Early Downward Trends in Neurodevelopmental Disorders Following Removal of Thimerosal-Containing Vaccines

David A. Geier, B.A.
Mark R. Geier, M.D., Ph.D.

ABSTRACT

Contemporaneously with the epidemic rise in neurodevelopmental disorders (NDs), first observed in the United States during the 1990s, the childhood immunization schedule was expanded by the U.S. Centers for Disease Control and Prevention (CDC) to include several additional thimerosal-containing vaccines (TCVs). On July 7, 1999, a joint recommendation was made by the American Academy of Pediatrics (AAP) and the U.S. Public Health Service (PHS) to remove thimerosal from vaccines. A two-phase study was undertaken to evaluate trends in diagnosis of new NDs entered into the Vaccine Adverse Event Reporting System (VAERS) and the California Department of Developmental Services (CDDS) databases on a reporting quarter basis, from 1994 through 2005. Significant increasing trends in newly diagnosed NDs were observed in both databases 1994 through mid-2002. Significant decreasing trends in newly diagnosed NDs were observed in both databases from mid-2002 through 2005. The results indicate that the trends in newly diagnosed NDs correspond directly with the expansion and subsequent contraction of the cumulative mercury dose to which children were exposed from TCVs through the U.S. immunization schedule.

Background

In 2004, the Department of Health and Human Services and the American Academy of Pediatrics (AAP) issued an Autism A.L.A.R.M., stating that 1 in 166 children currently have an autistic disorder, and 1 in 6 children have a developmental and/or behavioral disorder. Autism, once rare, is now more prevalent than childhood cancer, diabetes, and Down syndrome.[1] Epidemic trends in neurodevelopmental disorders (NDs) were first observed in the United States during the 1990s,[1-8] and cannot be explained by immigration, changed diagnostic criteria, or improved identification.[1,6-8]

Autism is an ND characterized by impairments in social relatedness and communication, repetitive behaviors, and stereotypic abnormal movements.[1] While genetic factors are important in the pathogenesis of autistic disorders, a role for environmental factors has received considerable attention.

Exposure to mercury has previously been shown to cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with autistic disorders, and with similarities in neuroanatomy, neurotransmitters, and biochemistry.[9-12] Furthermore, recent research that codes children's communicative, social, affective, repetitive behaviors, and toy play from videotapes of the toddlers' first and second birthday parties demonstrates that the regression associated with autistic disorders clearly manifests between the ages of 12 and 24 months,[13] concurrent with the exposure to thimerosal-containing childhood vaccines (TCVs).

Thimerosal is an ethylmercury-containing compound (49.6% mercury by weight) that was historically added to many vaccines at the preservative level (0.005% to 0.01%). The U.S. Centers for Disease Control and Prevention (CDC), from the late 1980s through the 1990s, expanded the number of doses of TCVs to be administered to U.S. infants. To five doses of diptheria-tetanus-whole-cell-pertussis (DTP) vaccine were added three doses of hepatitis B (Hep b) vaccine and four of *Haemophilus influenzae* type b (Hib) vaccine. Additionally, the CDC began recommending three doses of influenza vaccine for certain infant populations. An infant who received all of these vaccines on schedule could have received as much as 200 micrograms (µg) of mercury during the first 6 months of life.[14]

In response to theoretical concerns about the cumulative doses of mercury from TCVs, the AAP and the U.S. Public Health Service (PHS) issued a joint statement on July 7, 1999, calling for the removal of thimerosal from all vaccines.[14] It has been estimated that the last thimerosal-containing Hep b, diphtheria-tetanus-acellular-pertussis (DTaP) and Hib vaccines were manufactured in 2000-2001 and expired at the end of 2002 (or early 2003).[14] Table 1 summarizes significant historical dates in the use of pediatric TCVs in the United States.

Considering all significant environmental exposures to mercury, such as through breast milk, TCVs represent almost 50% of the total mercury dose some infants received.[15] The 187.5 µg of mercury through TCVs plus the average of 164 µg from breast milk during the first 6 months exceeded the methylmercury safety guidelines established by the U.S. Environmental Protection Agency (EPA), Health Canada, the World Health Organization (WHO), the Agency for Toxic Substances Disease Registry (ATSDR), and the U.S. Food and Drug Administration (FDA).[15] With no additional exposure from any source, these doses also exceeded the methylmercury guidelines for the first year of life set by all of these agencies except the FDA.[15]

Despite its removal from many childhood vaccines, thimerosal is still routinely added to some formulations of influenza vaccine administered to U.S. infants, as well as to several other vaccines (e.g. tetanus-diphtheria and monovalent tetanus) administered to older children and adults. In 2004, the Institute of Medicine (IOM) of the U.S. National Academy of Sciences (NAS) retreated from the stated 1999 goal of the AAP and the PHS to remove thimerosal from U.S. vaccines as soon as possible.[16] Furthermore, many nations still add thimerosal to many of their pediatric vaccines, and WHO and several vaccine manufacturers still advocate the continued use of thimerosal in pediatric vaccines. As a result, assessing the safety of TCVs is a matter of significant importance.

Examinations of the Vaccine Adverse Event Reporting System (VAERS), the U.S. Department of Education, and the Vaccine Safety Datalink (VSD) databases showed significant links between exposure to TCVs and NDs.[17,2-3] Specifically, data from VAERS showed that additional doses of mercury from thimerosal-containing DTaP in comparison to thimerosal-free DTaP (administered in the late 1990s), and additional doses of thimerosal-containing DTP and Hib in comparison to thimerosal-

Table 1. Significant Dates Regarding the Use of Thimerosal in U.S. Pediatric Vaccines

Date	Significant Events
Middle 1980s	Thimerosal is present in virtually all whole-cell diphtheria-tetanus-whole-cell-pertussis (DTP) vaccines administered to children four times, starting at age 2 mon, during the first 18 mon of life (maximum of 25 µg Hg/dose). Maximum Hg exposure in 18 mon: 100 µg.
Late 1980s	Thimerosal-containing *Haemophilus influenzae* type b (Hib) vaccine is administered to children at age 18 mon (maximum of 25 µg Hg/dose). Maximum Hg exposure in 18 mon: 125 µg.
Early 1990s	Four doses of thimerosal-containing Hib are recommended within 18 months, starting at age 2 mon (maximum of 25 µg Hg/dose). Maximum Hg exposure in 18 mon: 200 µg.
Early 1990s	Three doses of thimerosal-containing hepatitis B (Hep b) vaccine are recommended within the first 6 mon, starting on the day of birth (maximum of 12.5 µg Hg/dose). Maximum Hg exposure in 18 mon: 237.5 µg.
Middle 1990s	Some DTP and Hib vaccines are combined to produce DTPH vaccine, which has only 25 µg of mercury per immunization, reducing mercury levels of exposure for some children, but is rapidly replaced by diphtheria-tetanus-acellular-pertussis (DTaP) vaccines beginning in 1996 (DTaP vaccine is almost exclusively produced separately from Hib vaccine).
1996-1997	GlaxoSmithKline introduces a new thimerosal-free DTaP vaccine (Infarix) that contains 2-phenoxethanol as a preservative. Aventis Pasteur introduces a new Hib vaccine (ActHIB) that contains no preservative.
Late 1990s	Three doses of thimerosal-containing influenza vaccine are increasingly recommended for administration to children during the first 18 mon, starting at age 6 mon (12.5 ìg Hg/dose). Maximum Hg exposure: 200 µg in first 6 mon and 275 µg in first 18 mon.
July 7, 1999	AAP and PHS request removal of thimerosal from all pediatric vaccines as rapidly as possible, and AAP suggests delaying Hep b vaccine until after age 6 mon for children born to hepatitis B negative mothers.
August 27, 1999**	Thimerosal-free Recombivax HB (Merck) is licensed by the FDA.
March 28, 2000	Thimerosal-free Engerix-B (GlaxoSmithKline) is licensed by the FDA.
March 7, 2001	Thimerosal-free Tripedia (Aventis Pasteur) is licensed by the FDA.
Late 2002/ Early 2003	CDC and FDA claim that the last remaining doses of thimerosal-containing DTaP, Hep b, or Hib vaccines are administered to U.S. children.

** Thimerosal-containing formulations continued to be distributed/administered following FDA licensing of thimerosal-free formulations.

free diphtheria-tetanus-pertussis-hemophilis b (DTPH) vaccines (administered in the early to mid-1990s), were associated with a significant 2- to 8-fold increase in risk of NDs, depending upon the symptoms or outcomes examined. The one other U.S. epidemiological study that has examined the relationship between TCVs and NDs, by Verstaeten et al. from the CDC, initially found a significant relationship between TCVs and some types of neurodevelopmental disorders (NDs), but upon examining a different dataset, it did not find a consistent effect.[2 4] The lead author concluded that this study could neither accept nor reject a causal relationship between TCVs and NDs.[2 5]

Now that a number of children have received reduced doses of mercury from TCVs for several years, the present rapid sampling study was undertaken to check for an effect on the occurrence of NDs. The first phase consisted of an evaluation of newly diagnosed NDs received by VAERS. The second phase examined whether the VAERS observations were consistent with trends in the new autism reports in the California Department of Developmental Services (CDDS).

Materials and Methods

Phase I: The Vaccine Adverse Events Reporting System

The VAERS database has been maintained by the CDC since 1990 as a surveillance tool to evaluate vaccine safety. Specific adverse events following vaccination are required by law to be reported to this database. The VAERS Working Group of the CDC has previously reported that less than 5% of the reports come from parents. The VAERS Working Group and the FDA analyze and publish epidemiologic studies based upon analyses of VAERS. They note that VAERS is simple to use, flexible by design, and provides data in a timely fashion, but warn that the potential limitations may include systematic error due to underreporting, erroneous reporting, frequent multiple exposures, multiple outcomes, and lack of precise denominators.[2 6]

Analysis Methods: The online public access VAERS database (updated through August 31, 2005) was examined using Microsoft Access.[2 7] The entire database was surveyed for duplicate reports (i.e. those having the same VAERS ID number), and these were eliminated. An ecological method was employed to evaluate NDs reported following immunizations, including autism (Costart Term = Autism) and speech disorders (Costart Term = Speech Dis), among children = 5 years old). Descriptions of these adverse events by those reporting them were coded by VAERS technical staff into defined symptom fields. The total new number of adverse event reports for each type of ND received on a reporting-quarter basis (January through March, April through June, July through September, and October through December) for 36 consecutive reporting quarters, from January 1, 1994, through December 31, 2002, and for 14 consecutive reporting quarters from January 1,

Table 2. Regression Equations for the VAERS and CDDS Databases.

Time Period Examined	Line Equation	95% CI: Slope of the Line	r value	95% CI: r value	R^2 value	*P* value
	Vaccine Adverse Event Reporting System (VAERS)					
January 1, 1994 through December 31, 2002	Number of New Autism Events = 0.014 Reporting Quarter – 483	0.098 to 0.018	0.77	0.60 to 0.88	0.60	< 0.0001
January 1, 2002 through June 30, 2005	Number of New Autism Events = -0.0302 Reporting Quarter + 1,179	-0.054 to -0.0067	-0.63	-0.87 to -0.15	0.38	< 0.02
January 1, 1994 through December 31, 2002	Number of New Speech Disorder Events = 0.0076 Reporting Quarter – 263	0.0056 to 0.0095	0.80	0.65 to 0.90	0.65	< 0.0001
January 1, 2002 through June 30, 2005	Number of New Speech Disorder Events = -0.010 Reporting Quarter + 413	-0.019 to -0.0014	-0.59	-0.85 to -0.084	0.35	< 0.03
	California Department of Developmental Services (CDDS)					
January 24, 1994 through January 6, 2003	Number of New Autism Cases = 0.23 Reporting Quarter – 7,775	0.19 to 0.27	0.89	0.79 to 0.94	0.79	< 0.0001
January 3, 2002 through October 4, 2005	Number of New Autism Cases = -0.016 Reporting Quarter + 6,753	-0.31 to -0.0043	-0.52	-0.82 to -0.017	0.28	< 0.05

2002, through June 30, 2005, were evaluated in VAERS. The reporting quarter periods were defined so as to overlap slightly, to maximize the possibility of capturing the peak reporting period in both groups. Assuming a 3- to 4- year lag time between birth and diagnosis of an ND,[2-4] the peak followed by a decline in NDs would be expected to occur around 2002 if thimerosal had a significant impact on NDs.

Phase II : California Department of Developmental Services

The California regional center system consists of 21 nonprofit and independent agencies, which are under contract with the Department of Developmental Services to provide services to persons with developmental disabilities. The CDDS system was created in 1969. Originally, autism was not included in the Lanterman Developmental Disabilities Services Act that established the statewide system of services. Autism, a low-incidence disorder in 1969, was added in 1971, largely because the impact of autism on children was substantially disabling and expected to be a lifelong condition. The CDDS recognizes only professionally diagnosed individuals with mental retardation, autism, epilepsy, cerebral palsy, and conditions similar to mental retardation as conditions eligible for services. Persons diagnosed with one of the other Pervasive Developmental Disorders (PDD), including Pervasive Developmental Disorder, Not Otherwise Specified (PDD, NOS), Asperger's Disorder, Rett's Disorder, and Childhood Disintegrative Disorder are not eligible for regional center services.[1]

Analysis Methods: The online public access CDDS database (updated through October 4, 2005) was examined using Microsoft Access.[1,2,8] The total new number of autism reports received by the CDDS from 36 consecutive reporting quarters (from that starting on January 24, 1994, through that ending on January 6, 2003), and for 15 consecutive reporting quarters (from that starting on January 3, 2002, through that ending on October 4, 2005) were analyzed. These periods of examination in the CDDS database were selected in an attempt to mirror the VAERS reporting periods analyzed in the present study.

The simple linear regression test in the StatsDirect (Version 2.4.2) statistical package was used to determine the equations for the regression lines, the slope of the regression lines, the correlation coefficients (r), the regression coefficients (R^2), and *P*-values for the number of newly diagnosed NDs reported to VAERS and CDDS during the two time periods before and after removal of thimerosal. The null hypothesis was that the slope of the lines for each of the two periods would be equal to zero. Additionally, the data were examined using the Kruskal-Wallis test statistic to determine whether the introduction, followed by removal, of thimerosal from childhood vaccines produced a discernable trend in the two separate reporting quarter periods examined in the VAERS and the CDDS databases. The null hypothesis was that the total number of newly diagnosed NDs should not be affected by the introduction/removal of thimerosal from childhood vaccines; in other words, that the slope of the lines for the two periods would be the same. A two-sided *P*-value of < 0.05 was considered statistically significant.

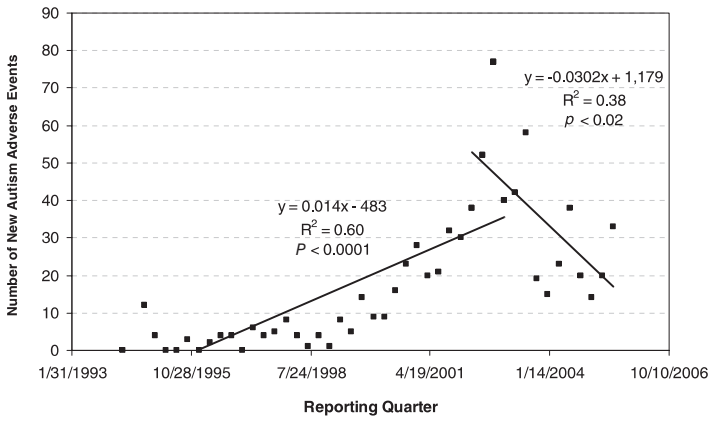

Figure 1. Trends in New Autism Adverse Events Reported to VAERS. The trend from Jan 1, 1994, through Dec 31, 2002, is significantly increasing, with $P < 0.0001$. The trend from Jan 1, 2002, through June 30, 2005, is significantly decreasing, with $P < 0.02$. The difference in the slope of the regression lines for the number of new autism adverse events in the earlier compared with the later periods is significant, with $P < 0.0005$.

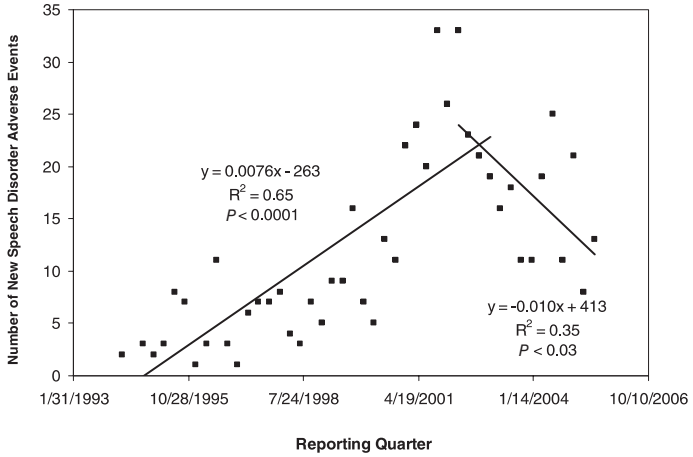

Figure 2. Trends in New Cases of Speech Disorders Reported to VAERS. The trend from Jan 1, 1994, through Dec 31, 2002, is significantly increasing, with $P < 0.0001$. The trend from Jan 1, 2002, through June 30, 2005, is significantly decreasing, with $P < 0.03$. The difference in the slope of the regression lines for the number of new speech disorder adverse events in the earlier compared with the later periods is significant, with $P < 0.005$.

Results

Figures 1 and 2 show the trend for new cases of autism and speech disorder (among those $\leq$ 5 years old) reported to VAERS for the 36 consecutive reporting quarters from January 1994 through December 2002, compared with that for 14 consecutive reporting quarters from January 2002 through June 2005. There was a significant difference in the trends, from an increasing to a decreasing slope, ($P < 0.0005$ for autism and $P<0.005$ for speech disorder).

Figure 3 evaluates the trend of new cases of autism entered into the CDDS for the 36 consecutive reporting quarters from January 24, 1994, through January 6, 2003, and for the 15 consecutive reporting quarters from January 3, 2002, through October 4, 2005. For new cases of autism, the trends were significantly different ($P < 0.0001$). About 350 fewer cases of autism were reported to the CDDS in the reporting quarter ending on October 4, 2005, than would have been expected from extrapolating the trend line for the first set of 36 reporting quarters. About 200 fewer new cases of autism were reported to the CDDS in the last reporting quarter of the second set of 15 consecutive quarters than in the first of that set.

Table 2 summarizes the equations of the regression lines, the slope of the regression lines, the correlation coefficients, the regression coefficients, *P*-values, and 95% confidence intervals (CIs) in the present study.

Discussion

In the present study a novel rapid sampling epidemiologic technique was employed to evaluate trends in new NDs entered into two separate databases, the VAERS and the CDDS. It was observed that consistent significant trends were found in both databases with apparent by limited effects from systematic error/bias.

There is a median lag time of 3 to 4 years between the time of birth and the diagnosis of an ND.[2 4] As a result, the first children evaluated, whose reports were entered into the VAERS and CDDS databases in early 1994, were probably born in the late 1980s or early 1990s. As was summarized in Table 1, these children received approximately 100 µg mercury from four doses of thimerosal-containing DTP vaccine, starting at 2 months of age. Subsequently, the children who were entered into the VAERS and CDDS databases from early 1994 through mid-to-late 2002 were probably born from the late 1980s to early 1990s through the late 1990s. These children, as shown in Table 1, received increasing doses of mercury from additional TCVs (Hib, Hep b, and in some cases influenza) as they were added to the recommended immunization schedule. Peak exposure from TCVs during the first 18 months of life was 275 µg mercury. Lastly, children entered into the VAERS and CDDS databases in the last period, beginning in mid-2002, were probably born from the late 1990s through the early 2000s. Table 1 shows that after July 7, 1999, as thimerosal was removed from vaccines, the total mercury dose children received from TCVs was gradually reduced, and what mercury remained in childhood vaccines was administered in a significantly less rigorous schedule than in previous time periods. Overall, it appears that the increasing and subsequent decreasing trends in the rates of NDs, observed in both the VAERS and CDDS databases, correlate with temporal periods when the cumulative amount of mercury in the childhood immunization schedule expanded and later contracted.

The consistency of the effects observed for the spectrum of NDs, including autism and speech disorders, and the agreement between the observations from two separate databases, support the conclusion that the effect is real and not a chance observation. The magnitude of the change in the trend lines is substantial. Moreover, other data are confirmatory: provisional data from the U.S. Department of Education show a recent decrease of 529 in the number of new autism diagnoses recorded among children 3 to 5 years old, after years of annual increases. There were 1,451 new cases in 2001-2002; 1,981 in 2002-2003; 3,707 in 2003-2004; and 3,178 in 2004-2005.[2 9]

The biological plausibility of the present findings is further supported by recently emerging extensive toxicokinetic, molecular, and animal studies.

Burbacher et al. have evaluated infant monkeys following injection of doses of mercury comparable to the dosing schedule (weight- and age-adjusted) that U.S. children received during the 1990s.[30] These researchers confirmed that thimerosal crosses the blood-brain barrier and results in appreciable mercury content in

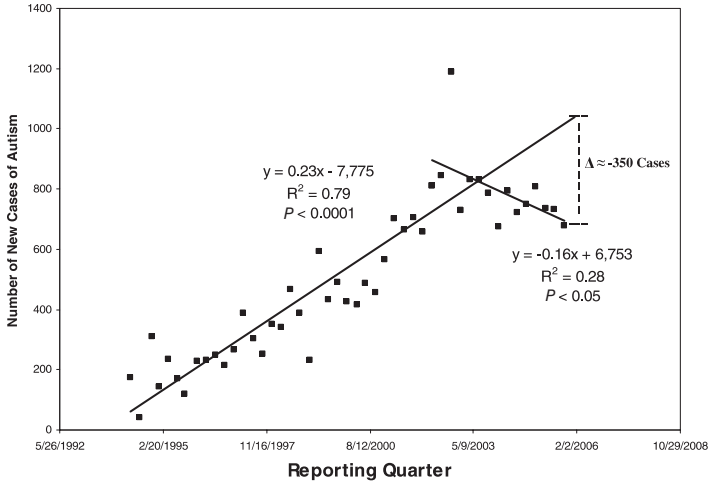

Figure 3. Trends in New Cases of Autism Entered into the CDDS. The trend from Jan 24, 1994, through Jan 6, 2003, is significantly increasing, with $P < 0.0001$. The trend from Jan 6, 2002, through Oct 4, 2005, is significantly decreasing, with $P < 0.05$. The difference in the slope of the regression lines for the number of new autism cases in the earlier compared with the later periods is significant, with $P < 0.0001$.

tissues including the brain. They determined that the overall half-life of mercury in the brain of the infant monkeys examined was approximately 24 days. In addition, it was determined that the concentration of inorganic mercury in the brains of the thimerosal-treated infant monkeys averaged 16 ppb following the dosing schedule, and the half-life of this inorganic mercury was very long (> 120 days).

In a series of in vitro studies with neurons it has now been shown that nanomolar (nM) to micromolar (μM) concentrations of thimerosal are capable of inducing neuronal death, neurodegeneration, membrane damage, and DNA damage within hours of exposure.[3,13-8] Additionally, it has been shown that nM to μM concentrations of thimerosal are capable of disrupting critical signaling pathways and biochemical events necessary for neurons to undergo normal development.[3,9,1-1] Such disruptions include testosterone-mercury synergistic induced neurotoxicity, while estrogen significantly reduced mercury-induced neurotoxicity.[4,2,4,3]

Hornig et al. administered thimerosal to mice, mimicking the U.S. routine childhood immunization schedule of the 1990s (weight- and age-adjusted), and observed autistic symptoms in a susceptible mouse strain that included growth delay, reduced locomotion, exaggerated response to novelty, increased brain size, decreased numbers of Purkinje cells, significant abnormalities in brain architecture affecting areas subserving emotion and cognition, and densely packed hyperchromic hippocampal neurons with altered glutamate receptors and transporters.[4,4] In addition, thimerosal exposure at specific prenatal developmental stages in several animal models and in humans has been shown to result in mercury crossing the placental barrier and resulting in significant fetal lethality and teratogenecity.[4,54-7]

The findings of the present study are also further supported by recent clinical studies examining the body burden of mercury and mercury susceptibility in children with NDs. Bradstreet et al. showed that, following chelation, urinary concentration of mercury was significantly greater, by a factor of approximately six, in autistic children compared with neurotypical children, whereas urinary cadmium and lead concentrations were similar.[48] Matched vaccinated and unvaccinated neurotypical children had similar urinary mercury concentration following chelation. Holmes et al. examined first baby haircuts and determined that autistics had significantly higher body burdens of mercury in comparison to nonautistic matched controls, by demonstrating that the mercury level in hair, and thus the ability to excrete mercury, was inversely proportional to the severity of autism and overall much lower in the autistic group.[49] James et al. have evaluated biochemical susceptibility to mercury in autistic children, in comparison to age- and gender-matched control children, by evaluating the methionine cycle and transsulfuration metabolites. They found a significant 46% decrease in the plasma concentration of glutathione, a necessary metabolite for the excretion of mercury from the body. Additionally, autistic children had significantly increased oxidative stress, as shown by a three-fold decrease in the glutathione/oxidized glutathione redox ratio, in comparison to control children, which would correlate with a significant body burden of mercury.[50-53]

Conclusions

The present controlled assessment of VAERS and CDDS databases shows that very specific NDs are associated with TCVs. This conflicts with the 2004 conclusions of the IOM, largely based upon examination of vaccine safety data from the National Immunization Program (NIP) of the CDC. The IOM stated that the evidence favored rejection of a causal relationship between thimerosal and autism, that such a relationship was not biologically plausible, and that no further studies should be conducted to evaluate it.[16]

From data presented here and other emerging data, it appears clear that additional research should be undertaken concerning the effects of mercury exposure, particularly from TCVs. This is especially true in light of the fact that the handling of vaccine safety data by the NIP has recently been called into question by the IOM.[5,4]

David A. Geier, B.A., is a graduate student in biochemistry, George Washington University. **Mark R. Geier, M.D., Ph.D.** is President, the Genetic Centers of America. Contact: Dr. Mark Geier at 14 Redgate Ct., Silver Spring, MD 20905. Telephone: (301) 989-0548, fax (301) 989-1543. E-mail: mgeier@comcast.net.

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Potential conflict of interest: David Geier has been a consultant in vaccine/biologic cases before the no-fault National Vaccine Injury Compensation Program (NVICP) and in civil litigation. Dr. Mark Geier has been an expert witness and a consultant in vaccine/biologic cases before the no-fault NVICP and in civil litigation.

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