent concordant: 72.4; percent discordant: 24.5; percent tied: 3.1.

Variable	OR	Scatterthwaite Adj. F p-value	95% Wald CI
HepB3	0.27	0.0125	{0.10, 0.72}
Age, years	1.25	0.0168	{1.05, 1.49}
Health status	1.53	0.0410	{1.02, 2.29}

Note: *A total of 66 observations were deleted due to missing values for one or more explanatory variables.

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unvaccinated boys. Boys were also at greater odds to receive EIS than were both vaccinated and unvaccinated girls. The finding of a significantly greater proportion of boys with developmental disability is consistent with reports in the literature (Bailey et al. 2004; Montes and Halterman 2006). However, the association between vaccination with the triple series Hepatitis B vaccination and receiving EIS is a new finding, and warrants discussion.

An FDA study (Ball, Ball, and Pratt 2001), found that some infants may have been exposed to cumulative levels of ethyl Hg during the first 6 months of life that exceed EPA recommended limits. Since thimerosal removal from Hepatitis B vaccines began mid-1999 in United States, it is possible that children included in this study could have sustained infant exposure beyond EPA recommendations. According to the CDC (2000), it was not until March of 2000 that all US children had access to hepatitis B vaccines that were free of thimerosal, a preservative with ethyl Hg as an active ingredient. This represents a greater than 96% reduction from the 12.5 mcg in the previous SmithKline Beecham Biologicals (SKBB) vaccine (CDC 2000). Thus, vaccination with Hepatitis B vaccine triple series for the children in this study sample indicates thimerosal exposure.

James et al. (2005) found an association between thimerosal-induced cytotoxicity and depletion of glutathione in human brain cells. Additional studies reported an association between lower glutathione levels and male gender (Lavoie and Chessex 1997; Rush and Sandiford 2003). Thus, it is plausible that differences in glutathione levels might contribute to the divergent effects between boys and girls of vaccination with thimerosal-containing hepatitis B upon the likelihood of developmental disability. However, this hypothesis has not been scientifically validated in the pediatric population with neurodevelopmental disorders, and there may be additional unmeasured influences upon these gender disparities. For example, the inherent immunizing properties of the Hepatitis B vaccine may interact with other influences to contribute to the gender disparity. The inverse association in girls between triple Hepatitis B vaccination and neurodevelopmental disability may be indicative of the intended protective effect for susceptible girls. Specifically, certain high risk subgroups, i.e., girls born into families with Hepatitis B virus carriers or to Hepatitis B antigen positive mothers, would be at risk for infection (CDC 1991). It is plausible that girls within these high risk subgroups would exhibit an inverse relationship between Hepatitis B triple series vaccination and neurodevelopmental disorders. Those vaccinated, and thus protected from chronic Hepatitis B illness, might be less likely to require and qualify for EIS compared to unvaccinated girls, especially if they are not susceptible to the possible adverse effects of ethyl Hg exposure from the thimerosal in those vaccines. Just as

Hepatitis B immunization stimulates protection against the virus, might the immunization process, itself, especially when administered to male neonates of undetermined susceptibility, stimulate morbidity? This study does not answer that question, nor the question of why boys were not similarly protected by vaccination.

The association between NICU stay for boys and developmental disability suggests a health risk susceptibility for boys that is consistent with findings reported by Vieux et al. (2006) regarding male gender as a predictor for NICU stay, as well as NICU prognosis (Effer et al. 2002; Wilson et al. 2000; Larroque et al. 2004; Synnes et al. 2006). Thus, NICU represents a proxy for pre-existing vulnerabilities such as low birth weight that are indications for admission to the hospital's intensive care unit for newborns. However, Lanphear et al. (2000) did not find a significant association between whether a child received care in the NICU and cognitive test performance. Moreover, Granjean et al. (1997) found an association between higher Hg levels and increased birth weight. According to Bailey et al. (2004), while for some families problems with labor and delivery may lead to early detection of disability, for most families with a child receiving EIS, the child was considered normal at birth by both parents and doctor.

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Might the NICU introduce additional risk factors? Vohr et al. (2004) concluded that there were large differences in outcomes among children discharged from the 12 different centers of the Neonatal Research Network of the National Institute of Child Health and Human Development, after adjustment for demographics and antenatal interventions. Donadieu et al. (2006) contrasted French CT scan utilization in the NICU with that of United States: CT scans were utilized in less than 1% of the French patients in Donadieu's study and in 12% of United States infants. These researchers noted that a single CT scan of the head exposes the premature neonate to more than 10 times the median effective dose resulting from all standard radiographs in a given infant, and combined CT scans of the head and abdomen deliver approximately 30 times this dose. Rodier (2005) identified ionizing radiation, as well as methyl Hg, as environmental agents with the property of destroying neurons as they are born, and the ability to interfere with brain development beyond the gestational period. Additional research is warranted to identify variations in NICU practice patterns associated with adverse developmental outcomes that might provide opportunities for quality of care improvements.

The significantly positive association that age has with EIS is supported by the literature. According to Bailey et al. (2004), pediatricians are more likely to identify and refer children older than 3 years of age and children with more severe disabilities for special services. These researchers identified the need for children's physicians to incorporate developmental screening into existing medical surveillance efforts. Their study also reported that EIS are provided to children with a developmental delay (62%), a diagnosed condition with a high probability of resulting delay (22%), and one or more risk factors (17%), e.g., low birth weight. It is plausible that parents of children with a diagnosed condition are more likely to report health status as less than optimal, thus accounting for the significance of this adjusted factor. As discussed previously, a history of NICU stay provided a proxy for a risk factor for developmental delay, yet raised questions about how variations in practice patterns might adversely affect developmental outcomes.

There may be additional influences not measured by this study, such as childhood exposures to other immunizations, whether an infant was first vaccinated at birth or later, as well as non-vaccine-related influences. A retrospective case-control study with larger sample size might yield more information to ascertain the extent to which access, genetics

or cultural factors such as language barriers, as well as the factors previously discussed, might influence which subsets of children have specific developmental disabilities and, consequently, receive early intervention or special education services.

To address other Hg exposures a supplemental analysis examined the relationship between total blood Hg levels, which predominantly measure methyl Hg (Mahaffey 2005), and EIS in children aged 1–5 years; the NHANES subset for which total blood Hg levels were measured. Results showed a statistically significant inverse relationship between total blood Hg levels and receipt of EIS. This finding might be counterintuitive in that one would expect increased total blood Hg levels to be associated with an enhanced chance of developmental disability. Of note, due to sample size limitations, caution is warranted in drawing conclusions regarding the inverse relationship between total blood Hg and developmental disability in the general population of children aged 1–5 years. However, consideration of what this inverse relationship might mean is merited by (1) this study's findings of a statistically significant inverse relationship in the NHANES sample children aged 1–5 years and (2) statistically significant difference in blood Hg means across gender and vaccination subgroups by EIS, as well as (3) emerging scientific findings. Regarding the latter, a study of monkeys exposed to either oral methyl Hg or intramuscular injections of thimerosal found a pattern of decline in total blood Hg that occurred over time only after intramuscular injections of thimerosal (Burbacher et al. 2005). Burbacher et al. also reported that the average brain-to-blood total Hg concentration ratio was higher for the thimerosal-exposed monkeys, and that a higher % of the total Hg in the brain was in the form of inorganic Hg. The brains of the thimerosal-exposed monkeys had absolute inorganic Hg concentrations about twice that of the MeHg-exposed monkeys. Could the lower total blood Hg levels in the NHANES EIS children be due to a similar process as experienced by Burbacher and colleagues' monkeys – a decrease in total blood Hg after thimerosal-containing injections of Hg? Further research is warranted to determine the extent to which the inverse relationship between total blood Hg levels and developmental disability in humans might be associated with (1) the biotransformation and distribution of thimerosal as inorganic Hg into tissue sites over time, (2) subsequent decreased total blood Hg, (3) and inorganic Hg accumulation in the brain.

Another question raised by the supplemental analysis is that of access. There were 53 children with total blood Hg levels that fell above the CDC-reported NHANES 95th percentile ($\geq 2.21\,\mu g\,L^{-1}$) for children aged 1–5, years, none of whom received EIS. Black and Mexican-American children comprised the majority of this group (64%). The proportion of white children aged 1–5 years that comprised the EIS group ($n = 11$ of 21) (42%) was significantly greater ($p = 0.03$) than the proportion of white children in the non-EIS group ($n = 162$ of 678) (24%), although this significance did not hold in multivariable analysis with MEC weights. Of note, this study's subset of the NHANES dataset included children with total blood Hg levels up through $10.4\,\mu g\,L^{-1}$, whereas the CDC-reported NHANES data reported total blood Hg levels up though $3.66\,\mu g\,L^{-1}$, and indicated that total blood Hg $\geq 5.8\,\mu g\,L^{-1}$ mostly reflected methyl Hg exposure (CDC 2004b). Bailey et al. (2004) reported that minority families were more likely to report dissatisfaction with their EIS experiences, particularly with regard to finding out about and accessing EIS. The lack of statistical significance for the difference in proportions of white children in EIS compared to non-EIS in the study of children aged 1–9 suggests that access may be less of a problem for older than it is younger minority children. Again, a case control study might provide additional insights.

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Conclusion

This study contributes to answering an unresolved question of the Institute of Medicine's (IOM's) 2001 Immunization Safety Review (IOM 2001) as well as the same question not addressed by the IOM's 2004 review (IOM 2004), namely, whether there is an association between thimerosal-containing vaccines and neurodevelopmental disorders, in general (McCormick 2004). As did the IOM in their 2004 study, Parker et al. (2004) more specifically concluded that studies did not demonstrate a link between thimerosal-containing vaccines and autism, and cited supporting evidence from cohort studies conducted in the United Kingdom (UK), Denmark, and Sweden. However, unlike the United States, past (CDC 1991; CDC 1998) and present (CDC 2006b), these countries' vaccination schedules do not recommend universal vaccination of newborns with the Hepatitis B vaccine (ECDC 2006a, b). Sweden recommends that Hepatitis B be given at birth only to infants of mothers positive for Hepatitis B (ECDC 2006c). In 1998, the UK vaccinated newborns with the Hepatitis B vaccine, but again, only to infants of mothers positive for Hepatitis B (Ovetchkine and Reinert 1998). Thus, it is reasonable to question the applicability of findings from the UK, Denmark and Sweden studies to the US immunized pediatric population.

This study found statistically significant evidence of an association between the thimerosal-containing Hepatitis B triple series vaccine and EIS, a proxy for developmental disability. Although Hepatitis B vaccines administered to children in United States no longer contain thimerosal, those administered to children in developing countries without the means to prepare single dose vials do contain thimerosal (WHO 2004, 2006). Moreover, influenza vaccines distributed in United States do contain thimerosal (CDC 2006a). Thus, children's previous and potential future exposure to thimerosal remains an important public health concern. Future research should (1) examine how public health efforts might better identify harmful exposures and susceptible children; (2) institute effective protective and quality improvement measures; (3) conduct cost-benefit analyses that more comprehensively consider the costs and more accurately assess the risks for the US population of children, especially subpopulations of susceptible children.

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