

Post-publication Peer Review (P³R) is an online forum for ongoing peer review. When an article is eligible for P³R, a link to the response form is available within the full-text article. You must be a current subscriber who has activated the online portion of your subscription in order to send a P³R. Any reader can read published P³Rs.


Post-publication Peer Reviews to:

ARTICLE:

Nick Andrews, Elizabeth Miller, Andrew Grant, Julia Stowe, Velda Osborne, and Brent Taylor

Thimerosal Exposure in Infants and Developmental Disorders: A Retrospective Cohort Study in the United Kingdom Does Not Support a Causal Association

Pediatrics 2004; 114: 584-591 [\[Abstract\]](#) [\[Full text\]](#)

 P³Rs: [Submit a response to this article](#)

P³Rs published:

- ▼ **THIMEROSAL DOES NOT BELONG IN VACCINES**
Mark R. Geier, MD, Ph.D., David A. Geier, Medcon, Inc. (8 September 2004)
- ▼ **Re: THIMEROSAL DOES NOT BELONG IN VACCINES**
Elizabeth Miller, Nick Andrews, Brent Taylor (10 September 2004)
- ▼ **Does weight confound?**
John P. Heptonstall (30 October 2004)
- ▼ **Re: Does weight confound?**
Nick J Andrews, Elizabeth Miller (10 November 2004)

THIMEROSAL DOES NOT BELONG IN VACCINES

8 September
2004



Mark R. Geier, MD,
Ph.D.,
geneticist/vaccinologist
*THE GENETIC CENTERS
OF AMERICA*,
David A. Geier,
Medcon, Inc.

Send letter to journal:
[Re: THIMEROSAL DOES NOT BELONG IN VACCINES](#)

[E-mail](#) Mark R.

The authors of the Andrew et al. study failed to disclose their significant conflicts of interests to the readership of Pediatrics: Elizabeth Miller disclosed in her 2001 publication (1) and in 2002 to the Committee on the Safety of Medicines previously disclosed that she has received funding to study vaccines from Aventis Pasteur, Wyeth Vaccines, SmithKline Beecham, Baxter Health Care, North American Vaccine, Wyeth- Lederle Vaccine, and Chiron Biocine; and Nick Andrews, Julia Stowe, and Brent Taylor all disclosed in 2001 that they received funding to study vaccines from Wyeth Vaccines and SmithKline Beecham (1). These companies all are or were makers of thimerosal-containing vaccines.

Geier, MD, Ph.D., et al.

This study seems disingenuous, since the British Government has announced the removal of thimerosal from their routine childhood vaccines effective the end of September 2004. The BBC wrote on 7 August 2004, "Vaccine scrapped over autism fear. A vaccine containing mercury given to babies when they are eight weeks old is to be scrapped amid fears of a link with autism. The move follows recent research in America that suggests a connection between mercury used to preserve whooping cough vaccine, and autism." Health Minister John Hutton confirmed the changes stating, 'Childhood immunization has been extremely effective in protecting children from serious-life threatening diseases, We are continually looking at ways to improve this program as new, more effective products become available.' We congratulate the British Government for doing the right thing, and predict that the new vaccine will soon result in a concomitant drop in the currently devastating rate of neurodevelopmental disorders in England as has already potentially been seen in California which has reported a three-consecutive quarter decrease in the number of new cases of autism for the first time in approximately 20 years among children receiving childhood vaccines with reduced thimerosal content.

Unfortunately, thimerosal continues to remain in many vaccines in the US. Influenza vaccine has been added to the routine childhood immunization schedule, and the CDC has refused to state a preference for children to receive thimerosal-free influenza vaccine despite their position of encouraging the removal of thimerosal from childhood vaccines,

The current study was extremely underpowered in its ability to discern the effects of thimerosal on neurodevelopmental disorders because it only examined a maximum exposure of 75 micrograms of mercury in the first year of life and further limited potential thimerosal exposure differences by excluding children that had not received 75 micrograms of mercury from childhood vaccines by age one. The study did contain analyses for tics based upon exposure at 3, 4, and all mercury exposure, when using a reference group of children not receiving any mercury from thimerosal-containing childhood vaccines during the first year of life. The results of these analyses showed that there were statistically significantly increased hazard ratios for tics at 3 months. By comparison, there was no statistically significant correlation between mercury exposure from thimerosal-containing vaccines and tics by excluding children not receiving thimerosal-containing vaccines during the first year of life. The authors provide no other complete data for any other outcomes when employing children receiving no mercury during the first year of life as the reference population. The tic result in the Andrews et al. study is similar to a previous study, from the Vaccine Safety Datalink (VSD) database (2), indicating an apparent causal relationship between mercury containing childhood vaccines and the development of tics.

This study has virtually no applicability to the US experience with thimerosal. Despite incorrect statements to the contrary by Andrews et al., by 4 months of age US children received approximately 2-fold higher doses of mercury from vaccines (125

micrograms) compared to those England (75 micrograms). This study contains significant biases because sicker children were the ones that tended to have vaccinations delayed resulting in an apparent preventive effective for mercury on the risks of neurodevelopmental disorders.

It has become apparent from recently emerging clinical, animal model, and molecular evidence that thimerosal is indeed responsible for neurodevelopmental disorders in a substantial number of children, regardless of the findings of large population-based epidemiological studies. Independent investigators have shown children with autistic spectrum disorders have significantly higher body-burdens of mercury than those of neurotypical children (3-5), a genetically susceptible mouse strain develops autistic features, including: 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 following administration of thimerosal mimicking the US childhood immunization schedule (6), and molecular studies in vitro have demonstrated that acute thimerosal exposure at extremely low concentrations (i.e. at parts-per-million or lower) (7-9), that are comparable to the expected body distribution of mercury resulting from thimerosal-containing vaccines that were administered in the US, can kill or significantly adversely effect neuronal growth and development. Pharmacokinetic studies on infant primates exposed to solutions containing similar concentrations of thimerosal, as thimerosal-containing vaccine childhood vaccines, have shown that the half-life of mercury in the brain of the infant primates was approximately 28 days (10). Male mice were at considerably more sensitive than females to the neurotoxic effects of low dose alkyl mercury exposure (11). These results were consistent with some human fetal/infant population exposures to low doses of alkyl mercury where it has been observed that males were more sensitive than females to psychomotor retardation. Autistic spectrum disorders, of course, are significantly more prevalent in males than females (12).

In conclusion, we are, and always have been, strong supporters of the US vaccine program and of pediatricians that administer vaccines, but given the fact that many US states now have either banned (Iowa), or are in the process of banning thimerosal, (California, Missouri, Nebraska, and New York, among many others) and given that fact that there is now a bipartisan national bill introduced in the US House of Representatives (Weldon/Maloney bill) to ban it nationally, we now strongly suggest that the United States pediatricians should insist on giving only thimerosal-free vaccines, lest they become involved in the terrible morass of lawsuits that are already beginning on this issue.

References

1. Miller E, Waight P, Farrington CP, Andrews N, Stowe J, Taylor B.

- Idiopathic thrombocytopenic purpura and MMR vaccine. *Arch Dis Child* 2001;84:227-9.
2. Verstraeten T, Davis RL, DeStefano F, Lieu TA, Rhodes PH, Black SB, Shinefield H, Chen RT; Vaccine Safety Datalink Team. Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases. *Pediatrics* 2003;112:1039-48.
 3. Bradstreet J, Geier DA, Kartzinell JJ, Adams JB, Geier MR. A case-control study of mercury body-burden in children with autistic spectrum disorders. *J Am Phys Surg* 2003;8:76-9.
 4. Holmes AS, Blaxill MF, Haley BE. Reduced levels of mercury in first baby haircuts of autistic children. *Int J Toxicol* 2003;22:277-85.
 5. Hu LW, Bernard JA, Che J. Neutron activation analysis of hair samples for the identification of autism. *Trans Am Nucl Soc* 2003;89.
 6. Hornig M, Chian D, Lipkin WI. Neurotoxic effects of postnatal thimerosal are mouse strain dependent. *Mol Psychiatry* 2004;9:833-45.
 7. 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.
 8. 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.
 9. 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.
 10. Institute of Medicine (US). Immunization Safety Review: Vaccines and Autism. Washington, DC: National Academy Press, 2004.
 11. Clarkson TW, Nordberg FJ, Sager PR. Reproductive and developmental toxicity of metals. *Scand J Work Environ Health* 1985;11:145-54.
 12. Bertrand J, Mars A, Boyle C, Bove F, Yeargin-Allsopp M, Decoufle P. Prevalence of autism in a United States population: the Brick Township, New Jersey, investigation. *Pediatrics* 2001;108:1155-61.

Dr. Mark R. Geier has been a consultant and expert witness in cases involving vaccines before the National Vaccine Injury

Compensation Program and in civil litigation. David A. Geier has been a consultant in cases involving vaccines before the National Vaccine Injury Compensation Program and in civil litigation.

Re: THIMEROSAL DOES NOT BELONG IN VACCINES

10 September
2004



Elizabeth Miller,
Epidemiologist
Health Protection
Agency, UK,
Nick Andrews, Brent
Taylor

We write to correct inaccuracies and misunderstandings in the letter by Dr. Geier in response to our recent paper. First, in the fifth paragraph of his letter, Dr. Geier misunderstands what data are shown in Table 3 of our paper. It is clearly stated in the statistical methods that the main analysis included all children whether they received 0,1,2,or 3 doses at any age. The additional analysis, with the result only shown for tics, only included those receiving 3 doses by the age of one year. For all other outcomes the results were similar when restricting to those with 3 doses by the age one to those including all children. Dr. Geier has somehow misunderstood that the results shown are for the analysis that did include children receiving no doses during the first year of life. The tics result is discussed in detail in our paper.

Send letter to journal:
[Re: Re: THIMEROSAL DOES NOT BELONG IN VACCINES](#)

[E-mail](#) Elizabeth Miller,
et al.

We avoided the bias that sicker children delay vaccination by excluding such children where possible (see exclusion criteria).

His charge that our study is disingenuous because in the UK the "vaccine was scrapped over autism fear" is based on a misleading media report that bears no relationship to the truth. The recent decision in the UK to change the vaccine used for primary immunisation was driven by the need to change from oral to inactivated polio vaccine along with the availability of an acellular vaccine with high demonstrated efficacy. The vaccine happens to be thiomersal free which is consistent with the overall international aim of reducing the exposure of children to mercury from avoidable sources (www.dh.gov.uk).

The requirements by Pediatrics for the conflict of interest declaration were complied with by the authors and the Health Protection Agency's policy on the condition under which commercial funding is obtained for studies is available on our Website (www.hpa.org.uk/infections/about/dir/psp.pdf)

Does weight confound?

30 October 2004



John P. Heptonstall,
Graduate Mathematician
and Physicist. TCM
Practitioner.

Sir

Send letter to journal:
[Re: Does weight confound?](#)

[E-mail](#) John P.
Heptonstall

Mercury, whether in methyl or ethyl form, is a known neuro/nephrotoxin; "toxicity may be similar for ethyl and methyl mercury"; "delayed-type hypersensitivity reactions from thimerosal exposure are well -recognised" Ball et al 2001. "There is an established link between exposure to mercury and impaired childhood cognitive developments and early motor skills" Heron et al 2004.

The US EPA maximum recommended level for exposure to mercury

is 0.1 ug/kg/day, the WHO 0.47ug/kg/day. Each shot of DTP/DT vaccine contains 25ug of ethyl mercury which vaccinators inject into babies and young children despite those maximum safety limits of the EPA and WHO being expressed as weight of toxin, per weight of person, per day. A 2-month-old child weighs on average 3 to 5kg, a 3-month-old 4.3 to 6.8 kg, a 4-month-old 5 to 7.4kg, and a 6-month-old 5.9 to 8.8kg. If heavier body weight reduces toxic potential from mercury, lower weight children should be more susceptible to mercury vaccines than heavier children. Why did Andrews et al 2004 and Heron et al 2004 not assess exposure of babies and young children to ethyl mercury in vaccines according to weight of toxin per weight of child on the vaccination day, but instead assess cumulative exposure to ethyl mercury by age over time? The criterion is not consistent with that of the EPA and WHO.

The 0.1ug/kg/day EPA maximum exposure level is exceeded in babies and young children at every 25ug ethyl mercury vaccine shot by 50 to 83 times for a 1 month old baby, 37 to 58 times for a 3 month old, 34 to 50 times for a 4 month old and 28 to 42 times for a 6 month old. This exposes gross failure in authorities tasked to protect the public from toxic exposure. Furthermore,

1. Andrews et al conclude that ethyl mercury in vaccines at existing levels is safe and that it can add protective value against some adverse neurological developments as shown by a 'reducing trend for developing ASDs with the increasing accumulation of mercury through 3 doses at monthly intervals' in the study. Could the 'reducing trend' with age for developing ASDs be due to the protective effects of growth, therefore increased body weight, at successive exposures to 25ug toxic mercury?

2. Andrews et al say the preterm cohort has an "increased risk of general development disorders compared to term children" (4.2%: 2.0%). As the preterm cohort generally weigh less than term children, and were found to have an increased risk of general development disorders, was this due to lower body weight at vaccination offering less protection against mercury poisoning than term weight children? (The birth date for preterm children is usually given as day of birth, not full gestation date).

3. The UK noted organisation JABS received information from parents that their children's 'reactions' to vaccines – of various kinds including neurological - varied according to brand/batch. Andrews et al and Heron et al ignore this/these possible confounders.

4. The effects of vaccine schedules superimposed on the mercury-containing DTP vaccinations eg. Hib, MMR, MMR1, MMR2, MR, Men C, OPV, DT, BCG (some of which have been implicated by parents in the onset of their childrens' disorders by JABS) are ignored as confounders by Andrews et al.

5. 'Validation checks' carried out on accuracy of GPRD data (diagnoses and codes) were through correspondence with general

practices and revealed a dismal 20% failure rate – this is offered by Andrews et al as a limitation of the study. Tiny ‘random subsets’ of the order of a few tens of diagnosed outcomes for analysis amongst an over 100,000 person strong cohort are used to ‘validate records’ of disorders yet errors in the GPRD may outweigh the relevance of such tiny datasets.

6. Heron et al subjects were also analysed in subsets taken from the 14,000 children in the Avon study, yet recorded levels of cognitive and behavioural development were judged from questionnaires sent to mothers at intervals between 6 months and 7 ½ years of age so were totally dependent on mothers conveying information they received, their own opinions and subjectivity – Heron et al state that “children’s cognitive and behaviour development was not assessed directly as this might ‘introduce subjectivity’” but what of mothers’ subjectivity? How can subjective values assessed by Heron et al, from a uniquely different cohort from only one relatively small area of the UK, validate Andrews et al?

7. Heron et al adjusted for birth weight only, not weight at vaccination. They state, “outcome questionnaires were less likely to be returned for children with low mercury exposure.... and whose demographic status was associated with poor developmental outcomes”. If these children suffered an adverse event for which parents refused to consent to further DTP vaccinations there is unresolved confounding.

8. Table 4 shows 95% CI for HR by dose for Tics, GDD, ADD and UDD. Other than Tics figures, the HRs for the disorders reduce at each successive dose, as therefore does the CI range; this is said to show “a reducing risk for those conditions with increasing doses”. Doesn’t it actually show a reducing risk for those conditions with increasing weight/age of child?

9. Andrews et al exclude from main analysis a group consisting of those with prenatal, perinatal, postnatal and ‘within 6 months’ outcomes. This will hide any cases of acute ethyl mercury poisoning that occurred in postnatal and ‘outcome within 6 months’ children; then combining them with prenatal and perinatal babies further obfuscates this confounder.

10. In UK/Europe ‘smoking mothers’ are said to relate to 11.7% of all SIDS deaths yet smoking mothers have lower birth weight children. Is it the low birth weight, therefore lower weight at vaccinations, the factor in suspected DTP vaccine-mercury-induced SIDS and not smoking? If so smoking mothers confound this study.

11. Young children and babies might suffer additional exposure to mercury through breast milk if, coincident with vaccination, mother regularly ate fish contaminated with mercury or had dental treatment with mercury amalgam fillings. Each filling releases about 10ug methyl mercury into mother’s blood stream daily so a mother’s dietary fish and dental visits coincident with vaccination,

therefore breast-feeding, confound the study.

12. The excluded group of children, postnatal and 'outcomes', who might have suffered mercury damage from vaccines number about 524 - a tiny fraction of the 103,043 cohort but a fair proportion of approximately 5,000 cited as having outcome conditions. Andrews et al state the exclusions were made "because the presence of such a condition is likely to affect both vaccination and future neurodevelopment outcomes", aren't these the very children the study should have focussed on?

13. Andrews et al 'validate' their results through "all the neurological development disorders were more common in boys than girls" yet testosterone enhances the neurotoxicity of mercury so boys would be expected to succumb more often to mercury poisoning than girls. This actually increases the probability that Andrews et al showed mercury poisoning in their subjects.

14. Andrews et al combine for analysis and statistical purposes outcomes that suggest nephrotoxic, neurotoxic, psychotic, behavioural, emotional, cognitive deficiency, and other events, possibly even social deficiencies. This cannot make statistical sense, and may obfuscate more than enlighten.

15. The year of birth range from 1988 to 1997, and GPRD records selection to 1999, suggest that many developmental disorders like autism would not be uncovered as they may not have been diagnosed during the data collection period. Until the mid 1990s in the UK it was not uncommon for autism to remain undiagnosed until age 7 or 8 years – my own son an example – so the 103,043 cohort may hide many children with undiagnosed developmental disorders from mercury toxicity and other causes, including other vaccines eg. MMR. When a child suffers a serious reaction to a vaccine (one expects ethyl mercury to cause acute events such as seizures, meningitis, encephalitis, developmental inhibition, speech/language impairment etc.) a parent would probably refuse further consent. If the first dose injures, there will be no second; if the second does injures, there will be no third etc. After each dose there will be a reducing trend for further vaccination in injured children, but the uninjured 'survivors' continue to the next dose and attain a 'less risk' status, or 'survivor' of the previous dose, yet they also may not be free of outcomes as they were only followed up for 4.7 years – too little time for diagnosis and recording of some developmental disorders so easily hidden that might confound the study.

16. Andrews et al conclude differently to the US VSD study, which found a risk from mercury in vaccines. They say that, other than for Tics, the study does not confirm the US findings. The UK cohort had similar thimerosal exposure to 4 months of age but the US exposure increased from 4 to 7 months and Andrews et al state "if the increased risk in the US study were attributed only to the additional thimerosal exposure after 4 months, it is possible the UK study is not able to detect the risks found in the US study which

had a longer follow up time.....preliminary results from the US study were probably attributed to confounding or chance". They ignore the probability that the continuation of harm to American children was due to their increasing weight after 4 months of age being insufficient to outweigh the increasing weight of ethyl mercury per dose the defenceless children were exposed to.

17. Andrews et al try to validate GPRD records referring to "other validation exercises found the GPRD accurate" omitting the fact that those studies had relatively easy conditions to diagnose and record whereas ASD/PDDs etc. are far more difficult to process accurately and no study has successfully validated the GPRD in that regard so it remains an unknown quantity on which childrens' lives cannot rely.

18. Andrews et al attempt validation using Danish study Hvlid et al JAMA 2003 yet when Madsen et al NEJM 2002 is compared to Hvlid et al one finds their totals for ASDs for Denmark for not dissimilar periods calculated from the same National Database that are 100% out of sync. If they cannot validate each other how can either validate Andrews et al?

We must consider that Andrews et al may have got it totally wrong and if one considers their results with respect to mercury toxicity, in terms of EPA exposure safety criteria, Andrews et al have probably shown that mercury becomes less toxic with growth/weight, therefore the increasing age of the child.

Perhaps the most telling statement Andrews et al make about their attempts at validation is "lack of specificity limits the study as it biases against finding an association". I must agree.

Regards

John H.

Re: Does weight confound?

10 November 2004



Nick J Andrews,
Statistician
CDSC, Health Protection
Agency,
Elizabeth Miller

Sir,

Send letter to journal:
[Re: Re: Does weight
confound?](#)

[E-mail](#) Nick J Andrews,
et al.

In our paper we are investigating whether the cumulative exposure to ethylmercury by age is associated with long-term developmental disorders. The study did not aim to answer the question about potential acute effects of individual doses of vaccine. Such acute problems would have a clear temporal relationship and none of the acute reactions caused by DTP vaccination (such as local reactions at the injection site) are associated with developmental disorders. We did address the issue of body weight by performing a separate analysis on pre-term children and also by looking at doses by 3 as well as 4 months of age. We did not have information on individual children's weight so we could not look at exposure by weight.

Responses to specific points made by Dr Heptonstall are as follows:

Points 1, 8 and 16. We do not conclude that thiomersal can have a true protective effect; we believe the hazard ratios that are below one are due to confounding that we were unable to adjust for. The reducing trend is not by age but is by exposure at a given age so cannot be explained by protective effects of increased body weight.

Point 2. The increased risk of developmental disorders in pre-term children compared to term children is not surprising. The analysis that looked separately at pre-term children found no evidence of an increased risk of developmental disorders by thiomersal exposure in this group. Therefore there is no evidence that the increased risk of developmental disorders in pre-term children could be explained by thiomersal exposure.

Point 3. All the DTP vaccines in this study contained the same amount of thiomersal. There is no reason that the specific batch or brand is of any importance for the particular question our study aims to investigate.

Point 4. We concentrated on DTP since this is the only routinely used thiomersal containing vaccine. There is no evidence of an association between developmental disorders and any other vaccines.

Point 5. Missing some cases of developmental problems will lead to almost no bias for these rare outcomes (we just lose power in the analysis). The validation sample cannot therefore be regarded as tiny. When validating the cases we did identify some lack of specificity, and this is acknowledged in the paper. In the discussion the potential bias arising from a 20% false diagnosis rate is indicated as reducing a true hazard ratio per dose or 1.20 down to 1.15.

Point 6. The study by Heron et al shows that effect of confounding on the outcomes examined was not large. This is clearly of relevance when interpreting our study in which we could not adjust for many confounding variables.

Point 7. It is true that an acute reaction that led to refusal to complete vaccination could lead to bias in our studies, but only if such an acute reaction is expected to lead to long-term problems. None of the recognised acute reactions to DTP are associated with subsequent developmental disorders and very few individuals fail to complete DTP vaccination (2.8% in our study). Of those who do fail to complete very few are likely to do so due to acute reactions.

Points 9 and 12. We are interested in possible long-term effects, not those occurring in the first 6 months.

Point 10. As already mentioned we looked at pre-term children separately and this gave similar results to the term babies. Therefore there is no evidence that thiomersal in vaccines is a risk factor in low birth-weight children.

Point11. There are many possible confounding variables, but as shown in the Heron paper these are not likely to be large enough to hide a large true effect. However, as with all observational studies it is possible that confounding may be a problem.

Point13. The validation mentioned here is that the conditions identified were indeed developmental problems that are known to occur more often in boys. It is not suggested that this validates the negative findings; just that it validates the accuracy of the diagnosis.

Point14. The outcomes chosen were based on the provisional results from the HMO study in the US (reference 6). Splitting outcomes into too many subgroups would lead to very small numbers for the analysis.

Point15. The data were analysed using survival analysis, which allows for censored data. Also see point 7.

Point 17. One of the studies we referenced when citing other validation exercises looked at autism (reference 15). We validated a large number of records (N=152) to ensure that in the majority of cases the condition reported was correct.

We hope this letter clarifies the issues raised in the letter by Dr Heptonstall.

Regards

Nick Andrews and Elizabeth Miller

[SUBSCRIPTIONS](#) [FUTURE CONTENTS](#) [CURRENT ISSUE](#)

[Copyright © 2004 by the American Academy of Pediatrics. \[Disclaimer\]](#)