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Thimerosal-Containing Vaccines and Autistic Spectrum Disorder: A Critical Review of Published Original Data

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ABSTRACT. *Objective.* **The issue of thimerosal-containing vaccines as a possible cause of autistic spectrum disorders (ASD) and neurodevelopmental disorders (NDDs) has been a controversial topic since 1999. Although most practitioners are familiar with the controversy, many are not familiar with the type or quality of evidence in published articles that have addressed this issue. To assess the quality of evidence assessing a potential association between thimerosal-containing vaccines and autism and evaluate whether that evidence suggests accepting or rejecting the hypothesis, we systematically reviewed published articles that report original data pertinent to the potential association between thimerosal-containing vaccines and ASD/NDDs.**

Methods. **Articles for analysis were identified in the National Library of Medicine's Medline database using a PubMed search of the English-language literature for articles published between 1966 and 2004, using keywords thimerosal, thiomersal, mercury, methylmercury, or ethylmercury alone and combined with keywords autistic disorder, autistic spectrum disorder, and neurodevelopment. In addition, we used the "related links" option in PubMed and reviewed the reference sections in the identified articles. All original articles that evaluated an association between thimerosal-containing vaccines and ASD/NDDs or pharmacokinetics of ethylmercury in vaccines were included.**

Results. **Twelve publications that met the selection criteria were identified by the literature search: 10 epidemiologic studies and 2 pharmacokinetic studies of ethylmercury. The design and quality of the studies showed significant variation. The preponderance of epidemiologic evidence does not support an association between thimerosal-containing vaccines and ASD. Epidemiologic studies that support an association are of poor quality and cannot be interpreted. Pharmacokinetic studies suggest that the half-life of ethylmercury is significantly shorter when compared with methylmercury.**

Conclusions. **Studies do not demonstrate a link between thimerosal-containing vaccines and ASD, and the pharmacokinetics of ethylmercury make such an association less likely. Epidemiologic studies that support a link demonstrated significant design flaws that invalidate their conclusions. Evidence does not support a change in the standard of practice with regard to administration of thimerosal-containing vaccines in areas of the world where they are used.** *Pediatrics* **2004;114:793–804;** ***thimerosal, thiomersal, mercury, vaccine, methylmercury, ethylmercury, autism, autistic disorder, autistic spectrum disorder, developmental disorder, neurodevelopmental disorder.***

ABBREVIATIONS. ASD, autistic spectrum disorders; MMR, measles, mumps, rubella; EPA, Environmental Protection Agency; FDA, Food and Drug Administration; NDD, neurodevelopmental disorder; VAERS, Vaccine Adverse Events Reporting System; AE, adverse event; DTaP, diphtheria, tetanus, acellular pertussis; CI, confidence interval; CDC, Centers for Disease Control and Prevention; DTP, diphtheria, tetanus, whole-cell pertussis; HMO, health maintenance organization; RR, relative risk; ADD, attention-deficit disorder; GPRD, General Practice Research Database; DT, diphtheria, tetanus.

The prevalence of autism and autistic spectrum disorders (ASD) seems to be increasing,[1–9] through an actual increase in incidence, an increase in diagnosis as a result of improved detection through service agencies and schools, changes in case definitions, or changes in reimbursement for medical services and other care. Regardless of the reason, determining the cause of autism is critical to permit appropriate diagnostic, treatment, and preventive measures to be enacted. The major categories proposed as causing autism are genetic influence and prenatal or postnatal environmental factors.[10] Vaccines, particularly measles, mumps, and rubella (MMR) vaccine and thimerosal-containing vaccines, have been postulated as a cause for this increased prevalence of ASD.[11–16]

Mercury is known to be neurotoxic, and methylmercury poisoning clusters have been described as a result of environmental contamination. With ongoing industrial practices that create a global cycling of mercury, environmental exposures in food and from other sources is common, and in some areas ~8% of US women of childbearing age have levels above the Environmental Protection Agency (EPA) recommended reference level.[17,18] Consumption of contaminated foods is the main route of nonoccupational exposure; one 5.6-oz can of tuna on average contains 11.5 μg of Hg.[17] The reader is referred to several excellent reviews on the topic for more detailed information.[17,19–25] On the basis of data from areas of environmental contamination, in 1997, the EPA revised its mercury intake guidelines; it is now the most conservative guideline, and is one fourth the intake guidelines of the Food and Drug Administration (FDA). Five points about the EPA guideline

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should be noted: it is based on oral ingestion of methylmercury, not ethylmercury; it is meant as a starting point for investigation, not a level at which toxicity is thought to occur; it has a 10-fold safety factor built in; it was set to avoid toxicity to a fetus; and it assumes a cumulative dose if ingested daily over a prolonged period of time. All of these points are not directly relevant to thimerosal in vaccines, yet EPA guidelines have been applied to ethylmercury in thimerosal.

In 1998, the FDA reviewed thimerosal-containing products and found that >30 licensed vaccines contained thimerosal, which is ~50% ethylmercury, and that with the number of vaccines given in the first 6 months of life the 1997 EPA guideline could potentially be exceeded. The FDA subsequently requested that vaccine manufacturers remove thimerosal, where possible, from vaccines.[26] As of 2001, thimerosal in quantities sufficient to act as a preservative was removed from all vaccines in the childhood immunization schedule in the United States except some influenza vaccines.[27] Trace amounts of thimerosal, introduced during the manufacturing process to ensure sterility, are present in some vaccines, but the amounts are so small that exposure is inconsequential.

Although thimerosal as a preservative is no longer present in recommended vaccines for children younger than 7 years in the United States (except most influenza vaccines), thimerosal-containing vaccines continue to be used worldwide. In addition, practitioners are questioned regularly by parents about the possibility of an association and asked to provide their opinion on the safety of these vaccines. In 2001, the Immunization Safety Review Committee of the Institute of Medicine evaluated this issue and concluded that the evidence is insufficient to accept or reject a causal relationship between exposure to thimerosal and neurodevelopmental disorder (NDD).[28] Subsequently, several epidemiologic studies have been published[29–37] as well as studies evaluating the pharmacokinetics of ethylmercury.[38,39] In addition, the Institute of Medicine reconsidered the hypothesis that vaccines are associated causally with autism and rejected a causal relationship between MMR vaccine and autism and thimerosal-containing vaccines and autism.[40]

Evidence from randomized, controlled trials generally is considered the "gold standard" used to support medical decisions made by practitioners. However, in the context of an existing vaccination program, randomized, controlled trials are not possible. Therefore, the hypothesis of an association between thimerosal and autism has been tested in epidemiologic studies. Because epidemiologic studies are subject to many potential biases that may affect the validity of results, appropriate design and analytic methods are critical to achieve meaningful results. The purpose of this article was to identify systematically and evaluate critically the design, methods, analysis, and conclusions of each original research publication that has assessed the epidemiology of thimerosal and ASD. To address a potential biological mechanism for a link between thimerosal and ASD, we also critique published studies of the pharmacokinetics of ethylmercury in children.

METHODS

Search Strategy

To identify original research publications linking thimerosal-containing vaccines and autism or other neurologic conditions and original laboratory research on the human pharmacokinetics of ethylmercury in thimerosal, we searched the National Library of Medicine's Medline database using PubMed, and the Cochrane Library for articles published between 1966 and 2004. The terms thimerosal, thiomersal, vaccine, mercury, methylmercury, ethylmercury, autism, autistic disorder, autistic spectrum disorders, developmental disorder, and NDDs were selected as MeSH headings, and text words were combined in the search strategy. In addition, we used the "related links" option on PubMed. We also reviewed references in all relevant published articles, including reviews, letters, and commentaries, to identify original research.

Study Selection and Evaluation

Studies were assessed as to whether they should be included in this review on the basis of their reporting original data examining a possible link between thimerosal and ASD/NDDs or describing human pharmacokinetics of ethylmercury, which is found in thimerosal. Once a study met the inclusion criterion, data were extracted including first author, journal, year of publication, country of study, type of study, and database or laboratory data examined. Assessment of study methods included study design, type and size of population studied, definition of exposures and outcomes, validation of developmental diagnoses, provision of sample size calculations and/or discussion of study power, and statistical methods including techniques to control for potential confounding. We also determined whether the authors discussed potential limitations to the study. Assessments of all eligible studies were conducted independently, with differences resolved by all-author consensus. Study authors were not contacted for additional information because our goal was to evaluate data available in the original publications. Attempts were made to validate data used in the reviewed publications when the data sources were available publicly.

RESULTS

Of the abstracts of articles reviewed, 14 seemed to report original data. Two pharmacokinetic studies were excluded: one because it modeled theoretical estimates of mercury concentrations[41] and another because it used previously published data for half-life extrapolation of ethylmercury rather than reporting original data.[42] Characteristics of the remaining 12 studies are summarized in Tables 1 and 2. Ten studies are epidemiologic: 5 cohort studies investigating an association between thimerosal and autism/developmental disorders,[29,32–35] 3 ecological studies comparing trends in the incidence of autism with thimerosal exposure,[36,37,43] and 2 studies that present both retrospective cohort and ecological data.[30,31] Two of the purely ecological studies have overlapping data sets, and 1 of the retrospective cohort studies uses the same database as these 2.[33] One of the ecological studies[43] and 2 of the studies reporting cohort and ecological results[30,31] use the same data, some of which were used by the same authors in a third article, 1 of the retrospective cohort studies.[29] Two studies are pharmacokinetic studies of thimerosal in a cohort of human infants.[38,39] Both examine small numbers of patients without matched control subjects and thus are descriptive. Several quality measures were used to evaluate the cohort studies (Table 2). A summary of each article is pre-

TABLE 1. Characteristics of Epidemiologic Studies

Country, Year Published	Source	Analysis, Years of Study	Database
UK 2004	Andrews et al[34]	Retrospective cohort, 1988–1997	Office of National Statistics GPRD
UK 2004	Heron et al[35]	Prospective cohort, 1991–1992	ALSPAC; Child Health Surveillance
Denmark 2003	Hviid et al[33]	Retrospective cohort, 1990–1996	Danish National Registries
USA 2003	Verstraeten et al[32]	Retrospective cohort, 1991–2000	Three HMOs
USA 2003	Geier and Geier[29]	Retrospective cohort, 1992–2000	VAERS
USA 2003	Geier and Geier[30]	Retrospective cohort and ecological, 1992–2000	VAERS, US Department of Education Report
USA 2003	Geier and Geier[31]	Retrospective cohort and ecological, 1997–2000	VAERS, US Department of Education Report
USA 2004	Geier and Geier[43]	Ecological, 1981–1985, 1990–1996	US Department of Education Report
Sweden/Denmark 2003	Stehr-Green et al[36]	Ecological, Sweden 1987–1999, Denmark 1983–2000	National Inpatient Data (Sweden), National Registry (Denmark)
Denmark 2003	Madsen et al[37]	Ecological, 1971–2000	Danish National Registry

ALSPAC indicates Avon Longitudinal Study of Parents and Children.

sented, followed by a summary of principal methodologic concerns.

Cohort Studies

Of the 10 epidemiologic studies, 7 included cohort data (Table 1). Three of these articles reported an association between autism and thimerosal exposure. All 3 are by the same authors, and the data sets are overlapping.[29–31] The first of these to be published is a retrospective cohort study that used the Vaccine Adverse Events Reporting System (VAERS) database.[29] The authors analyzed information from the VAERS database on adverse events (AEs) reported after use of thimerosal-containing diphtheria, tetanus, acellular pertussis (DTaP) vaccines from 1992 to 2000 ($n = 6575$) and after use of thimerosal-free DTaP vaccines from a different time period, 1997–2000 ($n = 1516$). The authors then defined a cohort that included 88 children who were reported as having autism, mental retardation, or speech disorders. Of these children, 81 were in the thimerosal group (18 with autism) and 7 were in the thimerosal-free group (1 with autism). Gender, age, and onset in days after vaccination were extracted. Risk ratios were calculated on the basis of relative incidence of each diagnosis for the thimerosal-containing compared with the thimerosal-free group: autism, 6.0; mental retardation, 6.1; and speech disorders, 2.2. No confidence intervals (CIs) were provided. The authors concluded that there is a significant ($P < .002$ to $P < .05$) increase in these disorders after receipt of thimerosal-containing vaccines and that children who receive an additional 75 to 100 μg of thimerosal may have an associated increase in NDDs. Furthermore, the authors stated that reactions tended to occur in older children and speculated that this may be explained by the toxic buildup of mercury from successive doses of thimerosal-containing DTaP vaccines.

We identified multiple methodologic concerns regarding this article. The key outcome measure, calculation and comparison of AE incidence for thimerosal-exposed and unexposed infants, requires accurate and unbiased assessment of the numerator (children with defined AEs) and denominator (exposure/no exposure to thimerosal-containing DTaP) for the 2 groups. Several factors contribute to substantial inaccuracy in the numerator of AEs. VAERS is a passive reporting system that is monitored by the Centers for Disease Control and Prevention (CDC) and the FDA and to which anyone—health care provider, vaccinee, or parent—may report an AE after vaccination.[44] Although the authors postulated complete reporting of AEs by stating that "all adverse reactions are to be reported to the VAERS database as required by US law," in fact, reporting is mandated only for events included in the "injury table" of the National Vaccine Injury Compensation Program; ASDs and NDDs potentially associated with diphtheria, tetanus, whole-cell pertussis (DTP)/DTaP or thimerosal exposure are not mandated. Moreover, for these and other adverse reactions, substantial underreporting occurs.[44–46] Underreporting is particularly common for events that are not in the compensation program, for events that are not defined by a specific diagnostic test, or when the temporal relationship with vaccination is not well defined, both of which apply to the conditions evaluated in this study. In addition, events in VAERS are classified on the basis of a reported diagnosis or a coder's interpretation of symptoms/signs included in a comment field. Diagnoses are not validated. The authors do not report which diagnosis or symptom terms they abstracted from the VAERS database or how they dealt with diagnostic overlap or incomplete records. This is particularly troubling because the disorders reported have a long differential diagnosis and because the mean age reported for children with autism (1.7 ± 1.1 year) is below the age at which a reliable diagnosis of that disorder is made.[47,48] Demonstrating the statistical fragility of analysis of this database, if only 1 child who has autism and did not receive thimerosal-containing DTaP were misclassified into the thimerosal group or if 1 such child were not reported to the VAERS system, then the reported risk ratio would be reduced by half and the P value would be $>.05$.

In addition, several biases may have led to differential reporting of events in children who received DTaP vaccines that did or did not contain thimerosal as a preservative affecting the ability to compare relative reporting rates. In a setting of incomplete

TABLE 2. Evaluation Criteria of Cohort Studies

	Cohort Inclusion/Exclusion Criteria Precisely Described	Outcome Measures (Diagnoses) Precisely Defined	Outcome Measures Validated for at Least a Sample or None of the Cohort	Methods to Calculate Risk Factor (Thimerosal) Exposure Described and Appropriate	Basis for Sample Size Described and/or Power Discussed	Study Controls for Bias and Confounding	Potential Impact of Bias on Results Discussed	Other Study Limitations Discussed
Andrews et al, 2004[34]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Heron et al, 2004[35]	Yes	No	No	Yes	No	Yes	Yes	Yes
Hviid et al, 2003[33]	Yes	Yes	No*	Yes	No	Yes	Yes	Yes
Verstraeten et al, 2003[32]	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Geier and Geier, 2003[29]	No	No	No	No	No	No	No	No
Geier and Geier, 2003[30]	No	No	No	No	No	No	No	No
Geier and Geier, 2003[31]	No	No	No	No	No	No	No	No

* Validity confirmed in a sample from the same database used for another study.

reporting, if parents or providers, either of whom can report to VAERS, are aware of a possible link between thimerosal exposure and NDDs, then reporting by either group may be greater among those who have been exposed ("reporting bias"). This bias also may have affected description of symptoms and had an impact on how events were coded. "Diagnostic bias," with providers more likely to diagnose autism or other NDDs among children who were exposed to thimerosal, also may have occurred. Because of FDA concern and subsequent recommendations by the American Academy of Pediatrics and the US Public Health Service for precautionary thimerosal removal in July 1999, with associated media interest, there was a substantial risk that these biases occurred in a study that includes AEs reported through 2000. VAERS data show markedly increased reporting of autism during the second half of 1999 and 2000, consistent with reporting bias.

An additional problem affecting numerator data is the inability to define accurately total thimerosal exposure in children with reported AEs. VAERS reports include only the vaccine type and manufacturers for the visit associated with the AE and within 4 weeks before that date. It is not possible to define whether a child received thimerosal-containing or -free DTaP vaccine at previous visits or other vaccines that may or may not have included this preservative. As NDD risk was hypothesized by the authors to be related to the total thimerosal exposure rather than only thimerosal in DTaP, the inability to define that exposure represents a significant limitation.

Substantial questions regarding the accuracy of the denominator data for the incidence calculation also exist. The denominator requires the total number of children in the United States who received thimerosal-containing DTaP (exposed) and the total number who received thimerosal-free DTaP (unexposed). The authors indicated the source of these data as the "Biological Surveillance Summaries of the CDC." However, CDC reports only aggregate doses distributed for DTaP and other vaccines and provides no manufacturer-specific data.[49] It is unclear how the authors estimated manufacturer-specific data because, on the basis of agreements with manufacturers, CDC does not release these data. No source is cited in the publication. The authors provided no details on how total DTaP doses distributed were translated into number of children vaccinated with specific thimerosal-containing or thimerosal-free vaccines, which is particularly problematic for a vaccine administered in a 5-dose schedule over a 4- to 5-year period.

Two other publications by Geier and Geier reported essentially the same data with minor differences and thus are discussed together.[30,31] The articles have 3 components: first, data from the VAERS database again were presented but analyzed on the basis of different levels of thimerosal exposure (cohort data); second, a comparison between the FDA and EPA exposure limits was made with the dose received in routine vaccination; and third, the US Department of Education report on numbers of chil-

dren with neurologic disorders was compared with mercury exposure in vaccinations over time (ecological data). The ecological data are discussed in the section on ecological studies.

The cohort data in 1 article[31] evaluated reports of autism, personality disorders, and mental retardation for children who were exposed to thimerosal-containing and thimerosal-free DTaP vaccines using VAERS reports between 1997 and 2001, and the other[30] assessed autism, speech disorders, and heart arrest on the basis of VAERS reports of children who were exposed to thimerosal-containing DTP and DTaP vaccines from 1992 to 2000 compared with thimerosal-free DTaP vaccines from 1997 to 2000. DTaP vaccines were not licensed in the United States for use beginning at 2 months of age until 1996. The analytic strategy comparing incidence rates in these 2 articles is the same as in their first publication. However, the authors stated that in each of these analyses, they compared children who received an average of 37.5 μg of ethylmercury with children who received an average of 87.5 μg. The overall conclusion of both publications is that there is an association of heart arrest and neurologic disabilities with thimerosal.

As in the first Geier and Geier article, completeness in reporting, diagnostic specificity and validation, and potential diagnostic and reporting bias cannot be evaluated properly in these 2 studies,[30,31] particularly for the study that included data through 2001.[31] In addition, the authors did not present methods on how the ethylmercury exposure estimates of 37.5 μg and 87.5 μg were determined. Because VAERS reports do not include a child's entire immunization history and because vaccines that are reported to have been received before an AE are not verified by medical record review, estimated ethylmercury exposure from the reported vaccination visit may be inaccurate and total previous exposure would not be possible to estimate.

Four of the 7 cohort studies do not identify an association between thimerosal and ASD. One study is from the Vaccine Safety Data Link group from the CDC in the United States.[32] Data were collected from 3 health maintenance organization (HMO) databases on a total of 140 887 vaccinees. Data were screened for potential associations between NDDs and cumulative thimerosal exposure at 1, 3, and 7 months of age with exposure analyzed as both continuous and categorical variables. Relative risks (RRs) were calculated using a proportional hazards model. In the first phase of the study, data from 2 HMOs were analyzed. In the continuous variable analysis, an association at HMO A between thimerosal exposure at 3 months of age and tics was found (RR: 1.89; 95% CI: 1.05–3.38). At HMO B, cumulative exposure to thimerosal at 3 and 7 months of age was associated with language delay (3 months: RR: 1.13; 95% CI: 1.01–1.27; 7 months: RR: 1.07; 95% CI: 1.01–1.13). In the categorical analysis, there was a negative association for speech delay with 87 to ≥175 μg Hg at 7 months in HMO A (87–162 μg: RR: 0.58; 95% CI: 0.37–0.93; ≥175 μg: RR: 0.58; 95% CI: 0.36–0.92). For HMO B, at 3 months of age, there was an association between ≥62.5 μg Hg and language delay (RR: 1.87; 95% CI: 1.08–3.23). Only HMO B included a sufficient sample size of patients with autism for analysis, and no association was found. An additional subanalysis was performed at HMO B, where children who were exposed to thimerosal-containing vaccines were compared with children who received only thimerosal-free vaccines; at 3 months of age, the only statistically significant association was a protective effect of thimerosal for attention deficit disorder (ADD; RR: 0.70; 95% CI: 0.52–0.95).

In the second phase, children in HMO C were assessed to evaluate further the associations seen in HMOs A and B, in an attempt to confirm the preliminary findings. There were no statistically significant associations. Because of limited numbers, RR at HMO C was calculated only for diagnoses of speech or language delay and ADD; no increased risk was found for either outcome. The authors concluded that no association can be confirmed or refuted between thimerosal and NDDs. The authors stated that because of the retrospective cohort study design and the need to resolve conflicting findings in the HMOs, additional studies need to be conducted.

This brief summary simplifies results of a complex analysis using a multifaceted data set. This cohort includes complete ascertainment of children with *International Classification of Diseases, Ninth Revision* coded diagnoses and complete vaccination histories, allowing accurate calculation of thimerosal exposure. Analytic methods are described clearly as are methods used to control for potential biases, such as differences in health care utilization. The authors found an association between thimerosal exposure and upper respiratory tract infection, suggesting that increased health care use may be a confounder, with children who have more visits receiving more vaccinations and being more likely to have a diagnosis of an NDD such as speech delay. To control for this, analyses for HMOs A and B were restricted to children who had made at least 1 visit to a clinic or an emergency department at the same age as cases. However, the authors did not document that this adequately controlled for differences related to health care use, and similar measures to control for potential confounding could not be implemented at HMO C.

The question of diagnostic accuracy was assessed for a subset of patients with an NDD by conducting chart review and documenting that the diagnosis was made by an appropriate specialist. Confirmation rates were variable, with a range from 28% for ADD to 92% for autism; rates varied by HMO. Interpreting associations for diagnoses with lower confirmation rates may be problematic.

Although this is the first peer-reviewed journal publication of these data, it is the third reanalysis of these data sets.[28,50] Each reanalysis has attempted to address methodologic problems, for example controlling for differences in health care–seeking behavior and analyzing data from HMOs A and B separately. Although these reanalyses may strengthen the overall analytic method, they create a risk of "investigator bias" whereby the investigators' beliefs re-

garding outcome could affect the analysis and results.

The fifth cohort study uses the Danish Civil Registration System to examine the rate ratio of ASD in children who received thimerosal-containing vaccinations to children who received thimerosal-free vaccinations.[33] In Denmark, the only thimerosal-containing vaccine given after 1970 was DTP; thimerosal was removed in 1992. Whole-cell pertussis vaccine continued to be administered until 1997, at which time Denmark changed to an acellular pertussis vaccine. Using the Danish Civil Registration System, Hviid et al[33] were able to connect registrants who were born between January 1, 1990, and December 31, 1996, to their vaccination records at the National Board of Health and their pertinent health records at the Danish Psychiatric Central Register, the National Hospital Discharge Register, and the Danish Medical Birth Registry. Medical histories of children were followed until pertinent diagnoses were made, children were lost from the system, or children reached 11 years of age.

On the basis of doses given at 5 weeks, 9 weeks, and 10 months of age, a child in Denmark before 1992 could receive a total of 125 μg of ethylmercury; after 1992, the exposure was 0. Incidence rates were analyzed with Poisson regression to calculate a rate ratio, per 25-μg ethylmercury increment, according to vaccination history. The rate ratio for autism for children who received any vaccinations that contained thimerosal (1 220 006 person-years) as compared with children who received only thimerosal-free vaccinations (1 660 159 person-years) is reported as 0.85 (95% CI: 0.06–1.20). For other ASDs, the rate ratio was 1.12 (95% CI: 0.88–1.43). When increments of 25, 75, and 125 μg Hg are compared, the rate ratios and CIs are similar. For assessing for possible misclassification of thimerosal-containing or thimerosal-free vaccine during the period of switchover (1992), data were reassessed excluding 1992, and results again were similar. For addressing possible confounders that might have changed in the population over time (eg, dietary mercury, ASD diagnostic criteria/incidence), the data were analyzed restricting the cohort to 1991–1993, and the results again were similar. Single imputation was used to evaluate the impact of missing values, and no impact was detected. The authors also evaluated the overall incidence of autism in Denmark during the study period and found a significant increase per calendar year (RR: 1.24; 95% CI: 1.17–1.31), even after discontinuation of thimerosal in vaccines. The authors concluded that although there is an increase in incidence of autism, there is no evidence of an association between thimerosal-containing vaccines and autism in the cohort that they studied and no indication of a dose-response association.

The organization of the Danish health system lends itself to the type of analysis presented in the article. The cohort includes complete ascertainment of children, developmental diagnoses, and immunizations. That all children in Denmark receive vaccines from a single manufacturer (the government) optimizes the ability to ascertain exposures accurately. Potential sources of error such as vaccinations received during the 1992 changeover period and changes in diagnosis of autism during the study period were anticipated and analyses were done to evaluate their possible impact. One weakness is that the validity of the ASD diagnoses was not ascertained because chart reviews were not performed. The authors dismissed this, citing a published paper using the same databases in which validity of ASD diagnosis was confirmed in 37 (92%) of 40 children.[51] On the basis of this information, it is unlikely to have significantly influenced the results for this diagnosis. Although the study population was large and included almost 3 million child-years of observation, no information is presented in the publication on the potential difference in the incidence in autism that the study is powered to detect. Moreover, the maximum thimerosal exposure in Denmark was 125 μg ethylmercury, which is less than what the potential maximum exposure would have been in the United States. However, thimerosal exposure started at an early age and would be important if sensitivity to thimerosal were age-related.

The sixth study in the cohort category was performed in the United Kingdom using the General Practice Research Database (GPRD).[34] In this retrospective cohort study, 100 572 term and 2471 preterm children who were born from 1988 to 1997 and had at least 2 years of follow-up were linked to their vaccination histories and codes for diagnoses of various NDDs. Data for an association between thimerosal and these disorders was evaluated using a Cox proportional hazards model. The thimerosal dose from DTP/diphtheria, tetanus (DT; the only thimerosal-containing vaccine in the United Kingdom in the routine childhood program) was calculated for each child using a calculation that reflected both the total dose and the age of vaccination such that comparisons could be made between children who received a higher dose of mercury earlier in life and children who received vaccination later in life and/or missed doses. In the term group, 96% of children eventually received all 3 doses of DTP/DT. However, there was sufficient variability in the timing of vaccination to enable comparison using this formula, which is well explained in the text of the article. The average length of follow-up was 4.7 years and ranged from 2 to 11 years. Overall, in the term group, 5831 (2.0%) neurodevelopmental diagnoses were made, 104 (0.1%) of these being autism and 70 (0.07%) being tics. Two-sided *P* values with hazards ratios and CIs were calculated for term and preterm infants separately, and the data also were analyzed after excluding all children who did not receive 3 doses of vaccine by age 366 days, to minimize potential bias related to exposure to medical care. The only diagnosis for which risk increased significantly with increasing thimerosal dose was tics (hazards ratio: 1.62; 95% CI: 1.05–2.50) for doses by 3 months. For general developmental disorder, unspecified developmental delay, and ADD, there was a protective effect associated with thimerosal exposure. Validation was performed by reviewing charts of primary care physicians for 152 children with neurologic diagnoses. The

dates of vaccination were found to be accurate, and in 122 (80%), it was confirmed that the child presented with the coded condition; in the other 30 (20%), there was no record of the diagnosis, it was coded incorrectly, or the diagnosis reflected parental concern only. In the 122 children with a confirmed diagnosis, 48 were transient problems and 31 were long term; specifically, 24 (89%) of 27 tics were reported as transient. The authors concluded that the borderline association found between thimerosal exposure and tics is likely to be a chance effect or the result of confounding and that there is no evidence of neurotoxicity in infants or children who are exposed to thimerosal in vaccines.

Similar to the VSD and Danish studies, the GPRD database includes longitudinal health care and immunization data on a large cohort of children.[34] Although of the 152 898 children in the database only 100 572 were included for analysis, the large majority of exclusions were because of missing birthdates, which would not be a source of bias. The remaining exclusions, of preterm infants and infants with prenatal or early postnatal conditions that would affect receipt of vaccination and NDD outcomes, are appropriate to avoid potential confounding. The methods, analytic approach, and statistical technique are described clearly and are appropriate. The high proportion of developmental diagnoses that were validated is reassuring, but the sample evaluated was small and validation rates are not presented by diagnosis. The authors discussed several potential impacts of confounding on study results. The apparent protective effect of vaccination for several NDDs may reflect an inability to exclude all children with underlying conditions that increase their risk of these outcomes and decrease their likelihood of timely vaccination. The authors also acknowledged an inability to control for socioeconomic status or to consider unrecorded medical conditions, although the possible impact of these factors is unclear. A potential limitation of all analyses that rely on diagnostic code data are the possible variability on how physicians record diagnoses and the potential impact of chief complaint on final diagnosis. However, this type of diagnostic bias could lead to spurious associations, rather than a lack of an association as found in this study. One limitation of this article is the lack of a discussion of the study power to detect significant associations for key NDDs, if such associations existed.

By contrast with the previous 3 studies, which analyzed diagnoses made by health care providers, the study by Heron et al[35] analyzed parental responses to questionnaires administered at 7 time points over 91 months. The Avon Longitudinal Study of Parents and Children in the United Kingdom evaluated development of children who were born in 1991 and 1992. Questionnaires included the Strengths and Difficulties Scales to define behavior ratings and the Denver II for fine motor development. Questionnaires also included screening questions for concerns about speech, tics, and special needs. Information on specific diagnoses, such as ASD, was not gathered but was expected to be reflected in the categories analyzed. Questionnaires also collected data on 9 potential confounders. Investigators were able to match 12 810 children who were evaluated in the Avon Longitudinal Study of Parents and Children study with their immunization histories in the UK Child Health Surveillance Database. Thimerosal dose was calculated as in the analysis of the GPRD database, taking into account both total dose and age at which the dose was given. Multivariate analyses, controlling for potential confounders, found negative associations for thimerosal exposure and conduct behavior, fine motor development, and tics. Only poor prosocial behavior at 47 months of age was significantly associated with thimerosal exposure at 3 months of age (odds ratio: 1.21; 95% CI: 1.01–1.23; $P = .031$). The authors concluded that the single association that they found may be expected given the 69 statistical tests performed and that early thimerosal exposure is not associated with a deleterious neurologic or psychological outcome.

Strengths of this study are that collecting data directly from parents avoids the potential confounding effects associated with health care utilization, and information could be collected on potential confounding variables such as socioeconomic status. There are a few concerns with this article, all of which are acknowledged by the authors. First, parental reports were not validated or compared with medical diagnosis. Second, developmental screens were problematic. Third, the questionnaire response rates varied from 65% for children with the maximum exposure to thimerosal to 48% for children with no exposure. The authors suggested that children with less thimerosal exposure also fall into a lower socioeconomic group and therefore have more risk factors for an adverse neurologic outcome, potentially creating a bias against finding an association. However, the potential impacts of response bias were minimized in the multivariate analysis, which controlled for socioeconomic status. Power was not addressed in this publication.

Ecological Studies

Five studies contain ecological data (Table 1). Two of these studies contain cohort data in addition to ecological data; the cohort data were reviewed above.[30,31] A separate ecological study by the same authors[43] reported essentially the same data as was presented in their cohort/ecological studies; thus, the ecological data of all 3 articles are discussed together. The authors compared the mean amount of ethylmercury in childhood vaccines with the number of cases of various disabilities reported in the US Department of Education system over time, using data from 1981 through 1985 and 1990 through 1996. To determine prevalence of disabilities, the US Department of Education report and the CDC's live birth surveillance data are analyzed.[52,53] Depending on the study, the conditions analyzed included autism, speech disorders, orthopedic impairments, visual impairments, and deaf-blindness. The authors then plotted the average thimerosal dose against the individual disabilities found and reported an association between speech disorders and autism with

thimerosal but no association with visual impairments, deaf-blindness, and orthopedic impairments. Odds ratios as compared with a baseline in 1984 and CIs >1 were reported. One of the studies also reported a correlation between the MMR vaccine and autism.[43]

There are several concerns with this analytic approach. The US Department of Education reports the number of people with each of the analyzed disabilities contained in their system, subdivided by age.[52] The authors determined prevalence by dividing these numbers by the number of live births recorded in the year in which that age group was born, as per the author reference to CDC data.[53] The accuracy of this approach depends on the assumption that the US Department of Education database is equally accurate and complete for each of the specified periods. If dropout was more common for the cohort born in 1984–1985 than that born in 1990–1994 and if reporting and diagnostic criteria differ during the time periods, then there may be spurious differences. Incidence of these disorders by birth cohort would provide a better measure of trends than does prevalence. To evaluate trends in exposure, the authors calculated the amount of ethylmercury administered on average to US children during the same time period. Although the ethylmercury dose did increase during the study period as a result of the widespread use of *Haemophilus influenzae* type b and hepatitis B vaccines, the methods did not consistently describe how ethylmercury exposure was calculated or which vaccines were evaluated. The authors stated that the ethylmercury dose "was based on the Biological Surveillance Summaries of the CDC," so the authors apparently divided the doses distributed by the birth year cohort to arrive at an average dose. Problems with this strategy include that the number of vaccines distributed in a certain year may not correspond with the number administered; and, again, the referenced report does not include manufacturer-specific data that would allow the investigators to separate thimerosal-containing from thimerosal-free vaccines distributed. In addition, the authors did not evaluate the vaccination histories of the children in the US Department of Education report; rather, they compared trends using 2 separate databases, thus the conclusion that the relationship between NDDs and ethylmercury is "linear," NDDs increasing with each microgram of mercury administered, is not valid. Although it is plausible that autism prevalence did increase at the same time that thimerosal exposure increased (with the introduction of new vaccines), a basic premise of epidemiology is that correlation does not make causation; this shortcoming and alternative hypotheses were not addressed.

The 2 other ecological studies reported data from Sweden and Denmark. The first article reported the incidence or case numbers of autism in Sweden and in Denmark from 1987 to 1999.[36] The authors then calculated cumulative ethylmercury exposure by multiplying the amount in vaccines used at the time by vaccination coverage rates (usually >95%) for each birth-year cohort and compared results with the incidence of autism. Both Sweden and Denmark discontinued thimerosal use during the study period, in 1992. The results for both countries were similar. Autism incidence or case numbers increased throughout the study period and continued to increase (although with some fluctuation) after elimination of thimerosal as a preservative in vaccines. The data are most compelling for Denmark, where autism prevalence rises substantially after thimerosal discontinuation. The authors concluded that their study constitutes compelling evidence against a thimerosal-autism correlation.

The design of this study is straightforward. The quality of records for autism diagnoses and vaccination rates and the size and stability of the population studied are strengths of this work. One concern is that incidence data were provided for Sweden but not for Denmark; however, these data were presented in a second publication, discussed below.[37] This study does have some limitations, which are discussed by the authors, and include the inability to control for or identify factors such as environmental exposure to methylmercury. Another limitation to all ecological data collected on this subject is that the criteria for the diagnosis of autism have changed and broadened over the years, making it difficult to interpret a reported increase in incidence or prevalence.

The last article in the ecological study category used the same data set but evaluated data from Denmark only.[37] This study expanded the Denmark information to include 1961–1970, when the cumulative ethylmercury dose was 200 μg in the first 15 months of life, and 1970–1992, when the dose was 125 μg in the first 10 months of life, as well as 1992–2000, when vaccines in Denmark did not contain thimerosal. The incidence of autism was stable until 1990 and thereafter increased throughout the study period, including the period when thimerosal was not included in vaccines. The authors concluded that there is no evidence for an association between thimerosal use in vaccines and autism.

The limitations of this study are similar to those discussed for the article by Stehr-Green et al.[36] In addition, because data were not available, outpatients with the diagnosis of ASD were not counted until 1995. This would increase the incidence rates for 1995 compared with previous years, as discussed by the authors. Rates continued to rise after 1995, however, when outpatients continue to be counted, so this is not likely to have affected overall conclusions of the analysis.

Laboratory Studies Describing Mercury Levels After Vaccination in Human Infants

Most studies of the pharmacokinetics and metabolism of organic mercury have evaluated methylmercury and have been performed with oral or inhalational absorption and are summarized elsewhere.[19,24] The first publication to describe ethylmercury (from thimerosal) pharmacokinetics in infants after injection was published by Stajich et al in 2000.[38] This study compared 20 infants in whom pre– and post–hepatitis B vaccination mercury levels were evaluated. Levels after vaccination were col-

lected at 48 to 72 hours. Fifteen infants who were born at <1000 g were compared with 5 infants who were born at >3500 g. Each dose of vaccine contained 12.5 μg of ethylmercury. The mean mercury level after vaccination was significantly higher ($P < .01$) in the preterm group compared with the term group (mean: 7.36 ± 4.99 μg/L vs 2.24 ± 0.58 μg/L, respectively). The mean value did not exceed the Department of Health and Human Services guidelines for "normal" blood mercury levels (<20 μg/L). On an individual basis, this value was exceeded in 1 preterm infant (range: 1.3–23.6 μg/L) but no infants in the term group (range: 1.4–2.9 μg/L). The authors raised concern for possible toxicity in the preterm population, although the significance of a 23.6-μg/L ethylmercury blood level in 1 infant is unknown. These data are useful in suggesting that the birth dose of hepatitis B vaccine does not substantially increase blood mercury levels in term infants and that levels are well below Department of Health and Human Services guidelines. It should be noted that the American Academy of Pediatrics and the Advisory Committee on Immunization Practices do not recommend hepatitis B vaccination in infants <1000 g unless the mother is HB surface antigen positive. For both the preterm and term groups, the small sample size limits the precision of the point estimates.

The publication by Pichichero et al[39] included data from 61 children: 40 recruited in Rochester, NY, who were exposed to thimerosal in vaccines compared with an unmatched control group of 21 children who were not exposed to ethylmercury in vaccinations recruited in Bethesda, MD. Although the Bethesda group is called a control, these children are not matched and the timing of blood mercury level testing is different. Children in the thimerosal-exposed group received up to 3 thimerosal preservative–containing vaccines (DTaP, hepatitis B, *Haemophilus influenzae* type b), and mercury levels were measured 3 to 28 days after vaccination. In the control group, samples were obtained at either the 2- or 6-month well-child visit. Urine and stool samples and maternal hair for total mercury content were studied for some infants, mostly in the thimerosal-exposed group. Results showed mercury concentrations below the limit of quantification in 12 of 33 infants in the study group and in 14 of 15 infants in the control group. Mean values were higher in younger patients, although exact means were not reported. The highest level reported was 20.6 nmol/L (parts per billion), which was less than the 29 nmol/L cited by the authors as thought to be safe in cord blood. Mercury also was found in stool specimens of infants who were exposed to thimerosal, suggesting excretion via the intestinal tract. The half-life of ethylmercury was calculated at 7 days (95% CI: 4–10 days), substantially less than the 20 to 70 days for methylmercury.

Although the absence of significantly elevated blood mercury levels in this study is reassuring, there are a number of limitations to the investigation. Most important, only 4 thimerosal-exposed children had blood specimens obtained within 5 days of vaccination—the period during which levels would be expected to be highest. In addition, baseline blood mercury levels were not obtained, so increases after exposure could not be characterized; and the exposed and comparison groups were not matched by age and were enrolled from different geographic areas. As the data showed higher mercury concentrations from maternal hair samples of the children who received thimerosal-containing vaccine, consistent with greater prenatal environmental exposure, the 2 groups are not the same at baseline and thus comparing them is problematic. Estimates of the half-life of ethylmercury were derived from a model and not from longitudinal observations of children. Although a difference between the half-lives of ethyl and methyl mercury is an important finding, directly assessing half-life would be more optimal than relying on modeled results.

Although not a pharmacokinetic evaluation, Geier and Geier[30,31] compared the FDA and EPA exposure limits with the thimerosal dose received in routine vaccination. They reported an "instantaneous excess" of mercury in vaccines on the basis of EPA and FDA standards of 3.2- to 32-fold. The data source and these calculations are understandable and reproducible. However, they are a misinterpretation of the EPA and FDA guidelines, which define their reference dose as "an estimate of daily exposure to the human population (including sensitive subpopulations) that is likely to be without a risk of adverse effects when experienced over a lifetime."[19] No standards exist for an "instantaneous," single-day dosage of ethylmercury delivered by intramuscular injection.

DISCUSSION

The quality and conclusions of 12 original studies on the potential association between thimerosal-containing vaccines and developmental disorders, including ASD, were examined in this review. Results of epidemiologic studies can contribute to assessment of causation but, by themselves, have several inherent limitations. Because they are observational rather than experimental, differences between study populations, multiple potential sources of bias, and the effects of confounding all can affect outcome. Thus, care in selecting the study group, defining and measuring exposures and outcomes, and analytic methods is crucial in obtaining meaningful results. Although consistency of results between multiple studies is 1 factor that can contribute to accepting or rejecting a causal relationship, a caveat is that only high-quality studies should be considered when evaluating consistency of findings. The 4 epidemiologic studies that support an association between thimerosal exposure and NDDs including autism, all by the same authors and using overlapping data sets, contain critical methodologic flaws that render the data and their interpretation noncontributory. The retrospective and prospective cohort studies that do not report an association, despite some limitations, generally were well designed and appropriately analyzed. Overall, these data support a conclusion of no association between thimerosal-containing vaccines and autism in children.

In a cohort study that finds no association, it is important to assess the study's power to detect a significant association, if it existed; none of the 4 quality cohort publications did so, although they did report CIs. Despite large numbers of children or child-years of observation included in the studies, because some of the measured outcomes were uncommon, power to detect significant associations may have been limited. One can assess the precision of a point estimate by CI width. For some analyses, the CI may include values that, taken individually, could seem clinically important; for example, a 95% CI from 0.78 to 1.71 represents a 5% chance that there is a 71% increase in the evaluated measure. Although this is not statistically significant ($P > .05$), some may believe that it is clinically significant. Conversely, when 4 quality studies do not consistently find statistically significant associations, an association that is found is most likely attributable to chance from multiple measures. In this context, although there may be a small chance that a clinically important association could not be detected by an individual study, the failure to detect an association in 4 well-designed cohort evaluations and 2 well-designed ecological studies supports that there truly is no association between thimerosal and ASD/NDDs.

A limitation in generalizing from the European studies to the United States is that total thimerosal exposure in the United Kingdom, Sweden, and Denmark were less than the potential maximum dose in the United States, and vaccination schedules differed; not including influenza, these amounts are 75 μg, 75 μg, 125 μg, and 237.5 μg of ethylmercury, respectively. However, a higher earlier exposure may be important if a true risk exists.

The pharmacokinetic studies, although limited by small sample sizes and differences in timing of specimen collection, suggest that blood mercury levels postvaccination in human infants are not in the range of known toxicity, making neurologic damage from thimerosal in vaccines unlikely. One caveat to this is that the blood level that could be associated with subtle neurotoxicity is controversial and thus makes pharmacokinetic studies difficult to interpret. The lowest Benchmark dose for a neurobehavioral endpoint after in utero exposure to methylmercury that the National Research Council considered reliable was 58 μg/L (parts per billion) in cord blood.[19,21] The postnatal threshold for subtle neurotoxicity is not known but likely would be greater than the lowest Benchmark dose for the more susceptible fetus. In any case, the highest levels found in these investigations are not in this range, although the timing of blood draws may not have been optimal. In addition, the results of the study by Pichichero et al,[39] demonstrating differences in the half-life and metabolism of ethylmercury and methylmercury, indicate that extrapolating experience with the latter to the former may be inappropriate.

Surprising, animal data on thimerosal pharmacokinetics are sparse. Magos[23,42] compared exposure to these 2 types of mercury in rats and found that methylmercury is actively transported across the blood-brain barrier, whereas ethylmercury is passively transported and is not as neurotoxic. An abstract published in 2003 on the pharmacokinetics in newborn monkeys also demonstrated a much shorter half-life for ethylmercury and lower brain levels.[54] Although there are anecdotal reports of mercury chelation aiding children with autism, there have been no controlled trials, and reports of mercury levels in autistic children are few. One study reported lower mercury levels in the hair of autistic children compared with control children; although the authors hypothesized that the mercury was absent from the hair because it was being retained in the brain, no evidence was presented to support this assumption.[55]

Ecological studies are subject to inherent limitations of this method. Changes over time in the diagnosis and reporting of autism and other NDDs make trends particularly difficult to evaluate. Nevertheless, data from Denmark and Sweden, where exposure to thimerosal in vaccines was eliminated in 1992 and where autism rates continued to increase, are consistent with the results of the quality cohort studies and the pharmacokinetic findings.

The evidence reviewed here indicates there is no association between thimerosal-containing vaccines and NDDs, including autism. Determining the cause of autism is important for future diagnosis, treatment, and prevention. However, as the evidence reviewed here suggests, these efforts may be substantially more productive if they are redirected to other hypotheses. Autism research dollars are limited, and parents of autistic children deserve to see finances directed to where they will do the most good. In addition, the evidence reviewed here does not support a change in the standard of practice with regard to administration of thimerosal-containing vaccines in areas of the world where their use is critical, such as economically developing countries. Removal of thimerosal as a preservative has resulted in the use of single-dose vials that are more expensive and increases the need for refrigerator space and other cold chain equipment. In much of the world, these constraints represent a substantial barrier and would result in far fewer children being vaccinated against serious and life-threatening vaccine-preventable diseases. It is well documented that unfounded concerns about vaccine safety can result in decreases in vaccination rates, subsequent disease outbreaks, and inefficient and ineffective utilization of scarce financial and research resources.[56,57] In the case of thimerosal and autism, a growing body of scientifically credible evidence suggests that there may be little to be gained from large additional research investments and, at a minimum, that it is time that additional significant investments in scientific or medical research related to thimerosal and autism be based on credible grounds that would lead one to believe that such investigations will contribute to understanding mechanisms that cause ASD.

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CERVICAL STITCHES ARE INEFFECTIVE

"A common surgical procedure long believed to help prevent premature births is ineffective, a new study has concluded. The study examined a technique called cervical cerclage, used in up to 2 percent of all pregnancies, according to Dr Kypros H. Nicolaides of the Kings College Medical School in London, an author of the study. The cervix is a sphincter of muscle that holds the fetus inside the uterus in pregnancy. Women whose cervixes have been damaged or are shorter than normal have long been thought to be at higher risk of premature deliveries. In cervical cerclage, stitches are inserted to shore up the cervix and give it added strength. The study, published on June 5 in *The Lancet*, involved more than 47 000 pregnant women in many countries. The women were examined with ultrasound. A group of 470 whose cervixes were short enough to put them at risk and who chose to participate were randomly assigned to get the procedure or not. Dr Nicolaides said the results confirmed that the length of the cervix accurately predicted preterm delivery. But the study also found that the cerclage procedure made no significant difference in the outcome; 22 percent of the women who had the surgery extended their pregnancy beyond 33 weeks, as did 26 percent of the control group."

O'Neil J. *New York Times.* June 8, 2004

Noted by JFL, MD

Thimerosal-Containing Vaccines and Autistic Spectrum Disorder: A Critical Review of Published Original Data

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