Danish Thimerosal-Autism Study in *Pediatrics*: Misleading and Uninformative on Autism-Mercury Link

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A report by Madsen *et al.* published by the American Academy of Pediatrics in their journal *Pediatrics*[1] claims to provide evidence against a link between autism rates and the mercury in thimerosal, a preservative used in childhood vaccines. Unfortunately, the study analysis is full of flaws and inaccuracies, invalidating the conclusions regarding thimerosal. The study adds little of value to the scientific literature on autism and mercury.

Thimerosal has been causally linked to autism and other neurodevelopmental disorders.[2,3] Madsen *et al.* claim to refute such a link by analyzing Danish psychiatric records to assess rates of autism. They compare the number of newly recorded autism cases prior to 1992, when thimerosal-containing vaccines were used, with those after 1992, when such vaccines were no longer produced in Denmark. The authors claim to observe a rise in autism rates after removal of thimerosal, and thus conclude that thimerosal plays no role in the etiology of autism. An in-depth analysis of the report reveals three major problems with the analysis and methodology.

1. The report provides information on autism rates in Denmark that is distorted and misleading. These distortions allow the authors to make assertions about a rising trend in autism "incidence" in the 1990s that has no basis in fact. The report's claims are based on the following distortions:

    - Autism counts were first based on hospitalized, inpatient records and then changed in the middle of the study period to add in outpatient records. This new outpatient registry was introduced in 1995. Therefore, their purported increases after 1994 can be explained entirely by the registration of an existing autism population that did not require hospitalization. The authors minimize this discrepancy and do not adjust for it in their chart (Figure 1), yet in a prior study using the same Danish data,[4] outpatients exceeded the inpatients by a ratio of 13.5 times, and represented over 93% of total cases. This huge gap clearly invalidates their inpatient data, the corresponding time period from 1970-94, and any evidence for a rising trend of autism in Denmark. The authors claim that inpatient admissions were rising also, but the "data [were] not shown". They did not explain this omission, the only bit of credible data in their possession, since it compared equivalent populations.

    - Additional discrepancies in the autism case counts make the trend assessment unreliable. After 1992, the registry added in patients from a large Copenhagen clinic, which accounted for 20% of the case load in Denmark.[5] The patients from this clinic were excluded prior to 1992. Their inclusion in subsequent years would drive apparent increases in rates from 1992-1995 that was yet another form of registration effect.

    - The diagnostic category used by the Danish psychiatric system changed after 1993 from "psychosis proto-infantilis" of ICD-8 to "childhood autism" of ICD-10. Psychosis proto-infantilis (code 299) is a category that has never been used in published autism surveys outside of Denmark. ICD-8 contained another, clearly more suitable code, 295.8 for "infantile autism", which provided diagnostic criteria similar to current criteria used in ICD-10 and DSM-IV. The *Pediatrics* report mentions the diagnostic change in passing but fails to quantify its effect. In another paper using the same inpatient registry,[6] two of the investigators in the *Pediatrics* report note that the psychosis proto-infantilis category includes *inpatient* cases that do not fulfill the criteria for autism (which would further reduce the value of this case finding tool), while also noting the that ouptatient cases of autism in Denmark would not be captured.

    - The autism trend data are described as an "incidence study", a marker of quality in an epidemiological analysis. But the report is in no way a proper incidence study. It relies instead for its definition of the "incidence" of autism on the date when cases were entered into the new registry of outpatients. Many of these children were between 7-9 years old, and most were over 4 years old, when recorded as part of an increasing "incidence" trend. Yet the onset of autism must occur, by definition in the diagnostic criteria, before three years of age. Recording an "incidence" event at, say, seven years of age is clearly incorrect. Yet the

authors record many such events to report an increase in registrations (especially after 1994) that they misleadingly describe as increasing incidence. The most widely used approach to assessing autism trends is to use year of birth as the "incidence time." This approach was used, for example, in the California Autism Epidemiology Report by Byrd *et al.*[7] Madsen *et al.* clearly have this information as part of their data set but chose not to report it. Failure to report the birth cohort incidence means that this study's autism rates cannot be fairly compared with incidence levels observed in other countries.

- A recent study[3] from same group reported Danish autism rates for children born in the 1990s of 6 per 10,000. This falls below the rates of autism reported in the U.S. (over 30 per 10,000) by more than 80%.[8,9] While emphasizing their illusory increase, the authors never mention that their rates are actually quite low. Although our estimates confirm that these Danish rates are very low in the 1990s compared to the U.S. or the U.K.,[10] the authors fail to provide the most basic statistics that might enable a full comparison with other reports. These crucial omissions suggest a clear bias toward elevating the perception of Danish autism rates later in their study period.

- The report also estimates inpatient rates for the pre-1993 "psychosis proto-infantilis" at well below 1 per 10,000. If these were true rates for autism, these would be among the lowest rates measured anywhere in the world at any time period. This low rate would also contradict the single published survey of autism rates from Denmark, which indicated an autism rate of over 4 per 10,000 as far back as the 1950s.[11] Normally, authors cite relevant studies in their introductory or discussion sections, but Madsen *et al.* fail to mention this study, as they fail to comment on the unusually low autism rates for the earlier years of their study period.

There are only three proper conclusions that one can draw about the autism rates in Denmark based on available data. 1) The rates in the 1990s are low compared to the U.S. and U.K. and possibly stable with respect to trend. 2) The 1990s Danish autism rates are similar to rates in the 1950s. 3) There are still no published, usable data about Danish autism rates in persons born between 1960-90.

2. The mercury exposure levels described in Madsen *et al.* are likely to be overstated. The authors describe a level of mercury exposure to Danish infants of 125 micrograms (mcg) by 10 months of age between 1970-92, a period in which they claim (without justification) that autism rates were low. All exposures came from the monovalent pertussis vaccine manufactured by Statens Serum Institut, which, according to the paper, provided the vaccine coverage rates reported therein.

    - These mercury levels of 125 mcg are substantially lower and later than those scheduled in the U.S. in the 1990s, 187.5 mcg by six months.[12]

    - The exposure level of 125 mcg requires full compliance by Danish parents. The authors assert coverage rates of over 90% for this schedule, yet a recent report using the same data suggests that completion rates were well below 90%.[5] The authors also fail to provide any information regarding the timing of the actual exposures. Given widespread Scandinavian concern over pertussis vaccine (Sweden banned pertussis vaccines in 1979) it would be surprising if coverage rates were as high as 90% and if on-time schedule compliance was common throughout the 1970-1992 period. Documentation of compliance rates by Statens Serum Institut is needed.

    - These ethyl mercury exposures --at 50 mcg per dose for the 9 week and 10 month injections-- are the highest amounts ever described in any single vaccine dose. The authors fail to acknowledge this unusual mercury level and to provide an explanation for why this formulation was so much higher than formulations used in all other countries and by all other manufacturers, which were typically 25 mcg per dose.

3. The context for the early mercury exposures was completely different in Denmark when compared to any other country, and particularly compared to the U.S. and U.K., where autism rates are being watched most closely. The Danish report describes a different world of vaccine exposures and ignores exposures that are present today that were not present in Denmark in the 1970s. Autism onset has been reliably associated with exposure to viruses.[13] In the cases where

increasing thimerosal exposures have accompanied autism increases, numerous additional confounders were present that were not present in Denmark.

- Between 1970-92, the only childhood vaccine given in Denmark until 5 months of age was the monovalent pertussis vaccine.

- In the United States in the 1990s, children were exposed to multiple doses of diphtheria, pertussis, tetanus, polio, hepatitis B and haemophilus influenza B (Hib) vaccines before five months of age.

- In the United Kingdom, injections before age 5 months included multiple doses of meningitis C, polio, diphtheria, tetanus, Hib, and pertussis vaccines. Increasing autism rates there were accompanied by earlier thimerosal exposures due to schedule changes, new exposures to MMR and Hib vaccines, and stringent on-time compliance procedures.

- Denmark did not administer thimerosal-containing Rho D immunoglobulin during pregnancy.

In summary, the report by Madsen *et al.* appears to be an attempt to present selectively chosen data that provide support for policy choices in which the authors and their collaborators are involved. Once again, rather than seriously evaluating the autism-mercury hypothesis and carrying out the research agenda specified by the Institute of Medicine[14] in 2001, public health authorities (now teamed with a Danish vaccine manufacturer) have chosen to issue another piece of propaganda masquerading as science, with the only possible outcome being that legitimate research and discussion might be suppressed. We sincerely hope that well-informed scientists and public officials will note the flaws in this report and be motivated to conduct the recommended investigations into the autism-mercury connection, which still await completion.

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