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# A two-phased population epidemiological study of the safety of thimerosal-containing vaccines: a follow-up analysis

**Authors' Contribution:**
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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**Potential Conflict of Interest:** Dr. Mark Geier has been an expert witness and consultant in cases in involving vaccines before the no-fault National Vaccine Injury Compensation Program (NVICP) and in civil litigation. David Geier has been a consultant in cases involving vaccines before the no-fault NVICP and in civil litigation

## Summary

**Background:** Thimerosal is an ethylmercury-containing preservative in vaccines. Toxicokinetic studies have shown children received doses of mercury from thimerosal-containing vaccines (TCVs) that were in excess of safety guidelines. Previously, an ecological study showing a significant association between TCVs and neurodevelopmental disorders (NDs) in the US was published in this journal.

**Material/Methods:** A two phased population-based epidemiological study was undertaken. Phase one evaluated reported NDs to the Vaccine Adverse Event Reporting System (VAERS) following thimerosal-containing Diphtheria-Tetanus-acellular-Pertussis (DTaP) vaccines in comparison to thimerosal-free DTaP vaccines administered from 1997 through 2001. Phase two evaluated the automated Vaccine Safety Datalink (VSD) for cumulative exposures to mercury from TCVs at 1-, 2-, 3-, and 6-months-of-age for infants born from 1992 through 1997 and the eventual risk of developing NDs.

**Results:** Phase one showed significantly increased risks for autism, speech disorders, mental retardation, personality disorders, and thinking abnormalities reported to VAERS following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. Phase two showed significant associations between cumulative exposures to thimerosal and the following types of NDs: unspecified developmental delay, tics, attention deficit disorder (ADD), language delay, speech delay, and neurodevelopmental delays in general.

**Conclusions:** This study showed that exposure to mercury from TCVs administered in the US was a consistent significant risk factor for the development of NDs. It is clear from these data and other recent publications linking TCVs with NDs that additional ND research should be undertaken in the context of evaluating mercury-associated exposures and thimerosal-free vaccines should be made available.

**key words:** **mercury • merthiolate • thimerasol • thiomersal • VAERS • VSD**

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## Background

The United States is in the midst of an epidemic of neurodevelopmental disorders [1–6]. It has been estimated that prevalence of autism has increased from 7.5 per 10,000 children (1 in 1,333 children) among children born in the mid-1980s to 31.2 per 10,000 children (1 in 323 children) among children born in the late-1990s, an approximate 4-fold increase in childhood autism in about one decade [6]. In 2004, the Department of Health and Human Services and the American Academy of Pediatrics issued an Autism ALARM stating that presently 1 in 166 children have an autistic disorder, and 1 in 6 children have a developmental and/or behavior disorder. Autism, once a rare disorder, has now been found to be more prevalent than childhood cancer, diabetes and Down Syndrome [6]. It has been reported that explanations such as immigration, or shifts in diagnostic criteria cannot explain the observed increase, and the phenomena is driven by factors beyond improved identification and diagnosis [1,6,7].

Thimerosal is an ethylmercury-containing preservative (49.6% mercury by weight) that historically has been added to many vaccines [8]. Thimerosal has been recognized by the California Environmental Protection Agency, Office of Environmental Health Hazard Assessment as a developmental toxin, meaning that it can cause birth defects, low birth weight, biological dysfunctions, or psychological or behavior deficits that become manifest as the child grows, and that maternal exposure during pregnancy can disrupt the development or even cause the death of the fetus. Despite this fact, thimerosal is still routinely added to several vaccines given to US children and pregnant women (e.g. influenza, Tetanus-diphtheria, meningitis, and monovalent tetanus). Further, many nations still add thimerosal to many of their pediatric vaccines. The World Health Organization (WHO) and several vaccine manufacturers still advocate the continued use of thimerosal in pediatric vaccines.

Standard vaccine practices in the United States during the past several decades exposed many children to levels of mercury that exceeded Federal Safety Guidelines for the oral ingestion of methylmercury, and also exposed children to levels of mercury that exceeded the United States Environmental Protection Agency (EPA)'s permissible hair mercury limit [8,9]. Concurrent with increasing trends in neurodevelopmental disorders in the United States, the Centers for Disease Control and Prevention (CDC) expanded the childhood immunization schedule. Under the expanded vaccine schedule, if infants received all thimerosal-containing vaccines, they could have been exposed to 12.5 micrograms (μg) of mercury at birth, 62.5 μg of mercury at 2 months, 50 μg of mercury at 4 months, 62.5 μg of mercury at 6 months, and 50 μg of mercury at approximately 18 months, for a total of 237.5 μg of mercury. Additionally, if three thimerosal-containing influenza vaccines were administered during the first 18 months of life, as were suggested for certain populations, then the total mercury exposure could have been as high as 275 μg of mercury [8,9].

Researchers have reported that exposure to mercury can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with autistic disorders, and that these similarities extend to neuroanatomy, neurotransmitters, and biochemistry [10–12].

An ecological study evaluating the relationship between the average mercury doses children received from thimerosal-containing vaccines in comparison to the prevalence of autism was previously published in this journal. The results of that study showed, when evaluating birth cohorts from the mid-1980s through the late 1990s, there was an increasing linear correlation between the amount of mercury children received from thimerosal-containing vaccines and the cohort prevalence of autism [13].

The purpose of this study was to extend previous epidemiological studies, and further evaluate the relationship between thimerosal-containing childhood vaccines and neurodevelopmental disorders in a two-phase study. The first phase consisted of an epidemiological examination of the publicly available Vaccine Adverse Event Reporting System (VAERS) database for the rate of reported neurodevelopmental disorders reported following thimerosal-containing Diphtheria-Tetanus-acellular-Pertussis (DTaP) vaccines in comparison to thimerosal-free DTaP vaccines. The second phase consisted of an epidemiological examination of the Vaccine Safety Datalink (VSD) database. In examining the VSD database, an evaluation of the amount of mercury children received from thimerosal-containing vaccines at specific times in the first year of life was studied. The risk of developing neurodevelopmental disorders was determined from such exposures. The two phases of the present study were employed, so as to see if one could observe a consistent overall association between thimerosal-containing vaccines and neurodevelopmental disorders, in two entirely different databases, whilst utilizing two entirely different epidemiological methods of study.

## Material and Methods

### Phase I: The VAERS database

The VAERS database 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 [7]. 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 [14].

In order to examine VAERS correctly in this study, a technique developed by Rosenthal et al. from the National Immunization Program (NIP) of the CDC [15] was employed. This technique involves comparing two different types of vaccines that were administered to aged-matched populations, and using the net number of doses distributed 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 is used as the denominator to determine incidence rates of reported adverse events to the VAERS data-

**Table 1.** The composition of the DTaP vaccines under study in the VAERS database.

| Vaccine Component | Thimerosal-Containing DTaP Vaccine (Aventis Pasteur – Connaught) | Thimerosal-Containing DTaP Vaccine (Wyeth – Lederle) | Thimerosal-Free DTaP Vaccine (SmithKline Beecham) |
|---|---|---|---|
| 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 |

base. 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.

The strength of the VAERS database 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. This would especially be true for the emergence of an unexpected new side-effect. So, when a new effect, such as autism, emerges in the database even prior to significant media attention, one must take the occurrence seriously. The reporting of vaccine-associated adverse events must also be evaluated to determine whether systemic error or bias is present in the data examined.

***Analysis methods***

In the first phase of the present study, a historical examination of the VAERS database (online public access version; reports entered through 31 March 2004) was undertaken using Microsoft Access™.

In this study a case-control epidemiological assessment of VAERS was undertaken by evaluating childhood neurodevelopment disorders reported following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. The neurodevelopmental adverse events analyzed in VAERS included: autism (Costart Term = Autism), mental retardation (Costart Term = Mental Retard), speech disorders (Costart Term = Speech Dis), thinking abnormalities (Costart Term = Thinking Abnorm), and personality disorders (Costart Term = Person Dis). 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.

The Biological Surveillance Summaries of the CDC, as segregated by vaccine manufacturer, determined the number of thimerosal-containing and thimerosal-free DTaP vaccines (1997 through 2001) doses distributed/administered. The Biological Surveillance Summaries indicated that 59,720,009 thimerosal-containing DTaP vaccines and 29,161,630 thimerosal-free DTaP vaccines were distributed/administered from 1997 through 2001. In Table 1, the composition of the DTaP vaccines analyzed are summarized [16].

A number of controls were employed to determine if systematic error or bias was present among the data examined. In this study control adverse events were evaluated to determine if potential bias was present in the reporting of adverse events in VAERS, including: accidental injury (Costart Code: Injury Accid), conjunctivitis (Costart Code = Conjunctivitis), and febrile seizures (Costart Code: Febrile Seizure). Neutral adverse events are those adverse events that based on their biological plausibility would not be expected to be affected by thimerosal in the vaccines under study.

The distribution, health status, and geographical dispersion of the data examined in VAERS were also evaluated because these factors might affect reporting of adverse events. In determining the distribution of the populations reviewed, the overall median age and total numbers of male and female reports of adverse events to VAERS were examined. In evaluating the health status of the populations reviewed, the total

number of reports specifying a past medical history in VAERS was examined. Similarly, in reviewing the geographical dispersion of the populations analyzed, one examined the total number of adverse event reports submitted to VAERS from large representative states in the western (California), central (Illinois), and eastern (Florida) regions of the US.

***Statistical analyses***

The premise of equality between the groups examined forms the basis of the null hypothesis employed in the present study. Odds Ratios (OR), 95% OR Confidence Intervals (CI) for reported adverse events, and *p*-values were determined from 2×2 contingency tables employed in the present study. The statistical package in StatsDirect™ (Version 2.4.1) was employed, and the nominal statistical tests of Yate's $\chi^2$ statistic or Fisher's exact test statistic ($n<5$) were used to determine statistical significance. In order for statistical significance testing to be performed for an adverse event, a total of 25 adverse events were required to be identified following the vaccines under study administered from 1997 through 2001 in the VAERS database. A two-sided *p*-value <0.05 was considered statistically significant.

**Phase II: The VSD database**

***Study participants***

In this study, the VSD database and CDC-VSD database research materials were analyzed. VSD was created in 1991 by the NIP of the CDC. The project links medical event information, vaccine history, and selected demographic information from the computerized clinical databases of four health maintenance organizations (HMO)s: Group Health Cooperative of Puget Sound (GHC) in Seattle, Washington; Kaiser Permanente Northwest (NWK) in Portland Oregon; Kaiser Permanente Medical Care Program of Northern California (NCK) in Oakland, California; and Southern California Kaiser Permanente (SCK) in Los Angeles, California. HMO members have unique HMO identification numbers that can be used to link data on their medical services within the HMO. Vaccination data are derived from computerized immunization tracking systems, maintained by each of the HMOs. Quality control comparisons of the computerized immunization data with information recorded in paper medical records have shown high levels of agreement. For medical encounters, each of the HMOs maintains computerized databases on all hospital discharges and emergency room visits; diagnoses from outpatient clinic encounters are available from some of the HMOs for certain years [17–19]. At the present time, only the CDC and the authors have access to the VSD database.

***Analysis methods***

In the present study, as independent researchers, we analyzed data from a cohort of children born between 1992 and 1997 into one of the two HMOs with the most complete automated outpatient data sets (GHC and NCK). For these two HMOs, follow-up data to the end of 1998 was analyzed. Children in the cohort, thus, have a follow-up time of 1 to 7 years.

To ensure capture of all vaccinations in the first year of life within the HMO the cohort was restricted to children who were born into the HMO, continuously enrolled for the first year of life, and received at least 2 polio vaccines within the HMO by the age of 1 year. Infants with ICD-9 codes indicative of congenital disorders, severe perinatal disorders, recipients of hepatitis B immunoglobulins, and those who were born at gestational age of less than 38 completed weeks were excluded.

***Exposure assessment***

The cumulative exposure to ethylmercury from individual automated vaccination records were calculated, assuming each vaccine to contain the mean dose reported by manufacturers to the Food and Drug Administration (FDA). This cumulative exposure was assessed at the end of the first, second, third, and sixth months of life. The thimerosal content of childhood vaccines used in the two HMOs is as follows: hepatitis B vaccine: 25 µg (12.5 µg of mercury); *Haemophilus Influenzae Type b* (Hib): 50 micrograms (25 µg of mercury); Diphtheria-Tetanus-Pertussis (whole-cell or acellular): 50 micrograms (25 µg of mercury); and Polio, Mumps, Rubella, Varicella, and Pneumococcal vaccines: 0 µg of mercury.

***Outcome assessment***

A case was defined as any child who was assigned one of the following developmental disability *International Classification of Diseases, 9*$^{h}$ *Revision* (ICD-9) codes, including: autism (299.0), other childhood psychosis (299.8), other unspecified childhood psychosis (299.9), stammering (307.0), tics (307.2), repetitive movements (307.3), sleep disorders (307.4), eating disorders (307.5), enuresis (307.6), disturbance of emotions specific to childhood and adolescence (313), attention deficit disorder (314.0), specific delays in development (315.x), mental retardation (317–319). No distinction was made on whether a code was assigned after a clinic visit or hospital stay.

***Statistical analyses***

A Cox proportional hazard model was used to compare the risk of developing any of the outcomes among different levels of exposure. By stratifying on HMO, year and month of birth, children were compared that were born within the same month at the same HMO. The data were adjusted in the models for gender only. By using the age of the child as the time variable in the proportion hazard model, it was possible to ensure comparison of children of equal age. The end point used was whichever of the following occurred first: the date of first diagnosis, the date of first disenrollment from the HMO or the last day of the follow-up period, December 31, 1998. To obtain 80% power in identifying a minimal relative risk of 2, it was estimated that the minimal number of cases for any outcome to be 50. The data was evaluated to determine the impact of increased mercury exposure on the risk of any individual outcome for which at least 50 cases were identified. Because of different coding practices between HMOs, and uncertainty on the specific neurological outcomes related to mercury exposure, the data was assessed for the entire category of neurodevelopmental disorders.

## RESULTS

**Phase I**

In this assessment of the VAERS database, it was revealed that 7,925 total adverse event reports were reported in those

**Table 2.** A summary of the population distribution, geographical dispersion, health status, and control events for reported adverse events examined in the VAERS database following thimerosal-containing and thimerosal-free DTaP vaccines administered from 1997 through 2001.

| Outcomes analyzed | Reported incidence per million thimerosal--containing DTaP (# of reports) | Reported incidence per million thimerosal-free DTaP (# of reports) | Odds ratio for reported events | 95% Odds ratio confidence interval for reported events | p-value (Yate's $\chi 2$ value) |
|---|---|---|---|---|---|
| Male Reports | 70.0 (4,151) | 72.0 (2,090) | 0.97 | 0.92–1.02 | 0.26 (1.27) |
| Female Reports | 60.0 (3,587) | 62.0 (1,815) | 0.97 | 0.91–1.02 | 0.22 (1.49) |
| Past Medical Histories | 108.0 (6,465) | 106.0 (3,098) | 1.02 | 0.98–1.1 | 0.39 (0.72) |
| California Reports | 10.0 (689) | 13.0 (375) | 0.90 | 0.79–1.02 | 0.10 (2.75) |
| Illinois Reports | 5.4 (323) | 5.2 (151) | 1.04 | 0.86–1.3 | 0.69 (0.15) |
| Florida Reports | 5.1 (304) | 4.8 (140) | 1.06 | 0.87–1.3 | 0.60 (0.27) |
| Febrile Seizures | 2.8 (169) | 2.3 (66) | 1.2 | 0.94–1.7 | 0.14 (2.17) |
| Conjunctivitis | 0.64 (38) | 0.51 (15) | 1.2 | 0.68–2.4 | 0.58 (0.31) |
| Accidental Injury | 0.47 (28) | 0.34 (10) | 1.4 | 0.68–2.9 | 0.50 (0.46) |

All *p*-values determined using the Yate's $\chi^2$ test statistic. The Biological Surveillance Summaries indicated that 59,720,009 thimerosal-containing DTaP vaccines and 29,161,630 thimerosal-free DTaP vaccines were distributed/administered from 1997 through 2001, and were used as the denominators to determine the above calculated reported incidence rates of adverse events to the VAERS database.

receiving thimerosal-containing DTaP vaccines and 3,948 total adverse events reports were reported in those receiving thimerosal-free DTaP vaccines (OR=0.98, $p$=0.31, 95% CI=0.94–1.02). The overall median age for the total adverse event reports reported was 1.3 years-old, among those receiving thimerosal-containing DTaP vaccines or thimerosal-free DTaP vaccines.

Table 2 summarizes the distribution, health status, and geographical dispersion included in adverse event reports submitted to the VAERS database following thimerosal-containing and thimerosal-free DTaP vaccines. It was found that both thimerosal-containing and thimerosal-free DTaP vaccines were administered to populations having a similar distribution, health status, and geographical dispersion. It was determined that the neutral control adverse events of accidental injury (OR=1.4, $p$=0.50, 95% CI=0.68–2.9), febrile seizures (OR=1.2, $p$=0.14, 95% CI=0.94–1.7), and conjunctivitis (OR=1.2, $p$=0.58, 95% CI=0.68–2.4) were reported similarly to VAERS following administration of thimerosal-containing and thimerosal-free DTaP vaccines.

The results of the first epidemiological assessment conducted in this study are shown in Table 3, where neurodevelopmental disorders reported to VAERS in the thimerosal-containing DTaP and thimerosal-free DTaP vaccines are compared. Specifically, a significant association was observed between thimerosal-containing DTaP vaccines and neurodevelopmental disorders, in comparison to thimerosal-free DTaP vaccines, for the following neurodevelopmental disorders, including: autism (OR=1.8, $p$<0.02, 95% OR CI=1.1–3.0), speech disorders (OR=2.6, $p$<0.001, 95% OR CI=1.5–4.6), mental retardation (OR=3.2, $p$<0.0002, 95% CI=1.8–5.9), personality disorders (OR=2.3, $p$<0.005, 95% OR CI=1.4–4.5), thinking abnormalities (OR=4.7, $p$<0.005, 95% OR CI=1.5–24).

**Phase II**

Table 4 shows the number of children included in the cohort and the effect of the different eligibility criteria on the present assessment of the VSD database. The final number of children thus included in the cohort examined was 109,993. Table 5 shows the number of cases encountered for each disorder, the mean age at first diagnosis, the distribution over the two HMOs, and the percentage males among cases.

In examining the VSD database, it was determined that there were significant ($p$<0.05) positive correlations (not adjusting for multiple comparisons) per 1 microgram exposure for the following outcomes, including: tics (3 months of age: relative risk =1.021, 95% CI=1.004–1.039), attention deficit disorder (ADD) (6 months of age: relative risk =1.006, 95% CI1.001–1.010), unspecified delays (2 months of age: relative risk =1.005, 95% CI=1.001–1.008), language delay (1 month of age: relative risk =1.019, 95% CI=1.004–1.019; 3 months of age: relative risk =1.021, 95% CI=1.012–1.030; and 6 months of age: relative risk =1.006, 95% CI=1.002–1.011), speech delay (1 month of age: relative risk =1.011, 95% CI=1.004–1.019; 3 months of age: relative risk =1.008, 95% CI=1.004–1.013; and 6 months of age: relative risk =1.002, 95% CI=1.000–1.004), and developmental delay (1 month of age: relative risk =1.007, 95% CI=1.002–1.012; 3 months of age: relative risk =1.007, 95% CI=1.004-1.010; and 6 months of age: relative risk =1.003, 95% CI=1.001–1.004). Therefore, it was observed, based upon the present assessment of the VSD database, that there were significant associations between cumulative thimerosal exposure and outcomes in a total of 12 categories out of a possible 44 thimerosal exposure-outcome categories examined (27% of the total thimerosal exposure-outcome categories examined), and there were significant associations between cumulative thimerosal exposure and outcomes in a total of six out of a possi-

**Table 3.** A summary of neurodevelopmental disorder adverse events reported to the VAERS database following thimerosal-containing and thimerosal-free DTaP administered from 1997 through 2001.

| Type of vaccine | Autism | Speech disorders | Mental retardation | Personality disorders | Thinking abnormalities |
|---|---|---|---|---|---|
| Reported incidence per million thimerosal-containing DTaP (# of reports) | 1.3 (78) | 1.2 (75) | 1.3 (79) | 1.1 (67) | 0.48 (29) |
| Reported incidence per million thimerosal-free DTaP (# of reports) | 0.72 (21) | 0.48 (14) | 0.41 (12) | 0.48 (14) | 0.10 (3) |
| Odds ratio for reported adverse events | 1.8 | 2.6 | 3.2 | 2.3 | 4.7 |
| 95% Odds ratio confidence interval for reported adverse events | 1.1–3.0 | 1.5–4.6 | 1.8–5.9 | 1.3–4.2 | 1.5–24 |
| *p*-value (Yate's $X^2$ value) | <0.02 (5.53) | <0.001 (11.01) | <0.0002 (15.02) | <0.005 (8.17) | <0.005* |

The Biological Surveillance Summaries indicated that 59,720,009 thimerosal-containing DTaP vaccines and 29,161,630 thimerosal-free DTaP vaccines were distributed/administered from 1997 through 2001, and were used as the denominators to determine the above calculated reported incidence rates of adverse events to the VAERS database. All p-values determined using the Yate's $\chi 2$ test statistic, except * determined using the fisher's exact test statistic.

**Table 4.** Number of children included in our VSD study.

| Selection parameter | Number of children |
|---|---|
| Born into Group Health Cooperative or Northern California Kaiser between 1992 and 1997 | 213,185 |
| Continuously enrolled for 1 Year | 142,264 |
| Not premature | 139,391 |
| Did not receive Hepatitis B immunoglobulin | 132,114 |
| No congenital or perinatal disorder | 109,993 |

ble 11 outcome categories examined (55% of the total outcome categories examined).

## Discussion

The results of the present examination of the VAERS database show a significant relationship between thimerosal-containing childhood vaccines 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 thimerosal-containing childhood immunizations. Importantly, all other neurodevelopmental disorders reflected a higher odds ratio than autism. This argues strongly against the possibility of media bias effect of reporting about the alleged association to autism. Taken collectively, the increased risk associated with all five disorders, any of which could independently be an indicator of possible mercury toxicity, favors an association between thimerosal-containing vaccines and neurodevelopmental disorders based on this controlled assessment of the VAERS database.

The CDC-developed epidemiological technique employed in this study continues to be used by the NIP of the CDC to evaluate the safety of vaccines in the VAERS database [20]. Chen and Rosenthal from the NIP have published that the potential limitations in VAERS database, such as: underreporting, erroneous reporting, frequent multiple exposures, multiple outcomes, and lack of precise denominators, should apply equally to both vaccines administered to similarly-aged populations, and allow for determination of accurate, relative, quantitative relationships between vaccines and adverse outcomes [21]. Additionally, a recent review has examined the utility of this method to analyze the VAERS database, and has concluded that studies examining the VAERS database 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 [22].

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

**Table 5.** Number of children identified per disorder and some patient characteristics.

| ICD-9 Code | Description | Total | Age* | GHC (%) | NCK (%) | Male (%) |
|---|---|---|---|---|---|---|
| | Neurologic developmental disorder | 3,114 | 32 | 36 | 64 | 69 |
| 299.0 | Autism | 127 | 42 | 14 | 86 | 83 |
| 299.8 | Other childhood psychosis | 51 | 49 | 22 | 78 | 92 |
| 299.9 | Other unspecified psychosis | 31 | 45 | 100 | 0 | 84 |
| 307.0 | Stammering | 105 | 40 | 51 | 49 | 71 |
| 307.2 | Tics | 104 | 44 | 36 | 64 | 67 |
| 307.3 | Repetitive movements | 2 | 20 | 100 | 0 | 50 |
| 307.4 | Sleep disorders | 150 | 27 | 42 | 58 | 57 |
| 307.5 | Eating disorders | 78 | 21 | 9 | 91 | 53 |
| 307.6 | Enuresis | 20 | 59 | 10 | 90 | 70 |
| 313.0 | Disturbances of emotions | 28 | 35 | 54 | 46 | 66 |
| 314.0 | Attention deficit syndrome | 374 | 49 | 20 | 80 | 80 |
| 315.31 | Developmental language delay | 351 | 34 | 4 | 96 | 74 |
| 315.39 | Developmental speech delay | 1,533 | 33 | 38 | 62 | 71 |
| 315.9 | Unspecified developmental delay | 555 | 25 | 50 | 50 | 65 |
| 317–319 | Mental retardation | 17 | 48 | 12 | 88 | 63 |

* at first diagnosis, in months.
GHC – Group Health Cooperative; NCK – Northern California Kaiser.

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. The probability that exposure to other sources of mercury were similar, among those receiving thimerosal-containing or thimerosal-free DTaP vaccines, is further supported by the fact that there were similar geographical dispersions and health statuses in both groups.

The second phase of the present study was designed to determine whether the affect from thimerosal-containing childhood vaccines on neurodevelopmental disorders observed in the VSD database was consistent with observations made in the VAERS database. The second phase revealed significant positive correlations between exposure to thimerosal-containing childhood vaccines at specific times and the relative risk of eventually developing neurodevelopmental disorders. Specifically, it was observed that there were significant positive correlations between exposure at 2 months of age and unspecified developmental delays, exposure at 3 months of age and tics, exposure at 6-months of age and attention deficit disorder, and exposure at 1, 3, and 6 months of age and language delay, speech delay, and neurodevelopmental delays in general.

In considering the results from the VSD database, there may have been some limitations. Some misclassification errors may have occurred in the assessment of the inclusion/exclusion criteria: some hepatitis B immunoglobulin administrations may have been missed and some premature children may not have been classified as such. Some misclassifications error may have also occurred in the exposure assessment: some vaccinations, particularly the neonatal hepatitis B vaccine dose, may not have been reported. It is not always possible to differentiate, using the available automated data, between single dose thimerosal-free Hib vaccines and multi-dose thimerosal-containing Hib vaccines. The analyses were done assuming all vaccines to come from multi-dose vials. An analysis assuming all Hib vaccines had come from single dose-vials did not substantially alter the results. It is likely that in the case of a true effect of thimerosal, all of these sources of potential errors were likely to bias towards the null hypothesis.

Some misclassification errors may have occurred in the outcome assessment in the VSD database as ICD-9 codes, that lack specificity for certain disorders and are prone to errors by the person (often administrative) coding and at data entry level, were used from automated data. Such misclassification is likely to cause an error in the findings for some specific ICD-9 codes that may not have an obvious clinical correlate such as ICD-9 code 315.30 (other developmental speech or language disorder) or ICD-9 code 315.9 (unspecified delay in development). There is no reason to think that this error would occur differentially among the exposure categories, and it is, therefore, unlikely to affect the results of our assessment of the VSD database. Additionally, no information was available on potential predisposing factors,

such as maternal smoking, lead exposure or fish consumption in this assessment of the VSD database. However, it is not clear how these factors would be related to the exposure measured and are felt to be unlikely to cause any bias, as they would be expected to occur equally in all exposure groups examined.

It is also important to realize that in the present assessment of the VSD database, analyses were limited to a list of potential outcomes based upon results gleaned from the VAERS database assessment. Other disorders potentially related to exposure to ethylmercury cannot be ruled-out. Only relatively severe conditions that come to medical attention in this assessment of the VSD database could be evaluated in the present study, and more subtle effects that would require neuropsychological testing could not be studied. Additionally, because a number of the disorders examined occurred at relatively low frequencies in the cohorts examined in the VSD, it is possible that other associations between thimerosal-containing vaccines and neurodevelopmental disorders may have been missed in this analysis of the VSD database.

Furthermore, there may be other limitations in considering results obtained from the VSD database. It should be noted that a number of potential outcomes in the VSD database were examined. Eleven total outcome categories were statistically evaluated in the VSD. Since each outcome category was evaluated based upon exposure to thimerosal at 4 different ages within the first 6 months of life, there were a total of 44 thimerosal exposure-outcome categories. Therefore, there is the possibility that false-positive statistically significant results may have been observed because a $p$-value $<0.05$ was accepted as significant. It is expected, based upon chance alone, that 1 in 20 analyses would yield a significant result. Since, there were a total of 44 possible thimerosal exposure-outcome categories, it is expected that approximately two of the 12 statistically significant associations observed between thimerosal-containing vaccines and neurodevelopmental disorder outcomes could be due to chance, and in the statistical examination of the 11 possible outcome categories, there is a potential that less than one of the six statistically significant associations observed between thimerosal-containing vaccines and neurodevelopmental disorder outcomes could be due to chance.

In considering this possibility, in an attempt to minimize the effects of observing false-positive statistically significant results in the present examination of the VSD database a number of controls were employed: (1) limiting the types of neurodevelopmental disorders examined in the VSD database to outcomes that were identified on an *a priori* basis as potentially associated with thimerosal-containing vaccines based upon an assessment of the VAERS database; (2) analyzing several cumulative exposure categories (i.e. cumulative thimerosal exposure at 1-, 2-, 3-, and 6-months of age) for consistency of the observed association between thimerosal exposure and the outcome; and (3) analyzing a dose-response effect for the association between thimerosal exposure and the outcome for each cumulative thimerosal exposure category (i.e. meaning that a statistically significant result was yielded from the statistical trend of multiple individual data points in a single cumulative thimerosal exposure category).

In addition, since the epidemiological methodology employed to evaluate the VSD database (cohort study) was completely distinct from the one used to examine the VAERS database (case-control study), and since the reporting base for VAERS and VSD are distinctive (i.e. VAERS has vaccine-associated reported adverse events, whereas VSD has the complete medical records of patients), one would have to consider the epidemiological evidence present in this study as strong evidence of a relationship between the administration of thimerosal-containing childhood vaccines in the United States and neurodevelopmental disorders. Additionally, authors from the CDC previously asserted that the method of analysis employed in this study is the appropriate manner by which to analyze vaccine safety concerns [23]. Therefore, one can conclude based upon observations from the present study, that indeed, there was a consistent significant overall causal association between thimerosal-containing vaccine exposure and neurodevelopmental disorders, observed in both the VAERS and VSD databases.

Other large population-based epidemiological studies conducted outside the United States have not shown an apparent relationship between thimerosal-containing childhood vaccines and neurodevelopmental disorders. However, they have been conducted in countries (e.g. England, Denmark, and Sweden) utilizing very different exposures to mercury from thimerosal-containing childhood vaccines [24–28]. In these countries, children were exposed to doses of mercury from thimerosal-containing childhood vaccines that were approximately 1/3$^{rd}$ as much as those administered in US childhood vaccines. Additionally, the children in these countries received thimerosal-containing childhood vaccines in a much less rigorous schedule (i.e. in the United States, mercury dosing from thimerosal-containing childhood vaccines began on the day of birth, and continued at periodic intervals, throughout the first 6 months of life).

There is one epidemiological study conducted in the United States that failed to report a significant association between thimerosal-containing vaccines and neurodevelopmental disorders. However, even this study 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 did not find a consistent effect. The lead author concluded that their study was neutral (i.e. could neither accept nor reject a causal relationship) regarding the relationship between thimerosal and neurodevelopmental disorders [29,30]. The remaining epidemiological studies that have been conducted in the United States have found a significant association between thimerosal-containing childhood vaccines and neurodevelopmental disorders [13,31–34].

It is important when evaluating the results of large population-based epidemiological studies to recognize that they represent an inference of effects on populations drawn many years after the occurrence of the event. Therefore, large population-based epidemiological studies provide one piece of evidence, indicating an area of research requiring more direct clinical and molecular studies to evaluate a given phenomena. In the case of thimerosal, there now have been extensive clinical and molecular studies that clearly describe the ability of thimerosal-containing childhood vaccines to occasion neurodevelopmental disorders.

A recent clinical study by Bradstreet et al. evaluated the concentration of heavy metals in the urine among a population of children with autistic spectrum disorders in comparison to a neurotypical control population [35]. Based on excretion following an identical three-day oral provocation with *meso* 2,3-dimercaptosuccinic acid (DMSA), it was observed that there were approximately 6-times significantly greater urinary mercury concentrations among vaccinated cases matched to vaccinated neurotyptical controls, whereas children with autistic spectrum disorders had similar urinary cadmium and lead concentrations in comparison to neurotypical controls. Similar urinary mercury concentrations were observed among matched vaccinated neurotypical children and unvaccinated neurotypical children following DMSA treatment. Similarly, Holmes et al. have examined the ability to excrete mercury by examining mercury levels in the first baby haircuts of autistic children in comparison to non-autistic control children [36]. They demonstrated that the severity of autism was inversely proportional to the level of mercury in their baby hair, which was very low compared to controls, and suggested that autistic children had an inability to excrete mercury. Together, these clinical observations suggest that autistic children have significantly higher body-burdens of mercury than neurotypical children following exposure to mercury.

The biochemical and genomic basis for the increased body-burden of mercury in autistic children have been identified. James et al. have evaluated the methionine cycle and transsulfuration metabolites in autistic children in comparison to age- and sex-matched control children [37,38]. It was determined that there were significant decreases in the plasma concentration of cysteine (19% reduction) and glutathione (46% reduction), both of which are crucial for mercury excretion, in autistic children in comparison to control children. Additionally, consistent with the DMSA treatment and first baby haircut study results, it was determined that autistic children had significantly increased oxidative stress (3-fold decrease in glutathione/oxidized glutathione redox ratio) in comparison to control children. Researchers have also identified specific genomic polymorphisms for enzymes in the methionine cycle and transsulfuration pathways in autistic children that would help to account for the distinct transsulfuration metabolite profiles observed by James et al. in autistic children [37,39].

The inability to properly eliminate mercury is particularly troubling since it was shown by Gasset et al. that administration of thimerosal to animals resulted in a substantial concentration of mercury present in blood and tissues (including the brain) of the treated animals and their offspring [40]. The authors concluded that thimerosal crosses the blood-brain barrier and placental barriers. Similarly, Slikker from the FDA has confirmed that thimerosal crosses the blood-brain barrier and placental barriers and results in appreciable mercury content in tissues including the brain [41]. Sager has recently reported the half-life of mercury in the brain of infant primates was approximately 28 days following administration of solutions containing vaccine comparable concentrations of thimerosal [42].

Baskin et al. have conducted a molecular study demonstrating that micromolar (μM) concentrations of thimerosal induced membrane and DNA damage, and initiated caspase-3 dependent apoptosis in human neurons and fibroblasts within hours of exposure [43].

Leong et al. recently examined neurite outgrowth following exposure to the same concentrations of mercury, aluminum, lead, cadmium, and manganese. The authors demonstrated that nanomolar (nM) concentrations of mercury markedly disrupted membrane structure and linear growth rates of imaged neurites in 77% of all nerve growth cones, whereas the other metals examined did not affect growth patterns of the neurons examined. The authors concluded that their study provides visual and biochemical evidence strongly implicating mercury as a potent factor in neurodegeneration [44]. Similar results have been observed in tissue culture systems with thimerosal [45–47].

In addition, it has been reported that the neurotoxicity of thimerosal is associated with depletion of glutathione. The ethylmercury in thimerosal binds to cysteine thiol (-SH) groups on intracellular proteins and inactivates their function. The cysteine-SH group of glutathione binds mercury and protects essential proteins from functional inactivation. Glutathione is the major mechanism of mercury excretion, and individuals with genetic deficiencies in glutathione synthesis will be less able to excrete mercury and will be more sensitive to its adverse effects [37–48].

Waly et al. have reported that methylation events play a critical role in the ability of growth factors to promote normal development [49]. The authors found that insulin-like growth factor-1 (IGF-1)- and dopamine-stimulated methionine synthase (MS) activity and folate-dependent methylation of phospholipids in SH-SY5Y human neuroblastoma cells, occurred via a PI3-kinase- and MAP-kinase-dependent mechanism. Thimerosal inhibited both IGF-1- and dopamine-stimulated methylation with an IC(50) of 1 nM and eliminated MS activity. The authors concluded that the discovery of the PI3-kinase/MAP-kinase/MS pathway, and its potent inhibition by thimerosal, a vaccine component, provides a molecular explanation for how increased use of vaccines could promote an increase in the incidence of autism and Attention-Deficit-Hyperactivity-Disorder (ADHD). In addition, Deth and Waly have reported that folate-dependent, phospholipid methylation in the lymphoblasts of autistic children were, in a dose-response manner, significantly more sensitive to thimerosal exposure than in unaffected siblings [50].

In addition to molecular studies, Hornig et al. have reported that the developing brain of a genetically-susceptible autoimmune-prone mouse strain is susceptible to the neurotoxic effects of thimerosal [51]. They administered thimerosal to mice mimicking the United States' routine childhood immunization schedule. The authors demonstrated that the genetically-susceptible autoimmune-prone mouse strain developed symptoms similar to autistic spectrum disorders following thimerosal exposure. Symptoms 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.

Clarkson et al. have also developed a mouse model to evaluate the neurotoxic effects of alkyl mercury exposure on fetuses/infants of different sexes [52]. The authors deter-

mined that at high dose mercury exposure, two day-old male and female mice had neurons that were similarly adversely affected. At low dose mercury exposure, the neurons of two day-old female mice were significantly much less severely adversely affected compared with male two day-old mice. The authors concluded males are considerably more sensitive than females to the neurotoxic effects of mercury, and that in some human fetal/infant population exposures to low dose alkyl mercury, it has been observed that males were more sensitive than females to psychomotor retardation [52,53], suggesting an interaction between testosterone and mercury toxicity [54]. It should be noted, as per data from this study and others [4–6], neurodevelopmental disorders are significantly more prevalent in males than females.

Recently, the Environmental Working Group (EWG) has issued a report following an extensive investigation into the relationship between mercury exposure, especially mercury exposure from thimerosal-containing childhood vaccines, and autistic disorders [55]. They reported that a signature metabolic impairment or biomarker in autistic children strongly suggests that these children would be susceptible to the harmful effects of mercury and other toxic chemical exposures. This impairment manifests as a severe imbalance in the ratio of active to inactive glutathione, the body's most important tool for detoxifying and excreting metals. It was determined that autistic children showed a significant impairment in every one of five measurements of the body's ability to maintain a healthy glutathione defense. The EWG concluded that these new findings significantly strengthen the possibility that mercury could cause or contribute to autism and other neurodevelopmental disorders, by identifying a metabolic imbalance common to nearly all autistic children that would make these children poorly equipped to mount a defense against a number of neurotoxic compounds, including mercury. In addition, they concluded that these findings raise serious concerns about the studies that have allegedly proven the safety of mercury in vaccines.

## Conclusions

Despite conclusions by the Institute of Medicine that there is no relationship between thimerosal and autism, and that no further studies should be conducted to evaluate the relationship between thimerosal and autism [42], it is clear from these data and other emerging data that has been recently published, additional neurodevelopmental disorder research should be undertaken in the context of evaluating mercury-associated exposures, especially when thimerosal-free vaccines are a readily available option for the most vulnerable populations. It should be a priority to improve access to thimerosal-free vaccines.

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