A meta-analysis epidemiological assessment of neurodevelopmental disorders following vaccines administered from 1994 through 2000 in the United States

David A. Geier [1] & Mark R. Geier [2]

[1] Vice-President, The Institute of Chronic Illnesses, Silver Spring, MD, USA.
[2] President, The Genetic Centers of America.

Correspondence to: Dr. Mark R. Geier
14 Redgate Ct., Silver Spring, MD 20905, USA.
PHONE: +1 (301)989-0548
FAX: +1 (301)989-1543
EMAIL: mgeier@comcast.net

Submitted: April 4, 2006 *Accepted: May 7, 2006*

Key words: **developmental delay; mercury; merthiolate; thimerosal; thiomersal**

Neuroendocrinol Lett 2006; **27**(4):401–413 **PMID:** 16807526 NEL270306A01

Abstract

BACKGROUND: Thimerosal is an ethylmercury-containing compound (49.6% mercury by weight) used as at the preservative level in vaccines (0.005% to 0.01%).

METHODS: Statistical modeling in a meta-analysis epidemiological assessment of the Vaccine Adverse Event Reporting System (VAERS) for neurodevelopment disorders (NDs) reported following Diphtheria-Tetanus-whole-cell-Pertussis (DTP) vaccines in comparison to Diphtheria-Tetanus-whole-cell-Pertussis-Haemophilus Influenzae Type b (DTPH) vaccines (administered: 1994–1997) and following Thimerosal-containing Diphtheria-Tetanus-acellular-Pertussis (DTaP), vaccines in comparison to Thimerosal-free DTaP vaccines (administered: 1997–2000), was undertaken.

RESULTS: Significantly increased adjusted (sex, age, vaccine type, vaccine manufacturer) risks of autism, speech disorders, mental retardation, personality disorders, thinking abnormalities, ataxia, and NDs in general, with minimal systematic error or confounding, were associated with TCV exposure.

CONCLUSION: It is clear from the results of the present epidemiological study and other recently published data associating mercury exposure with childhood NDs, additional ND research should be undertaken in the context of evaluating mercury-associated exposures, especially from Thimerosal-containing vaccines.

Conflict of interests: Dr. Mark Geier has been an expert witness and consultant in vaccine cases before the no-fault National Vaccine Injury Compensation Program (NVICP) and in civil litigation. David Geier has been a consultant in vaccine cases before the no-fault NVICP and in civil litigation.
Study Funding: None.

REVIEW ARTICLE

INTRODUCTION

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 Centers for Disease Control and Prevention (CDC) from the late 1980s through the 1990s expanded the number of doses of Thimerosal-containing vaccines to be administered to US infants. The routine childhood immunization schedule was gradually expanded from administration of five doses of Thimerosal-containing Diptheria-Tetanus-whole-cell-Pertussis (DTP) vaccine (the first dose being administered at two months of age) to eventually include three doses of Thimerosal-containing hepatitis B vaccine (the first dose administered on the day of birth), and four doses of Thimerosal-containing Haemophilus Influenzae type b (Hib) vaccine (the first dose administered at two months of age). Additionally, the CDC also began to recommend that three doses of Thimerosal-containing influenza vaccine be administered to certain infant populations (the first dose administered by the sixth month of age). As a result, under the expanded childhood immunization schedule recommended by the CDC, if infants received all Thimerosal-containing vaccines, their total nominal mercury exposure, based on the vaccine labeling, could have been as high as 200 micrograms (μg) of mercury during the first six months of life [3].

In evaluating the dose of mercury children received from Thimerosal-containing vaccines in the US, when factoring in significant environmental exposure (i.e. mercury in breast milk), it has been estimated the mercury in Thimerosal-containing vaccines represented almost 50% of the total mercury dose some infants received [8]. As a result, it has been determined that some infants who received 187.5 μg of mercury through Thimerosal-containing vaccines by the sixth month from the routine childhood vaccination schedule, in combination with environmental exposure from mercury in breast milk (164 μg of mercury), were exposed to cumulative doses of mercury by the sixth month of life in excess of the methylmercury safety guidelines established by the US Environmental Protection Agency (EPA), Health Canada, the World Health Organization (WHO), the Agency for Toxic Substances Disease Registry (ATSDR), and the US Food and Drug Administration (FDA). It was also determined that these same infants were in excess of the methylmercury guidelines established by the EPA, Health Canada, WHO and the ATSDR for the entire first year of life [8].

In response to theoretical concerns about the cumulative doses of mercury children received from Thimerosal-containing vaccines, on July 7, 1999 the American Academy of Pediatrics and the United States Public Health Service issued a joint statement calling for the removal of Thimerosal from all childhood vaccines [3]. Thimerosal has been removed from many vaccines administered to infants in the US, but still remains in some required vaccines administered to US infants (e.g. influenza), as well as to several other vaccines (e.g. Tetanus-diphtheria and monovalent tetanus). The Institute of Medicine (IOM) of the United States National Academy of Sciences has retreated from the stated goal issued by the American Academy of Pediatrics and US Public Health Service in 1999 that Thimerosal be removed from US vaccines as soon as possible [43]. Furthermore, many nations still add Thimerosal to many of their pediatric vaccines. As a result, assessing the safety of Thimerosal-containing vaccines is still of significant importance.

It has previously been reported that organic mercury can alter cell number and cell division; these impacts have been postulated as modes of action for the observed effects in neuronal development, and as a result the potential implications of such observations are evident when evaluated in context with research showing that altered cell proliferation and focal neuropathologic effects have been linked to specific behavioral deficits (e.g. autism) [21]. Researchers have determined that exposure to mercury can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with autistic disorders, and that the similarities extend to neuroanatomy, neurotransmitters, and biochemistry [5, 6, 10, 57]. It has also been reported in previous epidemiological studies that early postnatal mercury exposure was associated with delayed motor development, delayed language development, learning disabilities, attention deficits, and autism in children [1, 17].

In a series of previous epidemiological studies, various databases, including the California Department of Developmental Services (CDDS), Vaccine Adverse Event Reporting System (VAERS), US Department of Education, and the Vaccine Safety Datalink (VSD) database, have been examined, and significant links between exposure to Thimerosal-containing vaccines and neurodevelopmental disorders were found [24–33]. Specifically, it was determined, based upon assessment of the VAERS, that additional doses of mercury from Thimerosal-containing Diphtheria-Tetanus-acellular-Pertussis (DTaP) vaccines in comparison to Thimerosal-free DTaP vaccines (administered in the late 1990s), and from DTP and Hib vaccines in comparison to DTPH vaccines (administered in the early to mid-1990s), had 2- to 8-fold significantly increased risks, depending upon the symptoms or outcomes examined, for neurodevelopmental disorders. The one other epidemiological study conducted in the United States that has examined the relationship between Thimerosal-containing vaccines and neurodevelopmental disorders, by Verstaeten et al., from the CDC, initially found a significant relationship between Thimerosal-containing childhood vaccines and some types of neurodevelopmental disorders, but upon further examination of a different dataset, it did not find a consistent effect [63]. The lead author concluded that this study was neutral (i.e. could neither accept nor reject a causal relation-

ship) regarding the relationship between Thimerosal and neurodevelopmental disorders [64].

In light of this apparent inconsistency, the purpose of the present study was to use statistical modeling in a combined epidemiological analysis of previously examined data in the VAERS to determine whether the previously observed results in VAERS represent robust, genuine phenomena or simply were a transient artifact and/or a mere peculiarity of the years examined.

MATERIALS AND METHODS

The Institutional Review Board (IRB) of the Institute for Chronic Illnesses (Office for Human Research Protections, US Department of Health and Human Services IRB number: IRB00005375) approved the present study.

The Vaccine Adverse Event Reporting System

The VAERS is an epidemiological database that has been maintained by the CDC since 1990 as a surveillance tool to evaluate vaccine safety. Specific adverse events following vaccination are required to be reported to this database as mandated by law. The VAERS Working Group of the CDC has previously reported that less than 5% of the total adverse events reported to VAERS are reported by parents. The VAERS Working Group of the CDC 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 the data are available 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 [60].

In this study of VAERS, the general epidemiological technique employed was developed by Rosenthal et al. from the National Immunization Program (NIP) of the CDC [59]. This technique involves comparing two different types of vaccines that were administered to age-matched populations, and using the net number of doses distributed from the Biological Surveillance Summaries of the CDC to estimate the number of doses administered. This process corrects for doses not distributed or returned during the period examined in the Biological Surveillance Summaries of the CDC, and the net number of doses distributed is used as the denominator to determine incidence rates of reported adverse events to VAERS. It should be noted that even though the net number of doses of vaccine distributed were analyzed, there is the possibility that some doses of vaccine were not administered to children, but such a limitation should be minimal and should equally affect both vaccines under study. Comparison of reported adverse event incidence data between different vaccines establishes the relative safety and risk of the various agents.

Analysis Methods

In the present study, a historical examination of VAERS (online public access version; reports entered through 31 May 2005) was undertaken using Microsoft Access™. The entire database was surveyed for duplicate reports (i.e. having the same VAERS ID number), and these were eliminated.

In this study a combined epidemiological assessment of VAERS was undertaken whilst employing a Bradford Hill criteria framework to assess observed associations [38]. Childhood neurodevelopment disorders reported following Thimerosal-containing DTaP vaccines in comparison to Thimerosal-free DTaP vaccines (administered from 1997 through 2000), and following DTP vaccines in comparison to DTPH vaccines (administered from 1994 through 1997), were evaluated in the VAERS.

Based upon the purposed evaluations of the vaccines under study, there should have been, maximally, a nominal approximately 100 μg additional exposure to mercury among those children receiving DTP vaccines in comparison those receiving DTPH vaccines, because children receiving DTP vaccines were concurrently administered Hib vaccines in addition. When these two vaccines were combined in the DTPH vaccine, children receiving it were nominally exposed to 25 μg of mercury per vaccine administration. By contrast, children receiving DTP vaccines were nominally exposed to the 25 μg of mercury from the DTP vaccine and 25 μg of mercury from the Hib vaccine. Thus, considering the possible combinations/alternatives of vaccine administrated in accord with the immunization schedule, examining specifically DTP, Hib, and DTPH, it is observed that children receiving separate DTP and Hib vaccines potentially received a nominal maximum of 200 μg of mercury from these vaccines, whereas children receiving DTPH in the same schedule potentially received a nominal maximum of 100 μg of mercury from these vaccines during the first 18 months of life. These vaccines were administered for similar years, in the same childhood vaccination schedule, during the first 18 months of life at 2, 4, 6, and 15–18 months, in the United States. Similarly, there should have been maximally a nominal approximately 100 μg of additional exposure to mercury among those children receiving Thimerosal-containing DTaP vaccines in comparison those receiving Thimerosal-free DTaP vaccines, because children receiving Thimerosal-containing vaccines were nominally administered an additional 25 μg of mercury with each dose of vaccine, and thus, among the vaccines under study, children receiving Thimerosal-containing DTaP vaccines potentially received a nominal maximum of 100 μg of mercury from these vaccines, whereas children receiving Thimerosal-free DTaP vaccines in the same

schedule potentially received a nominal maximum of 0 μg of mercury from these vaccines during the first 18 months of life. These vaccines were administered for similar years, in the same childhood vaccination schedule, during the first 18 months of life at 2, 4, 6, and 15–18 months, in the United States. Therefore, the VAERS reports that indicate DTP or Thimerosal-containing DTaP were administered were considered to be exposed in the present study, and the VAERS reports that indicated DTPH or Thimerosal-free DTaP were administered were considered to be unexposed in the present study.

The neurodevelopmental adverse events analyzed in VAERS included: autism (Costart Term = Autism and/or Costart Term = Schizophrenic Reac), mental retardation (Costart Term = Mental Retard), speech disorders (Costart Term = Speech Dis), thinking abnormalities (Costart Term = Thinking Abnorm), personality disorders (Costart Term = Person Dis), ataxia (Costart Term = Ataxia), and neurodevelopmental disorders in general (one or more of the aforementioned adverse events as a Costart Term in an individual VAERS report). Descriptions of these adverse events were based upon those reporting them, and coded by VAERS technical staff into defined symptom fields contained in each report. Table 1 summarizes the neurodevelopmental disorder raw data examined in the present study of VAERS.

The Biological Surveillance Summaries of the CDC, as segregated by vaccine manufacturer, indicated that there were a total of 57,151,417 vaccines administered to children in the exposed group that received additional doses of mercury from Thimerosal-containing vaccines

Table 1. A summary of the neurodevelopmental disorder raw data evaluated in the Vaccine Adverse Event Reporting System broken down by vaccine type, vaccine manufacturer, year of vaccine administration, and adverse event type.

Vaccine Type [Manufacturer]	Year	Number of Autism Reports	Number of SD Reports	Number of MR Reports	Number of PD Reports	Number of Ataxia Reports	Number of TA Reports	Number of ND Reports
Wyeth – Lederle								
DTP	1994	1	3	6	3	1	1	8
	1995	1	1	1	1	2	0	4
	1996	0	1	0	1	0	2	2
	1997	3	2	3	1	0	1	6
DTPH	1994	3	2	6	1	1	1	9
	1995	6	7	15	13	2	2	31
	1996	9	9	18	23	3	4	47
	1997	8	6	7	8	2	2	21
DTaP	1997	7	2	5	3	0	1	11
	1998	14	12	12	5	5	3	31
	1999	17	14	12	7	4	4	34
	2000	11	14	6	11	2	2	25
Aventis Pasteur/ Connaught								
DTaP	1997	13	12	18	7	4	1	34
	1998	12	12	13	13	6	10	33
	1999	5	3	8	9	3	4	17
	2000	5	5	4	9	2	2	18
GlaxoSmithKline								
DTaP	1997	2	1	1	0	0	0	3
	1998	5	2	2	3	1	0	9
	1999	5	2	1	2	2	0	12
	2000	6	5	5	4	1	1	19
Totals		133	115	143	124	41	41	374

PD = Personality Disorder
MR = Mental Retardation
ND = Neurodevelopmental Disorder
SD = Speech Disorder
TA = Thinking Abnormalities

Table 2. The Biological Surveillance Summaries of the Centers for Disease Control and Prevention estimates of the net number of doses distributed/administered on a yearly basis broken down by vaccine type and vaccine manufacturer

Vaccine Type [Manufacturer]	Year	Net Number of Doses Distributed/ Administered[1]
Wyeth – Lederle		
DTP	1994	977,200
	1995	1,300,000
	1996	1,069,500
	1997	224,775
DTPH	1994	8,894,440
	1995	9,300,000
	1996	8,760,590
	1997	4,114,500
DTaP	1997	4,452,980
	1998	5,766,510
	1999	7,330,100
	2000	3,239,040
Aventis Pasteur/Connaught		
DTaP	1997	8,828,578
	1998	8,504,800
	1999	8,045,998
	2000	7,411,936
GlaxoSmithKline		
DTaP	1997	2,121,490
	1998	2,844,960
	1999	4,708,000
	2000	7,241,250

[1] These estimates of the number of doses of vaccine administered were adjusted for doses not distributed or returned during the period examined and were used as the denominators to determine the calculated incidence rates of reported adverse events to the Vaccine Adverse Events Reporting System database.

Table 3. The composition of the DTaP vaccines under study in the Vaccine Adverse Event Reporting System database

Vaccine Component	Thimerosal-Containing DTaP Vaccine (Aventis Pasteur – Connaught)	Thimerosal-Containing DTaP Vaccine (Wyeth – Lederle)	Thimerosal-Free DTaP Vaccine (GlaxoSmithKline)
Pertussis Toxin (micrograms/dose)	23.4	3.5	25
Filamentous Hemagglutinin (micrograms/dose)	23.4	35	25
Pertactin (micrograms/dose)	–	2	8
Fembrial Agglutinogens (micrograms/dose)	–	0.8	–
Diphtheria Toxoid (Lf/dose)	6.7	9	25
Tetanus Toxoid (Lf/dose)	5	5	10
How Toxoided	Formaldehyde	Formaldehyde	Formaldehyde
Aluminum (mg/dose)	0.17	0.23	0.50
Diluent	Phosphate-Buffered Saline	Phosphate-Buffered Saline	Saline
Preservative	Thimerosal	Thimerosal	Phenoxyethanol
Trace Constituents	Formaldehyde, Gelatin, Polysorbate-80	Formaldehyde, Gelatin, Polysorbate-80	Formaldehyde, Polysorbate-80

Table 4. A summary of potential confounders[1] following Thimerosal-containing vaccines in comparison to Thimerosal-reduced vaccines based upon analysis of the Vaccine Adverse Event Reporting System database.

Potential Confounder/ Exposure Category	Number of Reports	Conditional Maximum Likelihood Estimate of the Odds Ratio	*p*-value	95% Confidence Interval
Geographical Dispersion				
Texas (Western)				
Exposed Cases[2]	459	1.02	0.84	0.89–1.2
Unexposed Cases[2]	375			
Total	834			
Illinois (Central)				
Exposed Cases	262	0.95	0.56	0.79–1.1
Unexposed Cases	232			
Total	494			
Florida (Eastern)				
Exposed Cases	263	0.91	0.28	0.76–1.09
Unexposed Cases	243			
Total	506			
Medical History				
Past Medical Histories				
Exposed Cases	5,677	0.84	< 0.0001	0.81–0.87
Unexposed Cases	5,704			
Total	11,381			
Other Medications				
Exposed Cases	4,474	0.81	< 0.0001	0.78–0.85
Unexposed Cases	4,625			
Total	9,099			
Demographics				
Male Reports				
Exposed Cases	3,713	0.86	< 0.0001	0.82–0.90
Unexposed Cases	3,612			
Total	7,325			
Female Reports				
Exposed Cases	3,135	0.81	< 0.0001	0.77–0.85
Unexposed Cases	3,262			
Total	6,397			

[1] These potential confounders were examined using the conditional maximum likelihood estimate of the odds ratio and the nominal Fisher's exact test statistic to determine statistical significance, so as to evaluate there significance for statistical models developed in the present study. These potential confounders were considered for entry into the statistical model if they had an odds ratio > 1.25 (odds ratio < 0.80) and a *p*-value < 0.10.

[2] There were a total of 57,151,417 vaccines administered to exposed children that received additional doses of mercury from vaccines (i.e. DTP or Thimerosal-containing DTaP vaccines) and a total of 47,985,230 vaccines administered to unexposed children that received lower doses of mercury from vaccines (i.e. DTPH or Thimerosal-free DTaP vaccines).

Table 5. A summary of the crude and adjusted risk of neurodevelopmental disorders following vaccines containing additional doses of mercury from Thimerosal-containing vaccines in comparison to Thimerosal-reduced vaccines based upon analysis of the Vaccine Adverse Event Reporting System database.

Outcome/ Exposure Category	Number of Reports	Adjusted[1] Conditional Maximum Likelihood Estimate of Pooled Odds Ratio	Adjusted *p*-value	Adjusted 95% Confidence Interval
Autism				
Exposed Cases[2]	89	1.56	< 0.03	1.05–2.34
Unexposed Cases[2]	44			
Total	133			
Mental Retardation				
Exposed Cases	88	2.36	< 0.0001	1.54–3.62
Unexposed Cases	55			
Total	143			
Speech Disorders				
Exposed Cases	81	2.78	< 0.0001	1.75–4.48
Unexposed Cases	34			
Total	115			
Personality Disorders				
Exposed Cases	70	2.06	< 0.0008	1.33–3.21
Unexposed Cases	54			
Total	124			
Thinking Abnormalities				
Exposed Cases	31	5.85	< 0.0001	2.38–15.2
Unexposed Cases	10			
Total	41			
Ataxia				
Exposed Cases	29	2.22	< 0.04	1.01–5.10
Unexposed Cases	12			
Total	41			
Neurodevelopmental Disorders				
Exposed Cases	223	1.61	< 0.0001	1.27–2.05
Unexposed Cases	151			
Total	374			

Statistical models were developed using the conditional maximum likelihood estimate of the pooled odds ratio and the nominal Fisher's exact test statistic to determine statistical significance. The Woolf Q test statistic examining the non-combinability of the odds ratios and the Kendall test statistic examining for bias indicators were not significant for any adverse event examined.

[1] Adjusted for age, sex, year of vaccine administration, vaccine manufacturer, and vaccine type by stratifying the data based upon the year of vaccine administration, sex of the vaccine recipient, vaccine type, and vaccine manufacturer.

[2] There were a total of 57,151,417 vaccines administered to exposed children that received additional doses of mercury from vaccines (i.e. DTP or Thimerosal-containing DTaP vaccines) and a total of 47,985,230 vaccines administered to unexposed children that received lower doses of mercury from vaccines (i.e. DTPH or Thimerosal-free DTaP vaccines).

(i.e. DTP or Thimerosal-containing DTaP vaccines) and a total of 47,985,230 vaccines administered to children in the unexposed group that received lower doses of mercury from vaccines (i.e. DTPH or Thimerosal-free DTaP vaccines). Table 2 summarizes the vaccine administration years examined and the yearly breakdown of the net number of doses distributed/administered by vaccine type and vaccine manufacturer. In addition, Table 3 summarizes the composition of the DTaP vaccines examined in the present study [56].

In this study, control adverse events were evaluated to determine if potential bias or systematic error was present in the reporting of adverse events in VAERS following the vaccines under study. The control adverse events examined in the present study were selected on an *a priori* basis as not biologically plausibly linked to an increased risk following additional doses of mercury from Thimerosal-containing vaccines, and included the following outcomes: conjunctivitis (Costart Term = Conjunctivitis), lymphadenopathy (Costart Term = Lymphadeno), and febrile seizures (Costart Term = Febrile Seizure).

STATISTICAL ANALYSES

The premise of equality between the exposed and unexposed groups examined forms the basis of the null hypothesis employed in the present study. The statistical package in StatsDirect™ (Version 2.4.2) was employed. In this study, statistical models were developed using the conditional maximum likelihood estimate of the pooled odds ratio and the nominal Fisher's exact test statistic to determine statistical significance. Additionally, as part of the statistical models, the Woolf Q test statistic was employed to examine non-combinability of the odds ratios, and the Kendall test statistic was employed to examine for bias indicators.

Potential confounders, including geographic dispersion (based upon residence in representative states in the western (Texas), central (Illinois), and eastern (Florida) regions of the US), medical history (number of reports with previous medical histories and number of reports specifying other medications received), and demographic elements (male and female reports) were examined in the VAERS. Confounders were selected for inclusion into statistical models in the present study if they had odds ratios > 1.25 (or if they had odds ratios < 0.80) and p-values < 0.10, based upon using the nominal Fisher's exact test statistic to determine statistical significance, or were included in the models regardless for sex, age, vaccine type, and vaccine manufacturer. The results of this examination of confounders are summarized in Table 4. Based upon this examination of potential confounders in VAERS, the adverse events examined in the present study were adjusted for age, sex, year of vaccine administration, vaccine manufacturer, and vaccine type, by stratifying the data based upon: the year of vaccine administration (1994 through 2000), sex of the vaccine recipient (assuming there were approximately equal numbers of male and female vaccine recipients), vaccine type (DTP, DTPH, Thimerosal-containing DTaP, or Thimerosal-free DTaP), and vaccine manufacturer (Wyeth-Lederle, GlaxoSmithKline, Aventis Pasteur-Connaught).

In order for statistical significance testing to be performed for an adverse event, a total of 40 adverse events were required to be identified following the vaccines under study in VAERS. A two-sided p-value < 0.05 was considered statistically significant.

RESULTS

Table 5 summarizes neurodevelopmental disorders reported to VAERS following the vaccines under study. It was found that there were the following total number of neurodevelopmental disorder adverse events identified in VAERS: autism (133 reports), speech disorders (115 reports), mental retardation (143 reports), personality disorders (124 reports), thinking abnormalities (41 reports), ataxia (41 reports), and neurodevelopmental disorders in general (374 reports). It was observed that there were significant associations between neurodevelopmental disorder adverse events reported to VAERS in the exposed group, in comparison to the unexposed group for the following outcomes: autism (adjusted Odds Ratio (OR) = 1.56, $p < 0.03$, 95% Confidence Interval (CI) = 1.05–2.34), speech disorders (adjusted OR = 2.78, $p < 0.0001$, 95% CI = 1.75–4.48), mental retardation (adjusted OR = 2.36, $p < 0.0001$, 95% CI = 1.54–3.62), personality disorders (adjusted OR = 2.06, $p < 0.0008$, 95% CI = 1.33–3.21), thinking abnormalities (adjusted OR = 5.85, $p < 0.0001$, 95% CI = 2.38–15.2), ataxia (adjusted OR = 2.22, $p < 0.04$, 95% CI = 1.01–5.10), and neurodevelopmental disorders in general (adjusted OR = 1.61, $p < 0.0001$, 95% CI = 1.27–2.05).

Table 6 summarizes the control adverse events reported in the exposed and unexposed groups examined in VAERS. It was determined that the control adverse events of conjunctivitis (adjusted OR = 1.36, $p = 0.32$, 95% CI = 0.76–2.53), febrile seizures (adjusted OR = 1.02, $p = 0.90$, 95% CI = 0.80–1.31), and lymphandenopathy (adjusted OR = 0.72, $p = 0.074$, 95% CI =0.49–1.05) were similarly reported to VAERS for the vaccines under study.

DISCUSSION

The results of the present examination of the VAERS show a significant relationship between the Thimerosal-containing childhood vaccines evaluated and childhood neurodevelopmental disorders. The data demonstrate that a significant risk factor for the development of neurodevelopmental disorders was the amount of mercury children received from Thi-

Table 6. A summary of the crude and adjusted risk of control adverse events[1] reported following vaccines containing additional doses of mercury from Thimerosal-containing vaccines in comparison to Thimerosal-reduced vaccines based upon analysis of the Vaccine Adverse Event Reporting System database.

Outcome/ Exposure Category	Number of Reports	Adjusted[2] Conditional Maximum Likelihood Estimate of Pooled Odds Ratio	Adjusted *p*-value	Adjusted 95% Confidence Interval
Conjunctivitis				
Exposed Cases[3]	37	1.36	0.32	0.76–2.53
Unexposed Cases[3]	28			
Total	65			
Lymphadenopathy				
Exposed Cases	70	0.72	0.074	0.49–1.05
Unexposed Cases	55			
Total	125			
Febrile Seizure				
Exposed Cases	163	1.02	0.90	0.80–1.31
Unexposed Cases	214			
Total	377			

Statistical models were developed using the conditional maximum likelihood estimate of the pooled odds ratio and the nominal Fisher's exact test statistic to determine statistical significance. The Woolf Q test statistic examining the non-combinability of the odds ratios and the Kendall test statistic examining for bias indicators were not significant for any adverse event examined.

[1] Control adverse events were selected on an *a priori* basis as not biologically plausibly linked to an increased risk following additional doses of mercury from Thimerosal-containing vaccines.

[2] Adjusted for age, sex, year of vaccine administration, vaccine manufacturer, and vaccine type by stratifying the data based upon the year of vaccine administration, sex of the vaccine recipient, vaccine type, and vaccine manufacturer.

[3] There were a total of 57,151,417 vaccines administered to exposed children that received additional doses of mercury from vaccines (i.e. DTP or Thimerosal-containing DTaP vaccines) and a total of 47,985,230 vaccines administered to unexposed children that received lower doses of mercury from vaccines (i.e. DTPH or Thimerosal-free DTaP vaccines).

merosal-containing childhood immunizations. Taken collectively, the increased risk associated with all seven neurodevelopmental disorders examined, any of which could independently be an indicator of possible mercury toxicity, proffers significant evidence for an association between the Thimerosal-containing vaccines evaluated in the present study and neurodevelopmental disorders based on this controlled assessment of VAERS.

In considering the utility of VAERS, it has been repeatedly examined by the CDC/FDA to epidemiologically evaluate the safety of vaccines [12, 19, 34, 47, 50, 55, 59, 67]. Furthermore, the CDC-developed the general epidemiological technique, employed in this study, of comparing the incidence rate of reported adverse events following one vaccine, to the incidence rate of reported adverse events following another vaccine administered to a similarly aged population, continues to be used by the NIP of the CDC to evaluate the safety of vaccines in VAERS [47].

The strength of VAERS stems from its large reporting base (i.e. patients from the entire United States). Its potential weakness is that not all vaccine-associated adverse events experienced are reported. Therefore, VAERS contains a sample of adverse events that occurred following immunization, and hence, reporting of vaccine-associated adverse events must also be evaluated to determine whether systematic error or bias is present in the data examined. Chen and Rosenthal from the NIP have published that the potential limitations in VAERS (such as: underreporting, erroneous reporting, frequent multiple exposures, multiple outcomes, and lack of precise denominators) should apply equally when comparing vaccines administered to similarly aged populations, and should allow for determination of accurate, relative, quantitative relationships between vaccines and adverse outcomes [16]. Additionally, a recent review has examined the utility of this method to analyze VAERS, and has concluded that studies examining VAERS using the methods of analysis developed by Rosenthal et al. had good positive predictive value for determining vaccine-associated adverse events that were consistent with observations made in vaccine clinical trials and other databases, including the CDC's VSD database [28].

In this study differences in the populations examined as a result of systematic error/confounding were examined in VAERS, because such factors might have skewed the results. To ensure that the exposed and

unexposed populations examined in VAERS were similar, only individuals receiving the vaccines under study who reported an adverse event report to VAERS were analyzed (i.e. this was the entrance criteria for the present study). The comparison employed in this study between the exposed and unexposed populations examined in VAERS is also important with regards to systematic error/confounding because there are social and medical attributes associated with both avoidance or delay of vaccination and an increased risk of adverse events, and studies that fail to control adequately for such systematic error/confounding factors are likely to underestimate the risks of adverse events attributable to vaccination [22]. Since, both the exposed and unexposed populations examined in VAERS were immunized, vaccination-associated types of systematic error/confounding were likely to be minimal in the present study. Inherently, submission of an adverse event report to VAERS, in either the exposed or unexposed vaccine groups, should occur at a similar frequency, and not introduce systematic error/confounders toward one vaccine or another.

Further controls were employed in evaluating the exposed and the unexposed vaccine groups, by adjusting for age, sex, year of vaccine administration, vaccine manufacturer, and vaccine type in the statistical models employed in the present study. Additionally, the years examined in VAERS also helped to preclude systematic error in the reporting of neurodevelopmental disorders due to a presumed association between Thimerosal and neurodevelopmental disorders, because only adverse events were analyzed following vaccines administered from 1994 through 2000. As a result, out a total of 971 neurodevelopmental disorder adverse events examined in this study, a total of 787 neurodevelopmental disorder adverse events (> 81%) were reported to VAERS following vaccines administered from 1994 through 1998, and hence most were administered in years prior to the public announcement recommending removal of Thimerosal from vaccines in July of 1999 [3]. Also, a significant number of autism adverse events (33 autism adverse events, approximately 25% of the total 133 autism adverse events analyzed in this study) were received by VAERS prior to the first article by Bernard et al. [5] in April 2001 associating mercury exposure from vaccines with autism. Furthermore, the fact that autism has a median age for diagnosis of approximately 4 years-old [63], means that, at the time of the publication of the Bernard et al. [5] article in April 2001, only vaccines administered from 1994 through 1997 had the necessary, approximately 4-year follow-up period, and when taking this into account, it was observed that > 62% (33 out of a total of 53) of autism adverse events, reported following vaccines administered from 1994 through 1997, were reported prior to the publication of the Bernard et al. [5] article in April 2001. Finally, control adverse events, which were observed in the present study to be reported with similar frequencies in the exposed and unexposed groups examined, were employed to evaluate the specificity of adverse event reporting and the general health statuses of the exposed and unexposed groups examined in VAERS.

In this study, chance significant associations between Thimerosal and neurodevelopmental disorders were minimized. First, since only a limited number of specific neurodevelopmental disorders were evaluated in the present study (i.e. only a total of seven neurodevelopmental disorders were examined, and only a total 17 outcomes were examined), and since a p-value < 0.05 was considered significant (one in 20 outcomes would be expected to be found significant by chance), therefore, one would expect that less than one of the types of conditions examined in the present assessment of VAERS would, by chance, be found to be significantly associated with Thimerosal. Second, a series of different types of neurodevelopmental disorders were examined in VAERS, involving different types of symptoms/syndromes. All seven types of neurodevelopmental disorders examined in VAERS were significantly associated with Thimerosal. This consistency of observation across multiple types of neurodevelopmental disorders argues against the present observations resulting from a mere chance statistical association, or even from a simple reporting bias stemming from a presumed association between Thimerosal and a given outcome that resulted in an over reporting of a single type of adverse event.

In further evaluating the results of the present study, it must be noted that none of the children examined in this study of VAERS truly represent a Thimerosal-free population. Within the reports, it was observed that other vaccines containing Thimerosal, such as hepatitis B vaccine or influenza vaccine, were concurrently administered in addition to the specific vaccines under study. The difference in the total amounts of mercury received from Thimerosal-containing vaccines in the children examined in VAERS stems from the fact that some children received additional doses of mercury from DTP or Thimerosal-containing DTaP vaccines in comparison to those children receiving DTPH or Thimerosal-free DTaP vaccines. As a result, the increased risks observed for neurodevelopmental disorders probably represent a considerable underestimate of the overall risk mercury from Thimerosal-containing childhood vaccines posed to children.

Other sources of mercury such as anti-Rh_o immune globulin, seafood, manufacturing plant emissions, dental amalgams, and other pharmaceuticals, while potentially significant, probably had a limited effect on the VAERS results of this study because the populations analyzed were large, and there should have been equal exposure to other sources of mercury among the populations examined.

In weighing the validity of the results of the present study against any epidemiological studies conducted outside the United States that have not shown an apparent relationship between Thimerosal-containing childhood vaccines and neurodevelopmental disorders [2, 37, 42, 48, 61] one must note that these foreign studies

have been criticized for their inapplicability to the US exposure experience with Thimerosal-containing vaccines and for fundamental flaws in their methodology [7, 9, 58, 62].

The biological plausibility of the present findings are further supported by recently emerging extensive toxicokinetic, molecular, and animal model studies showing that the administration of Thimerosal-containing childhood vaccines resulted in a significant number of neurodevelopmental disorders in children.

Burbacher et al. have evaluated infant monkeys following injection of doses of mercury comparable to the dosing schedule (weight- and age-adjusted) US children received during the 1990s [15]. These researchers confirmed that Thimerosal crosses the blood-brain barrier and results in appreciable mercury content in 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 percentage of inorganic mercury in the brains of the Thimerosal-treated infant monkeys averaged 16 parts-per-billion following the dosing schedule, and the half-life of this inorganic mercury was found to be very long in the monkey brains (> 120 days).

In a series of molecular 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 [4, 13, 14, 41, 46, 54, 65, 68]. Additionally, it has been shown that nM to μM concentrations of Thimerosal are capable of disrupting critical signaling pathways/biochemical events necessary for neurons to undergo normal neuronal development [51, 53, 66], and it has also been shown that testosterone synergistically enhances Thimerosal neurotoxicity, whereas estrogen significantly ameliorates Thimerosal neurotoxicity [35, 52].

Hornig et al. administered Thimerosal to mice, mimicking the US 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 sub-serving emotion and cognition, and densely packed hyperchromic hippocampal neurons with altered glutamate receptors and transporters [40]. In addition, Thimerosal exposure at specific prenatal developmental stages in several animal models and humans has been shown to result in mercury crossing the placental barrier and to result in significant fetal lethality, developmental disorders, and teratogenecity [18, 23, 36, 44].

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 neurodevelopmental disorders [20, 49, 52]. Bradstreet et al. showed that, following chelation, there were approximately 6-times significantly greater urinary mercury concentrations among autistics matched to neurotyptical children, whereas autistics and matched neurotypical children had similar urinary cadmium and lead concentrations. Similar urinary mercury concentration levels were observed among matched vaccinated and unvaccinated neurotypical children following chelation [11]. Likewise, Holmes et al. examined first baby haircuts and determined that autistics had significantly higher body-burdens of mercury in comparison to non-autistic matched controls by demonstrating that the ability to excrete mercury in first baby haircuts was inversely proportional to the severity of autistics, which on the whole was very low compared to non-autistic matched controls [39]. James et al. have evaluated the biochemical susceptibility to mercury in autistic children in comparison to age- and gender-matched control children by evaluating the methionine cycle and transsulfuration metabolites. It was determined that there were significant decreases in the plasma concentration of cysteine (19% reduction) and glutathione (46% reduction), and that autistic children had significantly increased oxidative stress (3-fold decrease in glutathione/oxidized glutathione redox ratio) in comparison to control children [20, 45].

CONCLUSION

The present controlled assessment of VAERS shows that very specific adverse affects were attributable to Thimerosal. Thimerosal was associated with an increased risk of neurodevelopmental disorders, and potential systematic error or confounding were found to be minimal in VAERS. Despite conclusions by the IOM that the evidence favors rejection of a causal relationship between Thimerosal and autism, it is not biologically plausible for Thimerosal to cause autism, and that no further studies should be conducted to evaluate the relationship between Thimerosal and autism [43], it is clear from these data and other emerging data that have been recently published, that additional neurodevelopmental disorder research should be undertaken in the context of evaluating mercury-associated exposures, especially from Thimerosal-containing vaccines. Furthermore, studies should also be undertaken to evaluate additional databases/registries to assess the compatibility of the present results with trends in neurodevelopmental disorders in other US populations.

Acknowledgements

We wish to thank Dr. Paul G. King and Lisa Sykes for helping to review and revise our manuscript.

REFERENCES

1 Amin-Zaki L, Majeed MA, Greenwood MR, Elhassani SB, Clarkson TW, Doherty RA. Methylmercury poisoning in the Iraqi suckling infant: a longitudinal study over five years. J Appl Toxicol 1981; **1**:210–4.

2 Andrews N, Miller E, Grant A, Stowe J, Osborne V, Taylor B. Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United Kingdom does not support a causal association. Pediatrics 2004; **114**:584–91.

3 Ball LK, Ball R, Pratt RD. An assessment of Thimerosal use in childhood vaccines. Pediatrics 2001; **107**:1147–54.

4 Baskin DS, Ngo H, Didenko VV. Thimerosal induces DNA breaks, caspase-3 activation, membrane damage, and cell death in cultured human neurons and fibroblasts. Toxicol Sci 2003; **74**:361–8.

5 Bernard S, Enayati A, Redwood L, Roger H, Binstock T. Autism: a novel form of mercury poisoning. Med Hypotheses 2001; **56**:462–71.

6 Bernard S, Enayati A, Roger H, Binstock T, Redwood L. The role of mercury in the pathogenesis of autism. Mol Psychiatry 2002; **7** Suppl 2:S42–3.

7 Bernard S. Association between Thimerosal-containing vaccine and autism. JAMA 2004; **291**:180.

8 Bigham M, Copes R. Thiomersal in vaccines: balancing the risk of adverse effects with the risk of vaccine-preventable disease. Drug Saf 2005; **28**:89–101.

9 Blaxill MF. Concerns continue over mercury and autism. Am J Prev Med 2004; **26**:91.

10 Blaxill MF, Redwood L, Bernard S. Thimerosal and autism? A plausible hypothesis that should not be dismissed. Med Hypotheses 2004; **62**:788–94.

11 Bradstreet J, Geier DA, Kartzinel JJ, Adams JB, Geier MR. A case-control study of mercury burden in children with autistic spectrum disorders. J Am Phys Surg 2003; **8**:76–9.

12 Braun MM, Mootrey GT, Salive ME, Chen RT, Ellenberg SS. Infant immunization with acellular pertussis vaccines in the United States: assessment of the first two years' data from the Vaccine Adverse Event Reporting System (VAERS). Pediatrics 2000; **106**: E51.

13 Brown LE, Yel L. Thimerosal induces programmed cell death of neuronal cells via changes in the mitochondrial environment. UCI Undergrad Res J 2003; **6**:7–14.

14 Brunner M, Albertini S, Wurgler FE. Effects of 10 known or suspected spindle poisons in the in vitro porcine brain tubulin assembly assay. Mutagenesis 1991; **6**:65–70.

15 Burbacher TM, Shen DD, Liberato N, Grant KS, Cernichiari E, Clarkson TW. Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing Thimerosal. Environ Health Perspect 2005; **113**:1015–21.

16 Chen R, Rosenthal S. An errant critique that misses the mark. Arch Pediatr Adolesc Med 1996; **150**:464–5.

17 Counter SA, Buchanan LH, Ortega F, Laurell G. Elevated blood mercury and neuro-otological observations in children of the Ecuadorian gold mines. J Toxicol Environ Health. 2002; **65**:149–63.

18 Digar A, Sensharma GC, Samal SN. Lethality and teratogenecity of organic mercury (Thimerosal) on the chick embryo. J Anat Soc India 1987; **36**:153–9.

19 DuVernoy TS, Braun MM. Hypotonic-hyporesponsive episodes reported to the Vaccine Adverse Event Reporting System (VAERS), 1996–1998. Pediatrics 2000; **106**:E52.

20 Environmental Working Group. Overloaded? New science, new insights about mercury and autism in Susceptible Children. Washington, DC: EWG Action Fund; 2004.

21 Faustman EM, Silbernagel SM, Fenske RA, Burbacher TM, Ponce RA. Mechanisms underlying children's susceptibility to environmental toxicants. Environ Health Perspect 2000; **108** Suppl 1:13–21.

22 Fine PE, Chen RT. Confounding in studies of adverse reactions to vaccines. Am J Epidemiol. 1992; **136**:121–35.

23 Gasset AR, Itoi M, Ishii Y, Ramer RM. Teratogenicities of ophthalmic drugs II. Teratogenicities and tissue accumulation of Thimerosal. Arch Ophthalmol 1975; **93**:52–5.

24 Geier DA, Geier MR. An assessment of the impact of Thimerosal on neurodevelopmental disorders. Pediatr Rehabil 2003; **6**:97–102.

25 Geier MR, Geier DA Neurodevelopmental disorders after Thimerosal-containing vaccines: a brief communication. Exp Biol Med 2003; **228**:660–4.

26 Geier MR, Geier DA. Thimerosal in childhood vaccines, neurodevelopment disorders, and heart disease in the United States. J Am Phys Surg 2003; **8**:6–11.

27 Geier DA, Geier MR. A comparative evaluation of the effects of MMR immunization and mercury doses from Thimerosal-containing childhood vaccines on the population prevalence of autism. Med Sci Monit 2004; **10**(3):PI33–PI39.

28 Geier DA, Geier MR. A review of the Vaccine Adverse Event Reporting System database. Expert Opin Pharmacother 2004; **5**:691–8.

29 Geier DA, Geier MR Neurodevelopmental disorders following Thimerosal-containing childhood immunizations: a follow-up analysis. Int J Toxicol 2004; **23**:369–76.

30 Geier DA, Geier MR. A two-phased population epidemiological study of the safety of Thimerosal-containing vaccines: a follow-up analysis. Med Sci Monit 2005; **11**(4):CR160–70.

31 Geier DA, Geier MR. Early downward trends in neurodevelopmental disorders following removal of Thimerosal-containing vaccines. J Am Phys Surg 2006; **11**:8–13

32 Geier DA, Geier MR. An assessment of downward trends in neurodevelopmental disorders following removal of Thimerosal from childhood vaccines. Med Sci Monit 2006;**12**(6):CR231–9.

33 Geier DA, Geier MR. An evaluation of the effects of Thimerosal on neurodevelopmental disorders reported following DTP and Hib vaccines in comparison to DTPH vaccine in the United States. J Toxicol Environ Health A 2006;**69**:1481–95.

34 Haber P, Chen RT, Zanardi LR, Mootrey GT, English R, Braun MM; VAERS Working Group (2004) An analysis of rotavirus vaccine reports to the vaccine adverse event reporting system: more than intussusception alone? Pediatrics 2004; **113**:e353–9.

35 Haley BE. Mercury toxicity: genetic susceptibility and synergistic effects. Med Ver 2005; **2**:535–42.

36 Heinonen OP, Slone D, Shapiro S. Birth defects and drugs in pregnancy. Littleon, MA: Publishing Sciences Group, Inc, 1977.

37 Heron J, Golding J; ALSPAC Study Team. Thimerosal exposure in infants and developmental disorders: a prospective cohort study in the United Kingdom does not support a causal association. Pediatrics. 2004; **114**:577–83.

38 Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965; **58**:295–300.

39 Holmes AS, Blaxill MF, Haley BE. Reduced levels of mercury in first baby haircuts of autistic children. Int J Toxicol 2003; **22**:277–85.

40 Hornig M, Chian D, Lipkin WI. Neurotoxic effects of postnatal Thimerosal are mouse strain dependent. Mol Psychiatry 2004; **9**:833–45.

41 Humphrey ML, Cole MP, Pendergrass JC, Kiningham KK. Mitochondrial mediated Thimerosal-induced apoptosis in a human neuroblastoma cell line (SK-N-SH). Neurotoxicology 2005; **26**:407–16.

42 Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. Association between Thimerosal-containing vaccine and autism. JAMA 2003; **290**:1763–6.

43 Institute of Medicine (US). Immunization safety review: vaccines and autism. Washington, DC: National Academy Press, 2004.

44 Itoi M, Ishii Y, Kaneko N. Teratogenicities of antiviral ophthalmics on experimental animals. Jpn J Clin Opthal 1972; **26**:631–40.

45 James SJ, Cutler P, Myelnyk S, Jernigan S, Janak L, Gaylor DW, et al. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. Am J Clin Nutr 2004; **80**:1611–7.

46 James SJ, Slikker W 3rd, Melnyk S, New E, Pogribna M, Jernigan S. Thimerosal neurotoxicity is associated with glutathione depletion: protection with glutathione precursors. Neurotoxicology 2005; **26**:1–8.

47 Lloyd JC, Haber P, Mootrey GT, Braun MM, Rhodes PH, Chen RT; VAERS Working Group. Adverse event reporting rates following tetanus-diphtheria and tetanus toxoid vaccinations: data from the Vaccine Adverse Event Reporting System (VAERS), 1991–1997. Vaccine 2003; **21**:3746–50.

48 Madsen KM, Lauritsen MB, Pedersen CB, Thorsen P, Plesner AM, Andersen PH, Mortensen PB. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. Pediatrics 2003; **112**:604–6.
49 McGinnis WR. Oxidative stress in autism. Altern Ther Health Med 2004; **10**:22–36.
50 McMahon AW, Iskander J, Haber P, Chang S, Woo EJ, Bruan MM, et al. Adverse events after inactivated influenza vaccination among children less than 2 years of age: analysis of reports from the vaccine adverse event reporting system, 1990–2003. Pediatrics 2005; **115**:453–60.
51 Mutkus L, Aschner JL, Syversen T, Shanker G, Sonnewald U, Aschner M. In vitro uptake of glutamate in GLAST- and GLT-1-transfected mutant CHO-K1 Cells is inhibited by the ethylmercury-containing preservative Thimerosal. Biol Trace Elem Res 2005; **105**:71–86.
52 Mutter J, Naumann J, Schneider R, Walach H, Haley B. Mercury and autism: Accelerating Evidence? Neuro Endocrinol Lett 2005; **26**:439–46.
53 Parran DK, Barker A, Ehrich M. Effects of Thimerosal on NGF signal transduction and cell death in neuroblastoma cells. Toxicol Sci 2005; **86**:132–140.
54 Parry JM. An evaluation of the use of in vitro tubulin polymerisation, fungal and wheat assays to detect the activity of potential chemical aneugens. Mutation Res 1993; **287**:23–8.
55 Pool V, Braun MM, Kelso JM, Mootrey G, Chen RT, Yunginger JW, et al. Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after measles-mumps rubella vaccine in the United States. Pediatrics 2002; **110**:E71.
56 Plotkin SA, Orenstein WA. Vaccines, 3rd Edition. New York, New York: W. B. Saunders Company, 1999.
57 Redwood L, Bernard S, Brown D. Predicted mercury concentrations in hair from infant immunizations: cause for concern. Neurotoxicology 2001; **22**:691–7.
58 Rimland B. Association between Thimerosal-containing vaccine and autism. JAMA 2004; **291**:180.
59 Rosenthal S, Chen R, Hadler S. The safety of acellular pertussis vaccine vs whole-cell pertussis vaccine. A postmarketing assessment. Arch Pediatr Adolesc Med 1996; **150**:457–60.
60 Singleton JA, Lloyd JC, Mootrey GT, Salive ME, Chen RT. An overview of the vaccine adverse event reporting system (VAERS) as a surveillance system. VAERS Working Group. Vaccine 1999; **17**:2908–17.
61 Stehr-Green P, Tull P, Stellfeld M, Mortenson PB, Simpson D. Autism and Thimerosal-containing vaccines: lack of consistent evidence for an association. Am J Prev Med. 2003; **25**:101–6.
62 Trelka JA, Hooker BS. More on Madsen's analysis. J Am Phys Surg. 2004; **9**:101.
63 Verstraeten T, Davis RL, DeStefano F, Lieu TA, Rhodes PH, Black SB, et al. Safety of Thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases. Pediatrics. 2003; **112**:1039–48.
64 Verstraeten T. Thimerosal, the Centers for Disease Control and Prevention, and GlaxoSmithKline. Pediatrics. 2004; **113**:932.
65 Wallin M, Hartely-Asp B. Effects of potential aneuploidy inducing agents on microtubule assembly in vitro. Mutation Res. 1993; **287**:17–22.
66 Waly M, Olteanu H, Banerjee R, Choi SW, Mason JB, Parker BS, et al. Activation of methionine synthase by insulin-like growth factor-1 and dopamine: a target for neurodevelopmental toxins and Thimerosal. Mol Psychiatry. 2004; **9**:358–70.
67 Wattigney WA, Mootrey GT, Braun MM, Chen RT Surveillance for poliovirus vaccine adverse events, 1991 to 1998: impact of a sequential vaccination schedule of inactivated poliovirus vaccine followed by oral poliovirus vaccine. Pediatrics. 2001; **107**:E83.
68 Yel L, Brown LE, Su K, Gollapudi S, Gupta S. Thimerosal induces neuronal cell apoptosis by causing cytochrome c and apoptosis-inducing factor release from mitochondria. Int J Mol Med 2005; **16**:971–7.