Autism and Thimerosal-Containing Vaccines

Lack of Consistent Evidence for an Association

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Background: In 1999, concerns were raised that vaccines containing the preservative Thimerosal™ might increase the risk of autism and/or other neurodevelopmental disorders.

Methods: Between the mid-1980s through the late-1990s, we compared the prevalence/incidence of autism in California, Sweden, and Denmark with average exposures to Thimerosal-containing vaccines. Graphic ecologic analyses were used to examine population-based data from the United States (national immunization coverage surveys and counts of children diagnosed with autism-like disorders seeking special education services in California); Sweden (national inpatient data on autism cases, national vaccination coverage levels, and information on use of all vaccines and vaccine-specific amounts of Thimerosal); and Denmark (national registry of inpatient/outpatient-diagnosed autism cases, national vaccination coverage levels, and information on use of all vaccines and vaccine-specific amounts of Thimerosal).

Results: In all three countries, the incidence and prevalence of autism-like disorders began to rise in the 1985–1989 period, and the rate of increase accelerated in the early 1990s. However, in contrast to the situation in the United States, where the average Thimerosal dose from vaccines increased throughout the 1990s, Thimerosal exposures from vaccines in both Sweden and Denmark—already low throughout the 1970s and 1980s—began to decrease in the late 1980s and were eliminated in the early 1990s.

Conclusions: The body of existing data, including the ecologic data presented herein, is not consistent with the hypothesis that increased exposure to Thimerosal-containing vaccines is responsible for the apparent increase in the rates of autism in young children being observed worldwide.
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Introduction

In June of 1999, concerns were raised that children vaccinated with products containing the preservative Thimerosal™ could receive doses of organic mercury (specifically, the thiosalicylate salt of ethylmercury) that exceeded existing guidelines for intake of methylmercury.[1] These concerns were based on extrapolations from the known effects of prenatal methylmercury exposure.[2] Because there are limited data on the toxicology and pharmacokinetics of Thimerosal and ethylmercury, for the purpose of these extrapolations it was assumed that many features of the toxicity of ethylmercury were qualitatively similar to those of methylmercury.[1]

It was subsequently suggested that the apparent increase in the incidence of autism in the United States in the 1990s occurred at about the same time that *Haemophilus influenzae* b (Hib) and hepatitis B (hep B) vaccines were first universally recommended (i.e., in 1990 and 1991, respectively), thereby increasing the average cumulative exposure to Thimerosal from vaccines administered to infants. Prior to that time, the only sources of Thimerosal from vaccines on the recommended childhood immunization schedule were diphtheria–tetanus–pertussis (DTP) (later replaced by diphtheria–tetanus–acellular pertussis [DTaP]) and diphtheria–tetanus (DT) vaccines. Although the maximum theoretical dose of Thimerosal from vaccines varied depending on the brand and combination vaccines used, most children in the United States who received the four universally recommended doses of

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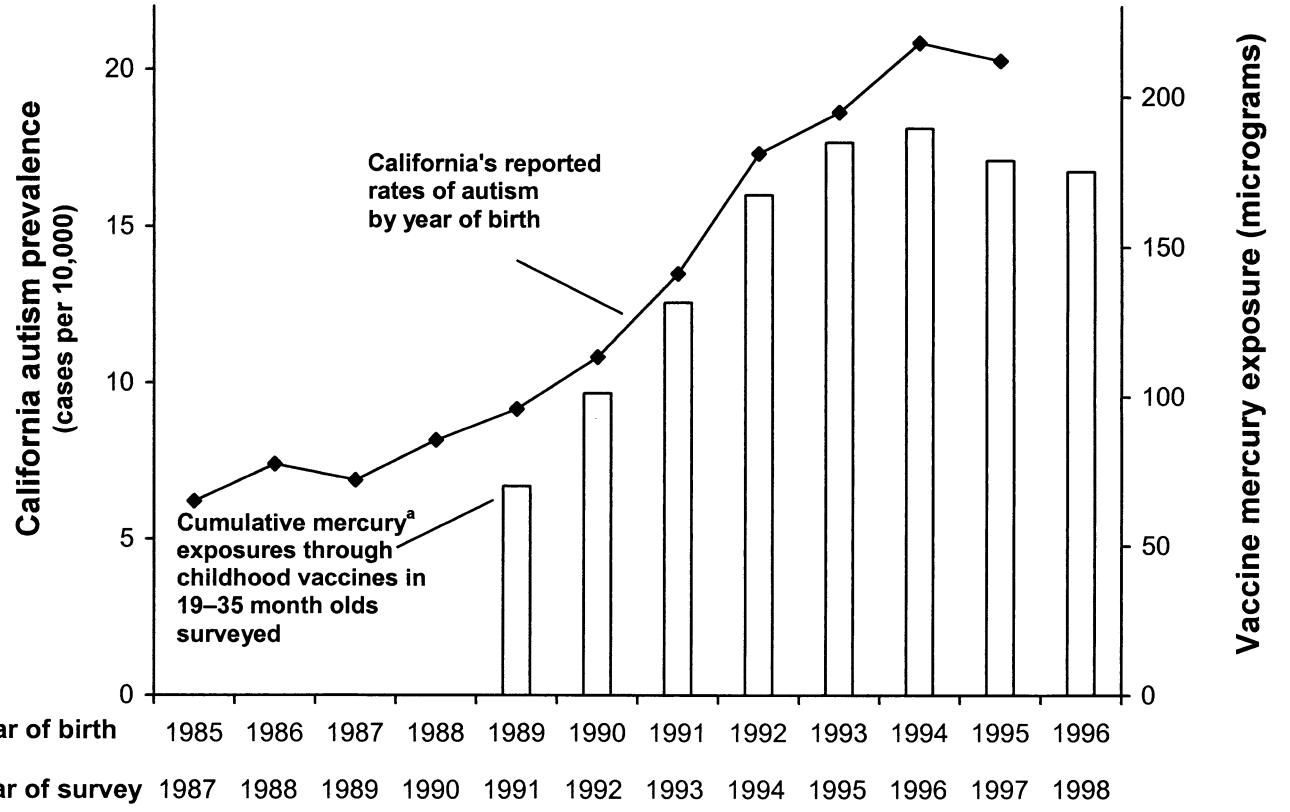

Figure 1. Graphical ecologic analysis presented by Blaxill[3] to the Institute of Medicine on July 16, 2001, comparing the estimated average cumulative dose of mercury exposure in the United States from vaccines, and the estimated prevalence (per 10,000 population) of children diagnosed with autism-like disorders seeking special education services for autism in California from 1987 to 1998, by birth-year cohort.
[a]Includes DPT, *Haemophilus influenza* B, and hepatitis B exposures weighted by survey year compliance.

DTaP/DTP/DT, four doses of Hib, and three doses of hep B in 1999 would have received a 237.5 μg cumulative dose of ethylmercury by age 2 years.

In July 2001, the Institute of Medicine (IOM) Immunization Safety Review Committee held a public meeting to review data and testimony regarding the alleged association of neurodevelopmental effects (including autism) and Thimerosal-containing vaccines. At this meeting, Blaxill[3] presented an ecologic analysis comparing the estimated average cumulative dose of mercury exposure (i.e., the average ethylmercury dose, calculated by multiplying the amount of Thimerosal in the various vaccines by the vaccine-specific coverage rate for U.S. children aged 19 to 35 months, by birth year cohort) to the estimated prevalence of autism in children in California per 10,000 population, by birth year. The prevalence of autism was defined as occurrence of persons with autism or other pervasive developmental disorders (PDD), based on an individualized client development evaluation performed at intake into the California Department of Developmental Services regional and developmental center system during 1987–1998 and coded as International Classification of Diseases (ICD)-9 codes 299.1, 299.80, or 299.88[4]; or (1) "Autism, full syndrome" (no ICD-9 code specified); (2) "Autism, residual state" (no ICD-9 code specified); or (3) "Autism suspected, not diagnosed" (no ICD-9 code specified).[5] The graphical presentation of these data (Figure 1) showed that the number of children in California coded as having autism-like disorders seeking special education services per 10,000 population remained reasonably constant through the mid-1980s, began to rise slightly in 1988, and then began to rise more dramatically in 1990.

As with most ecologic analyses, these data had several limitations. Nonetheless, because of the high level of public interest and the potentially important public health implications, collection of additional ecologic data to further examine this alleged association was performed. In conducting this investigation, we consulted with public health officials and researchers in Sweden and Denmark; both countries have historically maintained high-quality records on vaccine components, recommended vaccination schedules, population vaccination coverage rates, and the occurrence of autism-like disorders.

Methods

In Sweden, data were collected at the national level on cases of autism (defined as "infantile autism, including atypical autism" [ICD-9 codes 299.x for 1987–1997 and ICD-10 codes F84.x for 1997–1999]) diagnosed in inpatient settings among 2 to 10 year olds during from 1987 to 1999. Data collection also included vaccination coverage levels dating back to 1980 as well as administrative information from the Swedish Institute for Infectious Disease Control for the time period(s) of use and vaccine-specific amounts of Thimerosal for all vaccines used in Sweden.

For each birth-year cohort, the average cumulative dose of ethylmercury from vaccines was estimated by multiplying the amount of ethylmercury in Thimerosal-containing vaccines used in Sweden by the vaccine-specific coverage rate for Swedish children aged <2 years. The incidence rate of autism was calculated by dividing the number of cases of autism diagnosed among 2- to 10-year-old inpatients during 1987–1999 by the total number of person-years accumulated during that time period for each annual cohort of children born between 1980 and 1996 (multiplied by 100,000 person-years). Using these data, the ecologic association of the birth-year, cohort-specific administration of Thimerosal-containing vaccines, and the incidence of autism requiring hospitalization among children born in Sweden from 1980 to 1996 was examined.

In Denmark, we examined data on incident cases of autism diagnosed in both inpatient and outpatient settings. The data were from a national registry of children with neurological disorders and compiled by researchers at the Danish National Centre for Register-Based Research. This registry included children who had been admitted to a psychiatric hospital or received outpatient care prior to 1994 with a diagnosis of "psychosis proto-infantilis" (ICD-8 code 299.00); "psychosis infantilis posterior" (ICD-8 code 299.01); or, from 1994 onward, "infantile autism" (ICD-10 code F84.0) or "atypical autism" (ICD-10 code F84.1). Data were also collected at the national level on vaccination coverage levels dating back to 1981, in addition to administrative information from the Danish Statens Serum Institut for the time period(s) of use and vaccine-specific amounts of Thimerosal for all vaccines used in Denmark.

The average cumulative dose of ethylmercury from vaccines for each birth-year cohort was estimated by multiplying the amount of ethylmercury in Thimerosal-containing vaccines used in Denmark by the vaccine-specific coverage rate for Danish children aged <10 months. The number of autism cases diagnosed among 2 to 10 year olds was totaled for each year between 1983 and 2000. Using these data, the ecologic association of the birth-year cohort-specific administration of Thimerosal-containing vaccines and the annual number of cases of autism diagnosed between 1983 and 2000 among children aged 2 to 10 years in Denmark was examined.

Results

As shown in Figure 2, the incidence of autism diagnosed among Swedish inpatients aged 2 to 10 years old began to increase in the mid to late 1980s, rising from a rate of 5 to 6 inpatient-diagnosed cases per 100,000 person-years before 1985 to a peak rate of 9.2/100,000 in 1993. This was generally similar to the above-described trend in California during the same time period. Vaccination coverage has remained high in Sweden (i.e., almost always >95% for all age-specific antigens) since 1980, but the use of Thimerosal in vaccines in Sweden decreased and eventually disappeared by 1993. In fact, few vaccines containing Thimerosal were ever used throughout the history of childhood vaccination programs in Sweden. The major exception was the use of Thimerosal-containing DTP (used until 1979) and DT vaccines (used until 1992), both of which contained Thimerosal at a concentration of 0.01% (i.e., identical to the amount of Thimerosal contained in DTP and DT vaccines used in the United States). A very small number of children also received Thimerosal-containing single-antigen Hib vaccine and/or acellular pertussis vaccines used in a clinical trial prior to 1992. However, since 1992, Thimerosal has not been used in vaccines administered as part of the routine childhood vaccination program in Sweden, except for the very small number of children born to high-risk mothers (<1% of the annual birth cohort) who may have received Thimerosal-containing hep B. Thus, most children in Sweden who received the three recommended doses of Thimerosal-containing DTP/DT prior to 1992 would have received a 75-μg cumulative dose of ethylmercury by age 2 years.

As shown in Figure 3, the experience in Denmark was similar to that in Sweden, where the annual number of autism cases rose from <10 cases among 2 to 10 year olds before 1990 to a peak of 181 cases in 1999. This increase, which began around 1990, affected all age groups aged >2 years and resulted in an estimated prevalence of 8.1 cases per 10,000 persons at the end of 2000.[6] As in Sweden, vaccination coverage in Denmark has remained high (i.e., almost always ≥90% for all age-specific antigens) since 1980. In Denmark, throughout the period between 1970 and 1989, Thimerosal was used only in whole-cell pertussis (wP)-containing vaccines at a concentration of 0.01% (i.e., identical to the amount of Thimerosal in DT and pertussis-containing vaccines in the United States and Sweden). Therefore, children in Denmark who received the three recommended doses of Thimerosal-containing wP between 1970 and 1991 would have received a 125-μg cumulative dose of ethylmercury by age 10 months. In April 1992, the last batch of Thimerosal-containing wP vaccine was produced in Denmark, and its use was eliminated entirely by the end of 1992. Consequently, the proportion of children who received a 125-μg cumulative dose of ethylmercury by age 10 months decreased dramatically between 1991 and 1993. Thus, the apparent rise in diagnosed autism cases in Denmark, as in Sweden, occurred during a time of decreasing use (and eventual elimination) of Thimerosal-containing vaccines.

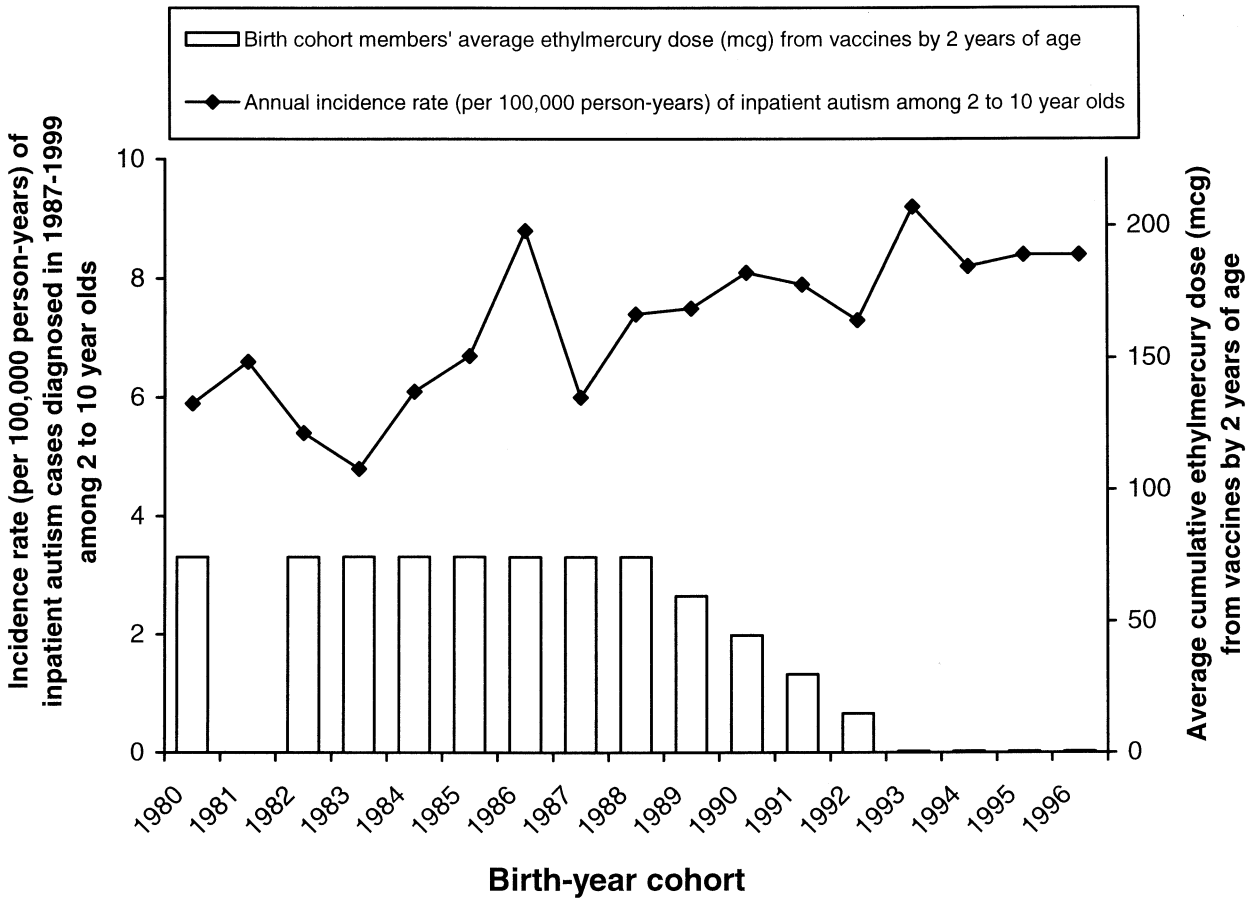

Figure 2. Graphical ecologic analysis comparing average cumulative ethylmercury dose received from vaccines and the incidence rate (per 100,000 person-years) of autism cases in children aged 2 to 10 years diagnosed during 1987–1999 in inpatient settings in Sweden, by birth-year cohort from 1980 to 1996. (Data not available for year 1981.)

Discussion

At first glance, since the increasing vaccination coverage levels in the United States in the early 1990s likely reflect an increasing average exposure to Thimerosal from those vaccines, the results of the ecologic analysis presented to the IOM in July 2001, which showed proximate increases in autism incidence in California, could be argued to be generally consistent with the existence of an etiologic association. On closer examination, however, the upward trend in the prevalence of autism in California (and elsewhere in the United States) appears to have started, albeit at a more moderate rate, in the late 1980s—before the increase in vaccination coverage rates and/or the introduction of additional Thimerosal-containing vaccines (i.e., Hib and hep B) in the early 1990s. Similarly, the rate of autism in Sweden also appears to have began to increase in the mid to late 1980s and, in fact, may have started much earlier. Population-based data representative of the city of Gothenburg (Sweden's second-largest city) show an earlier increase in the prevalence of autism and autism-like conditions (excluding Asperger syndrome) from 4.0/10,000 children in 1980, to 7.5/10,000 in 1984, to 11.6/10,000 in 1988.[7–9]

Although the data from California are the most complete data currently available in the United States, the case definition used by the California Department of Developmental Services (described above) is somewhat vague and, therefore, difficult to verify and/or replicate. Furthermore, these data are likely subject to potential biases. For instance, at least some of the increase of reported cases of autism in California may have been stimulated by the growing availability of special education services for affected children during this time period. And even though the data systems in Sweden and Denmark achieve a remarkable level of validity and accuracy, similar confounding influences or biases may be present. For instance, several external events in Denmark, summarized below, may have spuriously increased the apparent number of autism cases.

- Prior to 1992, the data in the national register did not include cases diagnosed in one large clinic in Copenhagen (which accounts for approximately 20% of cases occurring nationwide).
- Prior to 1995, the autism cases reported to the national register reflected only cases diagnosed in inpatient settings.

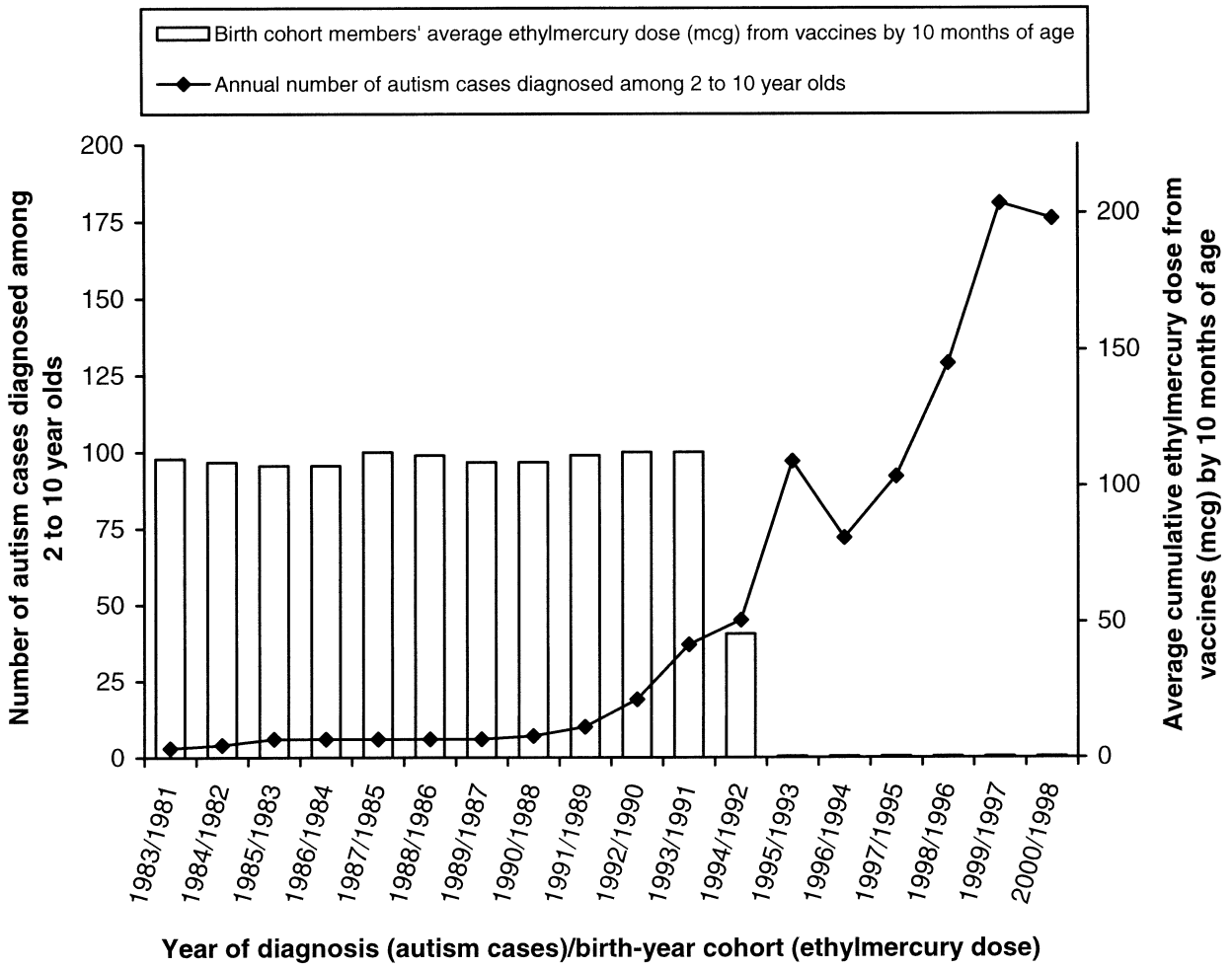

Figure 3. Graphical ecologic analysis comparing the average cumulative ethylmercury dose received from vaccines by birth-year cohort from 1981 to 1998, and the annual number of incident cases of autism in children aged 2 to 10 years diagnosed in Denmark from 1983 to 2000.

- In 1993, when Denmark switched from coding health outcomes using ICD-8 codes to ICD-10 codes, nationwide training seminars for clinicians on the new coding scheme may have stimulated reporting of autism cases (as well as other health outcomes).

Similarly, the data examined from Sweden reflected only cases diagnosed in inpatient settings, for which the data are readily available. Thus, changes over time in the rates of diagnosis of autism-like disorders in inpatient versus outpatient settings may have affected the ascertainment of cases, and differences in the distribution of the setting in which diagnoses have occurred may have affected the comparability of these results over time and among these three countries.

The apparent increase in diagnosed cases of autism may also be due, at least in part, to changes that have occurred over time in diagnostic criteria and increasing professional and public awareness of autism and related disorders. In fact, the diagnostic criteria for Asperger syndrome, Rett syndrome, and childhood disintegrative disorder were introduced for the first time in 1994 as subcategories of PDD.[4] Of note, these subcategories of PDD accounted for the largest increases in the reported California cases reflected in the data used in the ecologic analysis presented to the IOM.

Finally, at least some of the apparent discrepancy between the California findings and those in Sweden and Denmark are likely the result of the well-known shortcomings of ecologic data rather than a reflection of actual differences in the etiologic process of autism in these respective countries. Ecologic analyses, such as those presented herein, represent empirical investigations involving groups (as opposed to individual persons) as the unit of analysis. Such studies can be useful in exploring possible associations, as well as in searching for areas of possible further study, and are relatively easy to do since group-level data are often more readily available. However, the greatest difficulty in interpreting ecologic studies is that of adequately controlling confounding factors due to unavailability of data

and/or methodologic limitations.[10] Given the ecologic nature of the analyses presented herein and the lack of available detailed data, we were unable to investigate other aspects of this alleged association (e.g., the specific timing of exposure and/or the onset of autism, the existence/nature of a lag time between exposure and disease onset, or the role of genetic predisposition or other co-factors) or the potential influence of confounding factors.

Nonetheless, even though the observed rise in autism cases in both Sweden and Denmark during a time of decreasing use (and eventual elimination) of Thimerosal-containing vaccines in the early 1990s was based on ecologic evidence (and is, therefore, subject to the aforementioned limitations), these results provide compelling evidence in sharp contrast to the alleged association observed in California, during the same time period, which was based on similar ecologic data. More robust studies are currently being planned at the Centers for Disease Control and Prevention and elsewhere to examine the possible association of Thimerosal-containing vaccines and neurodevelopmental problems (including autism) that will be designed to eliminate (or at least mitigate) these limitations (W.C. Thompson, National Immunization Program, Centers for Disease Control and Prevention, personal communication, 2002).

Conclusion

After considering all the existing evidence, in September 2001 the IOM concluded that "the evidence is inadequate to accept or reject a causal relationship between exposure to Thimerosal from vaccines and . . . autism . . . . [However,]. . .the hypothesis is biologically plausible."[11] The authors of the IOM study found no consistent ecologic evidence linking the administration of Thimerosal-containing vaccines with an increasing incidence/prevalence of autism cases. Therefore, it is reasonable to conclude that the body of existing data, including the ecologic data presented herein, are not consistent with the hypothesis that increased exposure to Thimerosal-containing vaccines are responsible for the apparent increases in the rates of autism in young children being observed worldwide. Rather, it seems more plausible that other factors are affecting these changes, such as those mentioned above: an increased recognition of the disorder in the most and least developmentally delayed children (i.e., compared to children with IQs in the 50 to 70 range) and/or possibly other as-yet-unidentified environmental or genetic factors.

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References

1. Ball LK, Ball R, Pratt RD. An assessment of Thimerosal use in childhood vaccines. Pediatrics 2001;107:1147–54.
2. Grandjean P, Weihe P, White RF, et al. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol Teratol 1997;19:417–28.
3. Blaxill M. Rising incidence of autism: association with Thimerosal. In: Institute of Medicine. Thimerosal-containing vaccines and neurodevelopmental disorders. Washington DC: National Academy Press, 2001:49–50.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington DC: American Psychiatric Association, 1994.
5. California Department of Developmental Services. Changes in the population of persons with autism and pervasive developmental disorders in California's Developmental Services System: 1987 through 1998. Sacramento CA: California Health and Human Services Agency, 1999.
6. Madsen KM, Lauritsen MB, Pedersen CB, et al. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. Pediatrics 2003. In press.
7. Gillberg C, Steffenburg S, Schaumann H. Is autism more common now than ten years ago? Br J Psychiatry 1991;158:403–9.
8. Gillberg C. Infantile autism and other childhood psychoses in a Swedish urban region. Epidemiologic aspects. J Child Psychol Psychiatry 1984;25: 35–43.
9. Nordin V, Gillberg C. Autism spectrum disorders in children with physical or mental disability or both. I: clinical and epidemiological aspects. Dev Med Child Neurol 1996;38:297–313.
10. Morgenstern H. Uses of ecological analyses in epidemiologic research. Am J Public Health 1982;72:1336–44.
11. Institute of Medicine. Thimerosal-containing vaccines and neurodevelopmental disorders. Washington DC: National Academy Press, 2001.