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An assessment of the impact of thimerosal on childhood neurodevelopmental disorders

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Summary

The prevalence of autism in the US has risen from 1 in ~2500 in the mid-1980s to 1 in ~300 children in the mid-1990s. The purpose of this study was to evaluate whether mercury from thimerosal in childhood vaccines contributed to neurodevelopmental disorders. Neurodevelopmental disorder dose-response curves for increasing mercury doses of thimerosal in childhood vaccines were determined based upon examination of the Vaccine Adverse Events Reporting System (VAERS) database and the 2001 US' Department of Education Report. The instantaneous dosage of mercury children received in comparison to the Food and Drug Administration (FDA)'s maximum permissible dose for the oral ingestion of methylmercury was also determined. The dose-response curves showed increases in odds ratios of neurodevelopmental disorders from both the VAERS and US Department of Education data closely linearly correlated with increasing doses of mercury from thimerosal-containing childhood vaccines and that for overall odds ratios statistical significance was achieved. Similar slopes and linear regression coefficients for autism odds ratios in VAERS and the US Department of Education data help to mutually validate each other. Controls employed in the VAERS and US Department of Education data showed minimal biases. The evidence presented here shows that the occurrence of neurodevelopmental disorders following thimerosal-containing childhood vaccines does not appear to be coincidental.

Introduction

Thimerosal is an organic mercury compound. It is metabolized to ethylmercury and thiosalicylate and has been present since the 1930s as a preservative in many vaccines and pharmaceutical products to prevent bacterial and fungal contamination.

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One has published the first epidemiological evidence showing a direct association between thimerosal-containing childhood vaccines and neurodevelopmental disorders in children [1, 2]. It has been shown that there was from a 2–6-fold statistically significant increased incidence of neurodevelopment disorders following an additional 75–100 microgram dosage of mercury from thimerosal-containing childhood vaccines in comparison to thimerosal-free childhood vaccines [1]. One has also shown that there were dose-response curves demonstrating a close correlation between increasing mercury doses from childhood vaccines and childhood neurodevelopmental disorders [2].

The purpose of this study was to extend previous studies and integrate statistical and dose-response curve methodologies into a single analysis evaluating mercury doses from childhood vaccines and childhood neurodevelopmental disorders. In the first part of this study, the dose-response was evaluated of increasing mercury doses from thimerosal-containing Diphtheria-Tetanus-acellular Pertussis (DTaP) vaccine in comparison to thimerosal-free DTaP vaccines for neurodevelopmental disorders from 1997–2001, based upon examination of the Vaccine Adverse Events Reporting System (VAERS) database. Secondly, the 2001 US' Department of Education Report [3] was evaluated on the prevalence of neurodevelopmental disorders and the average dosage of mercury that children received as part of their childhood immunization schedules in birth cohorts in comparison to a baseline measurement. The final part of this analysis studied the instantaneous dosage of mercury children received in comparison to the Food and Drug Administration (FDA)'s maximum permissible dose for the oral ingestion of methylmercury as part of the 2002 recommended childhood immunization schedule. It was determined by the FDA in 1999 that, under the recommended childhood immunization schedule, infants might be exposed to cumulative doses of ethylmercury that exceed some federal safety guidelines established for oral ingestion of methylmercury [4].

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Methods

THE VAERS DATABASE

The incidence of neurodevelopmental disorders following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines was based upon analysis of the VAERS database using Microsoft Access. The VAERS database is an epidemiologic database maintained by the Centres for Disease Control and Prevention (CDC) since 1990. All adverse reactions are to be reported to the VAERS database as required by US law. The CDC requires written and telephonic confirmation of serious adverse reactions and follows up these patients 1 year later. The FDA inquires into deaths reported to the VAERS database by contacting the patient's healthcare provider and physician. The FDA also continually monitors reports to the VAERS database to determine whether any vaccine or vaccine lot has a higher than expected incidence rate of events. The VAERS Working Group of the CDC, the FDA and the authors analyse and publish epidemiologic studies based upon analysis of the VAERS database.

The neurodevelopmental disorders analysed were autism, personality disorders and mental retardation. These categories of adverse events were based upon descriptions of adverse events by those reporting them and by defined fields contained in the VAERS database. In addition, as control adverse events the number of febrile seizures, fevers, pain, oedema and vomiting were analysed following each of the vaccines under study. The number of each type of adverse event reported were determined following the doses equally divided into a first group receiving an average of 37.5 μg of mercury and a second group receiving an average of 87.5 μg of mercury. This grouping allowed one to be able to ascertain larger numbers for statistical analyses. It was hypothesized that DTaP vaccines, whether containing thimerosal or not, should have a similar incidence rate of adverse events. The assumption of similar reactogenicities following the vaccines under study forms the basis of the null hypothesis. DTaP vaccines administered by manufacturer were analysed, so that one could compare thimerosal-containing DTaP vaccines administered from 1997–2001 against thimerosal-free DTaP vaccines administered from 1997–2001. Denominators obtained from the Biological Surveillance Summaries of the CDC were used to determine the number of doses of each manufacturer administered. Based upon this information, one was able to calculate incidence rates of adverse events following vaccination. One is precluded from giving incidence rates, the number of doses administered or types of DTaP vaccines, because this information could reveal the identities of the manufacturers and the CDC claims this information is proprietary between them and the manufacturers [5].

The incidence rate was compared for each adverse event examined following thimerosal-containing DTaP vaccines against thimerosal-free DTaP vaccines in order to determine the odds ratios in a 2×2 contingency table. The standard errors for each adverse event examined were also determined from the 2×2 contingency tables. By definition, since it is assumed that the populations under study are similar and one is only tracking the amount of mercury that children received from the thimerosal-containing or thimerosal-free vaccines understudy, the initial point analysed was 0 μg of mercury and had a relative risk of 1. The odds ratios were plotted with their standard errors against the mercury dose received and linear regression coefficients and slopes were determined for each distribution examined.

US DEPARTMENT OF EDUCATION REPORT

The 2001 US Department of Education report was analysed to determine the number of children at various ages that had developed various conditions [3]. The conditions analysed included austim, speech disorders, orthopaedic impairments, visual impairments and deaf-blindness. The prevalence of each of these conditions was determined, based upon the number of births in each birth cohort as per the CDC's yearly live birth surveillance data [6]. The birth cohort years analysed were 1984, 1985 and 1990–1994. The amount of mercury that each child was on average administered as part of their birth cohort was based upon the Biologic Surveillance Summaries of the CDC and the number of births in each birth cohort as per the CDC's data. 1984 was established as a baseline-year that was compared against all other birth cohort years. 2×2 contingency tables were constructed to determine odds ratios and standard errors. Each respective odds ratio and the standard error analysed was plotted against the average dose of mercury that children received from their childhood immunizations and linear regression coefficients and slopes were determined for each distribution examined.

FDA EXPOSURE LIMITS

In this study, the amount of mercury children received as part of their routine childhood immuniza-

tion schedule and the FDA maximum permissible doses for the oral ingestion of methylmercury were determined from the Institute of Medicine (IOM) of the US National Academy of Sciences 2001 report [7]. The maximum permissible dose for the oral ingestion of methylmercury by the FDA is 0.4 μg/Kg body weight/day. The 2001 IOM report indicated that 25 μg of mercury per dose were present in DTaP, *Hemophilus influenza Type* b (Hib) and influenza vaccines and 12.5 μg of mercury per dose were present in paediatric hepatitis B vaccines. The recommended childhood immunization schedule was determined from the 2002 recommendations of the American Academy of Paediatrics. The average size of infants at various ages was determined from Geigy Scientific Tables [8].

Results

Figures 1–3 show the odds ratios of neurodevelopmental disorders following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines for increasing dosages of mercury based upon analysis of the VAERS database. These figures show that there is a close linear correlation between increasing mercury from thimerosal contained in childhood vaccines and the increased odds ratio of neurodevelopmental disorders. It was determined that the odds ratio of autism increased by 0.029 per μg of mercury, personality disorders increased by 0.012 per μg of mercury and mental retardation increased by 0.048 per μg of mercury. In addition, the overall odds ratios (OR) of autism (OR = 2.6), personality disorders (OR = 1.5) and mental retardation (OR = 2.5) were statistically significantly elevated following thimerosal-containing DTaP in comparison to thimerosal-free DTaP vaccines for increasing doses of mercury.

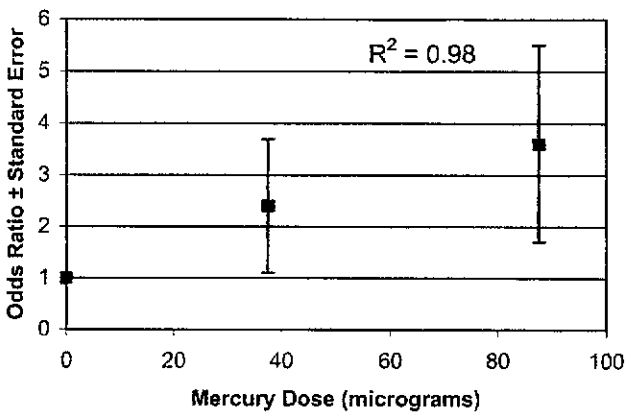

Figure 1 Autism reported following thimerosal-containing DTaP in comparison to thimerosal-free DTaP vaccines for increasing mercury dosage that children received from thimerosal

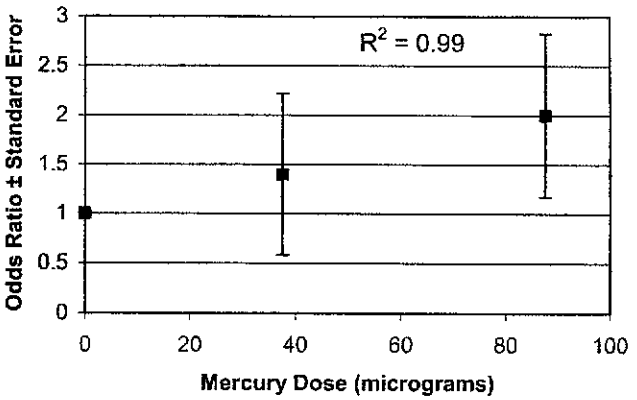

Figure 2 Personality disorder reported following thimerosal-containing DTaP in comparison to thimerosal-free DTaP vaccines for increasing mercury dosage that children received from thimerosal

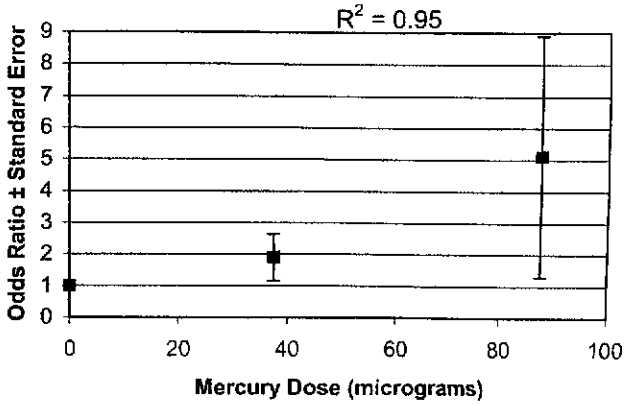

Figure 3 Mental retardation reported following thimerosal-containing DTaP in comparison to thimerosal-free DTaP vaccines for increasing mercury dosage that children received from thimerosal

Figures 4 and 5 show increasing odds ratios for autism and speech disorders following increasing doses of mercury from thimerosal in childhood vaccines in comparison to the baseline year of 1984, based upon analysis of data from the 2001 US Department of Education report. Figures 4 and 5 also show that there is a close linear relationship between increasing mercury from thimerosal in childhood vaccines and increasing odds ratio for neurodevelopmental disorders. It was determined that the odds ratio of autism increased by 0.014 per μg of mercury and the odds ratio of speech disorders increased by 0.12 per μg of mercury. In addition, the overall odds ratios of autism (OR = 2.5) and speech disorders (OR = 1.4) were statistically significantly elevated in comparison to the 1984 base-line measurement.

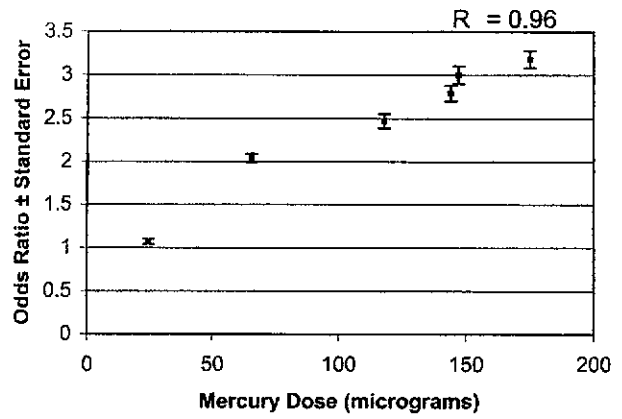

Figure 4 Autism disabilities reported in comparison to the average mercury dosage form thimerosal in childhood vaccines

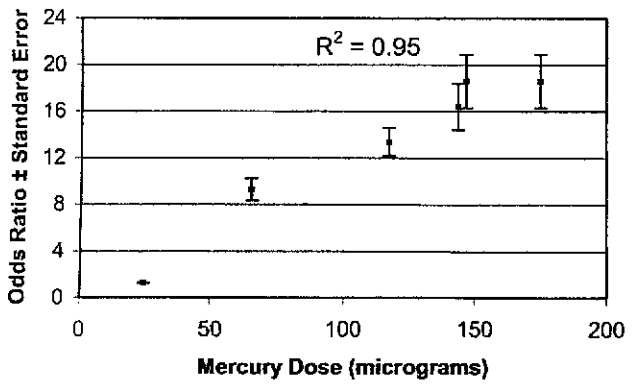

Figure 5 Speech disorders reported in comparison to the average mercury dosage form thimerosal in childhood vaccines

It was found that administration of thimerosal-containing DTaP vaccines slightly raised the odds ratios of febrile seizure, fever, pain, oedema and vomiting control adverse events compared to thimerosal-free DTaP vaccines, but the increased relative risks did not correlate with the mercury dose children received (data not shown). Similarly, the odds ratios of visual impairment, deaf-blindness and orthopaedic impairment control disabilities in comparison to the mercury concentration that children received from thimerosal contained in their childhood vaccines did not correlate with the increasing doses of mercury the children received (data not shown).

Table 1 shows the instantaneous mercury exposure of US infants at various times as part of their childhood immunization schedule in comparison to the FDA established limits. This table shows that the instantaneous relative excess mercury that US children received from their childhood immunizations ranged from 3.2–32-fold in comparison to the US FDA safety guidelines for the daily maximum oral ingestion of methylmercury.

Table 1 A summary of the instantaneous mercury exposure levels of US infants at various times in comparison to the maximum daily FDA established limits.

Age (months)	*Dose in μg from childhood vaccines*	*Average child's permissible FDA dose in μg (average weight in Kg)*
0	12.5	0.330 (3.30)
Instantaneous relative excess	—	9.5
2	62.5	0.486 (4.86)
Instantaneous relative excess	—	32
4	62.5	0.654 (6.54)
Instantaneous relative excess	—	24
6	50	0.780 (7.80)
Instantaneous relative excess	—	16
15	50	1.05 (10.5)
Instantaneous relative excess	—	12
60	25	1.86 (18.6)
Instantaneous relative excess	—	3.2

Discussion

It is clear from the analysis shown in table 1 that US infants and children are exposed to mercury levels from their childhood immunization schedule that exceed the FDA established maximum permissible levels for the daily oral ingestion of methylmercury. The fact that mercury in the vaccines is given by injection rather than by oral ingestion only makes the exposure levels worse because Geier *et al.* [9] showed that the distribution of foreign particles in mice reached several-logs higher concentration in organs following intravenous or intramuscular injections than via oral ingestion.

The dose-response curves (figures 1–5) show that the increases in odds ratios of neurodevelopmental disorders from both the VAERS and US Department of Education data closely linearly correlated with increasing doses of mercury from thimerosal-containing childhood vaccines and that for the overall odds ratios examined statistical significance was achieved. In addition, similar slopes and linear regression coefficients were observed for the odds ratios for autism from VAERS and the US Department of Education data, helping to mutually validate the data from each of these independent sources.

The lack of correlation between acute events and increasing mercury exposure levels in the VAERS data argues against reporting bias or differences in the vaccines themselves and argues for the specific effects of thimerosal on neurodevelopmental disorders. Likewise,

the lack of correlation between visual impairments, deaf-blindness and orthopaedic impairments and the increasing mercury exposure levels in the US Department of Education data, again, argues for the specific effects of thimerosal in childhood vaccines on the prevalence of autism and speech disorders. In addition, because thimerosal-containing and thimerosal-free DTaP vaccines were examined for the same years in the VAERS database, popular presentations in the media regarding vaccine reactogenecitis or yearly inherent population difference should have had limited effects upon the data examined.

It has been shown that there may have been significant concentrations of mercury once present in Rhogam and mercury continues to be present in seafood and other pharmaceuticals [2]. These other sources of mercury, while potentially significant, probably had a limited effect on the results of this study because the populations analysed were large and there should have been equal exposure to other sources of mercury among the populations examined.

In addition, recent studies have analysed the prevalence of autism from the mid-1980s through the mid-1990s and determined that the prevalence of autism has risen from one in ~2500 children in the mid-1980s to one in ~300 children in 1996 [10–12]. These studies have confirmed that the rise in the prevalence in autism reflects genuine phenomena and is not the result of population migration, differences in autism diagnoses or other potential confounders. This suggests that the autism raises observed in this study reflect genuine phenomena that is occurring in the US population.

The 2001 IOM report has concluded the hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders is biologically plausible [7]. Bernard *et al.* [13] have compared the similar biological abnormalities commonly found in autism and the corresponding pathologies arising from mercury exposure. Distinct similarities were found between autism and mercury exposure in their effects upon biochemistry, the immune system, the central nervous system structure, neuro-chemistry and neurophysiology. Magos *et al.* [14] compared the effects of the administration of similar doses of ethylmercury and methylmercury in rats. They determined that there was little difference in the neurotoxicites of ethylmercury and methylmercury treated rats when effects on the dorsal root ganglia or coordination disorders were compared. The authors also determined that microgram quantities of organic-mercury alone in the rat brain were in some cases associated with neurotoxicity indicating that the presence of inorganic mercury was not necessary for neurotoxicity. It has been determined that that brain preferentially takes up mercury 5–7 times greater than the blood [15, 16]. The reason for this stems from the fact that thimerosal contains the ethylmercury radical attached to the sulphur atom of the thiol group of salicylic acid. Generally, mercuric ions bind tightly but reversibly to thiol ligands [17]. It is likely, therefore, that the ethylmercury cation will dissociate from the thiosalicylic acid moiety immediately after injection to bind to the surrounding thiol ligands present in great excess in tissue proteins [15]. The concept of ethylmercury deposition in tissues fairly rapidly following administration of thimerosal from vaccines is suggested by a recent publication by Pichichero *et al.* [18]. The authors examined the concentrations of mercury in the blood, urine and stool from 3–28 days following thimerosal-containing vaccines in 40 full-term infants aged 6 months and younger in comparison to 21 control infants receiving thimerosal-free vaccines. The mean mercury doses of the infants exposed to thimerosal were 45.6 μg (range 37.5–62.5) for 2 month-olds and 111.3 μg (range 87.5–175.0) for 6 month-olds. Blood mercury in thimerosal-exposed 2 month-old infants ranged from less than 3.75 to 20.55 nmol/L; in 6 month-old infants all values were lower than 7.50 nmol/L. Only 15 blood samples from controls contained quantifiable mercury. Concentrations of mercury were low in the urine after vaccination, but were high in the stools of thimerosal-exposed 2 month-old infants (mean 82 ng/g dry weight) and in 6 month-old infants (mean 58 ng/g dry weight). The authors estimated that the blood half-life of ethylmercury was 7 days (95% confidence interval of 4–10 days). The study was unable to determine the ultimate disposition of most of the mercury with which infants were injected.

Conclusion

This study provides additional epidemiological evidence for a link between increasing mercury from thimerosal-containing childhood vaccines and neurodevelopmental disorders and shows that children received doses of mercury in their childhood vaccines that are in excess of the FDA permissible dose. In light of literature supporting the biologic mechanisms for mercury induced neurotoxicity, the concentration of mercury in thimerosal-containing childhood vaccines being in excess of the Federal Safety Guidelines for the oral ingestion of mercury and previous epidemiological studies showing overall statistically significant and dose-response effects from mercury contained in

thimerosal-containing childhood vaccines, the occurrence of neurodevelopmental disorders following thimerosal-containing childhood vaccines does not appear to be coincidental. It is suggested that, in light of the results of this and previous studies, thimerosal should be removed immediately from all childhood vaccines.

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