Neurodevelopmental Disorders after Thimerosal-Containing Vaccines: A Brief Communication

MARK R. GEIER[1] AND DAVID A. GEIER
The Genetic Centers of America, Silver Spring, Maryland 20905

We were initially highly skeptical that differences in the concentrations of thimerosal in vaccines would have any effect on the incidence rate of neurodevelopmental disorders after childhood immunization. This study presents the first epidemiologic evidence, based upon tens of millions of doses of vaccine administered in the United States, that associates increasing thimerosal from vaccines with neurodevelopmental disorders. Specifically, an analysis of the Vaccine Adverse Events Reporting System (VAERS) database showed statistical increases in the incidence rate of autism (relative risk [RR] = 6.0), mental retardation (RR = 6.1), and speech disorders (RR = 2.2) after thimerosal-containing diphtheria, tetanus, and acellular pertussis (DTaP) vaccines in comparison with thimerosal-free DTaP vaccines. The male/female ratio indicated that autism (17) and speech disorders (2.3) were reported more in males than females after thimerosal-containing DTaP vaccines, whereas mental retardation (1.2) was more evenly reported among male and female vaccine recipients. Controls were employed to determine if biases were present in the data, but none were found. It was determined that overall adverse reactions were reported in similar-aged populations after thimerosal-containing DTaP (2.4 ± 3.2 years old) and thimerosal-free DTaP (2.1 ± 2.8 years old) vaccinations. Acute control adverse reactions such as deaths (RR = 1.0), vasculitis (RR = 1.2), seizures (RR = 1.6), ED visits (RR = 1.4), total adverse reactions (RR = 1.4), and gastroenteritis (RR = 1.1) were reported similarly after thimerosal-containing and thimerosal-free DTaP vaccines. An association between neurodevelopmental disorders and thimerosal-containing DTaP vaccines was found, but additional studies should be conducted to confirm and extend this study. Exp Biol Med 228:660–664, 2003

Key words: autism; neurodevelopmental disorders; thimerosal; VAERS

In recent years, thimerosal, an organic mercury compound that is metabolized to ethylmercury and thiosalicylate and has been present since the 1930s as a preservative in some vaccines and pharmaceutical products to prevent bacterial and fungal contamination, has come under scrutiny. It was determined by the U.S. Food and Drug Administration (FDA) in 1999 under the recommended childhood immunization schedule that infants might be exposed to cumulative doses of ethylmercury that exceed some federal safety guidelines established for exposure to methylmercury, another form of organic mercury (1).

The hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders is not established and rests on indirect and incomplete information, primarily from analogies with methylmercury and levels of maximum mercury exposure from vaccines given in children. The hypothesis is biologically possible, but the possible relationship between thimerosal from vaccines and neurodevelopmental disorders of autism, attention deficit/hyperactivity disorder (ADHD), and speech or language delay remains seriously suspect. As of the present, there are no peer-reviewed epidemiological studies in the scientific literature examining the potential association between thimerosal-containing vaccines and neurodevelopmental disorders. Here, we show the first epidemiologic evidence, based upon tens of millions of doses of vaccine administered in the United States, that associates increasing thimerosal from vaccines with neurodevelopmental disorders.

Materials and Methods

In this study, the incidence of neurodevelopmental disorders in a comparative examination between thimerosal-containing diphtheria, tetanus, and acellular pertussis (DTaP) and thimerosal-free DTaP vaccines based upon analysis of the Vaccine Adverse Events Reporting System (VAERS) database was undertaken using Microsoft Access. The VAERS database is an epidemiologic database maintained by the Centers for Disease Control and Prevention (CDC) since 1990. All adverse reactions are to be reported to the VAERS database as required by U.S. law. The CDC requires written and telephonic confirmation of serious adverse reactions and follows up on these patients 1 year later.

This was independent research conducted by Mark R. Geier and David A. Geier. No funding was received.
[1] To whom requests for reprints should be addressed at The Genetic Centers of America, 14 Redgate Court, Silver Spring, MD 20905. E-mail: mgeier@erols.com

Received August 14, 2002.
Accepted December 16, 2002.

1535-3702/03/2286-0660$15.00

The FDA inquires into deaths reported to the VAERS database by contacting the patient's healthcare provider and physician. The FDA also continually monitors reports to the VAERS database to determine whether any vaccine or vaccine lot has a higher than expected incidence rate of events. The VAERS Working Group of the CDC, the FDA, and we analyze and publish epidemiologic studies based upon analysis of the VAERS database (2–7).

The neurodevelopmental disorders we analyzed in this study were autism, mental retardation, and speech disorders. These categories of adverse reactions were based upon descriptions of adverse reactions by those reporting them and by defined fields contained in the VAERS database. We determined the number of male and female reaction reports, the mean and standard deviation of age in years, and the mean and standard deviation of onset in days in those experiencing neurodevelopmental disorders after thimerosal-containing and thimerosal-free DTaP vaccines.

We hypothesize that DTaP vaccines, whether containing thimerosal or not, should have a similar incidence rate of adverse reactions. We analyzed DTaP administered by manufacturer so that we could compare thimerosal-containing DTaP vaccines administered from 1992 through 2000 against thimerosal-free DTaP vaccines administered from 1997 through 2000. We used denominators obtained from the Biological Surveillance Summaries of the CDC to determine the number of doses of each manufacturer administered and, based upon this information, we were able to calculate incidence rates of adverse reactions after vaccination. We are precluded from giving incidence rates, the number of doses administered, or types of DTaP vaccine because this information could reveal the identities of the manufacturers and the CDC claims this information is proprietary between them and the manufacturers (7).

We compared the incidence of adverse reactions after thimerosal-containing DTaP vaccines against thimerosal-free DTaP vaccines to determine relative risk (RR), attributable risk, percent association, and statistical significance. The RR value was obtained by dividing the incidence rate of the adverse reaction after thimerosal-containing DTaP vaccines by the incidence rate of the adverse reaction after thimerosal-free DTaP vaccines ([adverse reaction incidence after thimerosal-containing DTaP vaccines]/[incidence rate after thimerosal-free DTaP vaccines] = RR). The attributable risk value was determined by subtracting 1 from the RR value (RR – 1 = attributable risk). Percent association was calculated by dividing the RR value by the RR value plus 1 and multiplying this computed value by 100 ([RR /{RR + 1}] × 100). Statistical significance was determined by using Fisher's Exact Test. Our null hypothesis was that there would be a statistically similar incidence rate of adverse reactions after thimerosal-containing and thimerosal-free DTaP vaccines. We assumed that the incidence of adverse reactions after thimerosal-free DTaP vaccines was the expected rate and the incidence of adverse reactions after thimerosal-containing DTaP vaccines was the observed rate. The statistical package contained in Correl's Quattro Pro was used, and a P value of 0.05 was considered significant.

In addition, to determine if there were potential biases in our data, we used several controls. We examined the overall mean and standard deviation of the ages of thimerosal-containing and thimerosal-free DTaP vaccine adverse reactions reported to the VAERS to ensure that both types of vaccines were administered to similar-aged populations because different-aged populations may have a difference in the incidence of neurodevelopmental disorders. The mean ages of those reporting neurodevelopmental disorders after vaccination may also help to determine whether successive doses of thimerosal-containing DTaP vaccines build up concentrations of thimerosal to toxic levels, resulting in neurodevelopmental disorders in vaccine recipients. The usual course of DTaP vaccine in children consists of primary immunizations administered at 2, 4, and 6 months, followed up by booster doses at 18 months and at 5 years. We also examined the incidence rate of acute adverse reactions reported to the VAERS database after thimerosal-containing and thimerosal-free DTaP vaccines, including deaths, seizures, vasculitis, emergency department (ED) visits, total reaction reports, and gastroenteritis. This control served several purposes. First, if differences in manufacturing processes, other than the presence of thimerosal were present, there is a reasonable probability that this might have a significant impact on the incidence rate of acute adverse reactions. Second, if biased increased reporting rates of adverse reactions were present for thimerosal-containing DTaP vaccines, this would be reflected in an increased incidence rate of acute adverse reactions after thimerosal-containing DTaP vaccines in comparison with thimerosal-free DTaP vaccines. The years examined in this study also help to preclude the possibility of reporting biases based upon popular media publicity of an association between thimerosal and neurodevelopmental disorders in recent years because thimerosal-containing DTaP vaccines were analyzed for much earlier years (1992–2000) than were thimerosal-free DTaP vaccines (1997–2000).

Results

We determined based upon our examination of the VAERS database that there were a total of 6575 adverse reaction reports after thimerosal-containing DTaP vaccines and 1516 adverse reaction reports after thimerosal-free DTaP vaccines reported to the VAERS database. We found that thimerosal-containing DTaP vaccines and thimerosal-free DTaP vaccines were administered to similar-aged populations. The mean and standard deviations of the ages were 2.4 ± 3.2 years old and 2.1 ± 2.8 years old, respectively. In Table I, we summarize the number of male and female reports, mean and standard deviation of age in years, and mean and standard deviation of onset in days of neurodevelopmental disorders observed after thimerosal-containing DTaP vaccines and thimerosal-free DTaP vac-

Table I. A Summary of Neurodevelopmental Disorders Reported after Thimerosal-Containing DTaP Vaccines and Thimerosal-Free DTaP Vaccines

Type of reaction (vaccine type)	Number of female reports	Number of male reports	Mean age (years)	Mean onset (days)
Autism (thimerosal)	1	17	1.7 ± 1.1	22 ± 43
Mental retardation (thimerosal)	17	20	1.4 ± 2.0	10 ± 15
Speech disorders (thimerosal)	8	18	2.9 ± 1.9	7.7 ± 15.4
Autism (thimerosal-free)	0	1	1.2	—
Mental retardation (thimerosal-free)	0	2	1.6 ± 0.4	15
Speech disorders (thimerosal-free)	1	3	3.4 ± 2.2	3.4 ± 5.9

Note. There were a total of 6575 adverse reaction reports after thimerosal-containing DTaP vaccines and 1516 adverse reaction reports after thimerosal-free DTaP vaccines reported to the VAERS database.

Table II. A Summary of the Incidence of Neurodevelopmental Disorders after Thimerosal-Containing DTaP Vaccines in Comparison with Thimerosal-Free DTaP Vaccines

Type of reaction	Relative risk	Attributable risk	Percent association	Statistical significance
Autism	6.0	5.0	86	$P < 0.05$
Mental retardation	6.1	5.1	86	$P < 0.002$
Speech disorders	2.2	1.2	69	$P < 0.05$

cines. Our data showed large male/female ratios in those children reported to have developed autism (17) and speech disorders (2.3) after vaccination with thimerosal-containing DTaP vaccines. However, the male/female ratio was significantly less appreciable in children reported to have developed mental retardation (1.2) after thimerosal-containing DTaP vaccines. The mean ages of children developing neurodevelopmental disorders after thimerosal-containing DTaP vaccines indicated that older children were primarily affected. In Table II, we summarize the RR, attributable risk, percent association, and statistical significance of neurodevelopmental disorders after thimerosal-containing DTaP vaccines in comparison with thimerosal-free DTaP vaccines. We found statistical increases in the incidence of autism, mental retardation, and speech disorders after thimerosal-containing DTaP vaccines in comparison with thimerosal-free DTaP vaccines. The RRs were greater than two for each type of neurodevelopmental disorder analyzed. In Table III, we summarize the RR, attributable risk, and percent association of the acute control adverse reactions that we analyzed after thimerosal-containing DTaP vaccines in comparison with thimerosal-free DTaP vaccines. We found a slight increase in the incidence of seizures, ED visits, and total reaction reports after thimerosal-containing DTaP vaccines in comparison with thimerosal-free DTaP vaccines. We also found that gastroenteritis, vasculitis, and death occurred at comparable incidence rates after thimerosal-containing DTaP vaccines in comparison with thimerosal-free DTaP vaccines.

Table III. A Summary of the Incidence of Acute Control Adverse Reactions after Thimerosal-Containing DTaP Vaccines in Comparison with Thimerosal-Free DTaP Vaccines

Type of reaction	Relative risk	Attributable risk	Percent association
Deaths	1.0	0.0	50
Vasculitis	1.2	0.2	54
Seizures	1.6	0.6	61
Emergency department visit	1.4	0.4	58
Total reaction reports	1.4	0.4	58
Gastroenteritis	1.1	0.1	52

Discussion

The results of our analysis were extremely surprising. We observed statistically significant increases in the incidence rate of neurodevelopmental disorders after thimerosal-containing DTaP vaccines in comparison with thimerosal-free DTaP vaccines. We observed that the overall mean age for adverse reactions reported after thimerosal-containing DTaP vaccines and thimerosal-free DTaP vaccines were similar. We found that there were similar incidence rates of acute adverse reactions after thimerosal-containing DTaP vaccines in comparison with thimerosal-free DTaP vaccines, indicating that potential differences in the manufacturing of DTaP vaccines analyzed outside of thimerosal concentrations or potential population reporting biases may have had a limited effect on the general reactivity profiles of the DTaP vaccines examined. We also observed, based upon the mean ages of those developing neurodevelopmental disorders after thimerosal-containing DTaP vaccines, that these reactions tended to occur in older children. This potentially may be explained by the toxic buildup of mercury from successive doses of thimerosal-containing DTaP vaccines.

A study performed by Magos *et al.* (8) in rats compared the effects of the administration of similar doses of ethylmercury and methylmercury. They found that higher concentrations of inorganic mercury in the kidneys and brain

were present in ethylmercury-treated rats compared with methylmercury-treated rats. They determined that there was little difference in the neurotoxicites of ethylmercury- and methylmercury-treated rats when effects on the dorsal root ganglia or coordination disorders were compared. The authors also determined that microgram quantities of organic mercury alone in the rat brain were in some cases associated with neurotoxicity, indicating that the presence of inorganic mercury was not necessary for neurotoxicity.

The long mean onset times observed in this study for neurodevelopmental disorders after thimerosal-containing DTaP vaccines from about 8 to 22 days may be indicative of the decomposition rates of thimerosal. It has been shown by Tan and Parkin (9) that thimerosal *in vitro* decomposes in the presence of sodium chloride at approximately 4.3% per day. This means that during the 8- to 22-day temporal period of onset observed in this study for neurodevelopmental disorders, approximately 34.4% to 94.6% of the thimerosal had decomposed into its derivatives. The authors also report that it would be expected that the ethylmercury would display similar complexion and chemical characteristics to methylmercury. Therefore, considering that sodium chloride is integrally involved in the functioning of the nervous system and kidneys, is not potentially surprising that mercury accumulates in these organs, and in the brain, this accumulation manifests itself in the form of neurodevelopmental disorders in some children.

Bernard *et al.* (10) compared the similar biological abnormalities commonly found in autism and the corresponding pathologies arising from mercury exposure. Distinct similarities were found between autism and mercury exposure in their effects upon biochemistry, the immune system, the central nervous system structure, neurochemistry, and neurophysiology. The authors report that mercury toxicity shows great variability in its effects on the individual, so that at the same exposure level, some will be affected severely, whereas others will be asymptomatic. They provide the example of acrodynia, which arose in the early 20th century, resulting from the use of mercury teething powders, which afflicted only 1 in 500 to 1000 children given the same low dose. The authors conclude that due to the extensive parallels observed between autism and mercury exposure from thimerosal present in currently used vaccines, the likelihood of a causal relationship is great.

We were initially highly skeptical that differences in the concentrations of thimerosal in vaccines would have any effect on the incidence rate of neurodevelopmental disorders after childhood immunization. However, the results of our analysis suggest that children who received an additional 75 to 100 μg of thimerosal from thimerosal-containing DTaP vaccines may have an associated increase in neurodevelopmental disorders based upon analysis of the VAERS database. Despite showing similarities in the ages of vaccine recipients between thimerosal-containing and thimerosal-free DTaP vaccines, similarities in the incidence rate of acute control reactions after thimerosal-containing and thimerosal-free DTaP vaccines and a increased age of onset of neurodevelopmental disorders in those receiving thimerosal-containing DTaP vaccines, there may be factors other than thimerosal concentrations that potentially lead to differences in the incidence rates of neurodevelopmental disorders observed in this study.

The relative infrequency of neurodevelopmental disorders observed after thimerosal-containing vaccination may in part reflect the fact that the association between thimerosal and neurodevelopmental disorders was not known among those physicians and therefore was underreported to the VAERS database, and, in addition, may indicate that other factors than just thimerosal may effect the incidence rate of neurodevelopmental disorders. These factors may include the possibility that mercury is cleared at different rates, susceptibility among children may change with age or developmental status, and there may be variation in genetic composition among different children. It is possible that these factors may work independently, or more probably, may work synergistically to produce a neurodevelopmental response in a susceptible child.

It has also been hypothesized by Wakefield *et al.* (11, 12) that there may be a specific viral pathogenic mechanism for a new variant of inflammatory bowel disease among children with developmental disorders. They have recently shown a statistical increase in the detection of measles viral genes in gastrointestinal tissues in children with neurodevelopmental conditions in comparison with a control population (12). Krause *et al.* (13) have reported that various immune system abnormalities, including autoimmunity and defects in different subsets of immune cells, have been reported in children with autistic disorders, suggesting that immune factors may also play a role in the development of autism.

In light of the fact that many additional factors may play a potential role in the development of neurodevelopmental disorders in children, the observed statistical increase in neurodevelopmental disorders in children receiving thimerosal-containing DTaP vaccines may reflect a synergistic effect of multiple factors in a susceptible child. We recommend that additional studies be conducted to confirm and extend the results of this study. We suggest that even though there may be other factors related to the incidence of neurodevelopmental disorders in children, manufacturers should consider removing thimerosal from vaccines either by using another preservative or by producing single dose vials so that no preservative is necessary, for it is better to be safe than sorry. Despite these negative findings concerning the preservative thimerosal, vaccination has been and will continue to be an invaluable asset to control potentially debilitating and deadly infectious diseases.

1. Ball LK, Ball R, Pratt RD. An assessment of thimerosal use in childhood vaccines. Pediatrics **107**:1147–1154, 2001.
2. Geier MR, Geier DA. Hepatitis B vaccination safety. Ann Pharmacother **36**:370–374, 2002.

3. Geier DA, Geier MR. Rubella vaccine and arthritic adverse reactions: an analysis of the Vaccine Adverse Events Reporting System (VAERS) database from 1991 through 1998. Clin Exp Rheumatol **19:**724–726, 2001.
4. Geier DA, Geier MR. Anthrax vaccination and joint related adverse reactions in light of biological warfare scenarios. Clin Exp Rheumatol **20:**217–220, 2002.
5. Geier DA, Geier MR. An analysis of the occurrence of convulsions and death after childhood vaccination. Toxicol MechanismsMethods **12:**71–78, 2002.
6. Geier DA, Geier MR. Clinical implications of endotoxin concentrations in vaccines. Ann Pharmacother **36:**776–780, 2002.
7. Niu MT, Rhodes P, Salive M, Lively T, Davis DM, Black S, Shinefield H, Chen RT, Ellenberg SS. Comparative safety of two recombinant hepatitis B vaccines in children: data from the Vaccine Adverse Events Reporting System (VAERS) and Vaccine Safety Datalink (VSD). J Clin Epidemiol **51:**503–510, 1998.
8. Magos L, Brown AW, Sparrow S, Bailey E, Snowden RT, Skipp WR. The comparative toxicology of ethyl- and methylmercury. Arch Toxicol **57:**260–267, 1985.
9. Tan M, Parkin JE. Route of decomposition of thiomersal (thimerosal). Int J Pharm **208:**23–34, 2000.
10. Bernard S, Enayati A, Redwood L, Roger H, Binstock T. Autism: a novel form of mercury poising. Med Hypothesis **56:**462–471, 2001.
11. Wakefield AJ, Anthony A, Murch SH, Thomson M, Montgomery SM, Davies S, O'Leary JJ, Berelowitz M, Walker-Smith JA. Entercolitis in children with developmental disorders. Am J Gastroenterol **95:**2285–2295, 2000.
12. Uhlmann V, Martin CM, Sheils O, Pilkington L, Silva I, Killalea A, Murch SB, Walker-Smith J, Thomson M, Wakefield AJ, O'Leary JJ. Potential viral pathogenic mechanism for new variant inflammatory bowel disease. Mol Pathol **55:**84–90, 2002.
13. Krause I, He XS, Gershwin ME, Shoenfeld Y. Brief report: immune factors in autism: a critical review. J Autism Dev Disord **32:**337–345, 2002.