Analysis of the Danish Autism Registry Data Base in Response to the Hviid *et al* Paper on Thimerosal in *JAMA* (October, 2003)

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KEY FINDINGS

A large percentage of diagnosed autism cases are lost from the Danish registry each year. In the ten years preceding 2000, 815 cases were lost, more than the 710 remaining in the registry in 2000. The vast majority of those lost cases would represent older children in the 2000 registry. Since the relative risk of the Hviid study is based on finding fewer older thimerosal-exposed children than younger unexposed children, the validity of their conclusion exonerating thimerosal in autism is questionable. More likely, the finding is a result of missing records rather than true lower incidence rates among the exposed group.

Another approach to analyzing the trend data that avoids the above methodological bias by comparing same-age groups, has found a 2.3 times higher number of autism cases among 5-9 year olds exposed to thimerosal relative to 5-9 years old given thimerosal-free vaccines. Using this methodology, the incidence among the unexposed group is approximately 1 in 1,500, which is much lower than the US and UK rates. The incidence of autism in the thimerosal group is estimated to be 1 in 500, similar to US and UK rates, and 3 times higher than the unexposed group.

The Denmark registry has a number of inconsistencies and has experienced large changes to its record keeping practices over the years, making trend analysis difficult. Interpretation of the data is subject to bias which may be hard to detect. Analysis of this data set should be conducted by independent researchers unconnected with the promotion of vaccine programs.

METHODS

Safe Minds obtained a copy of a data set of the Danish Registry for autism cases, referred to here as the Registry Data Set.[1] The data set shows the number of cases in the registry for the years 1980 to 2002. For each registry year, the number of cases are broken down by age bands in 5 year increments, i.e., 0-4 year olds, 5-9 year olds, 10-14 year olds, etc. The total Danish population for each age band for each registry year, as well as the number of new autism cases added per year, are also provided.

Safe Minds analyzed this data set in light of the results and conclusions stated in the Hviid *et al* paper on thimerosal and autism appearing in the October 2003 issue of *JAMA*[2]. The Hviid study uses the 2000 registry to examine the rate of autism and exposure to thimerosal in vaccines among those born 1990-1996. Safe Minds compared their findings with the actual Registry Data Set, as well as with other published studies conducted recently by Danish investigators using the same registry.[3,4,5,6]

RESULTS

Loss of Records from the Registry

Review of the total cases by registry year (Registry Data Set, tab "Total Both Sex") shows that the registry does not retain all the cases which are entered into it. As illustrated in Table 1 below, for the registry year 1995, there are 97 cases in the 5-9 year old cohort. This same cohort, as it grows older, becomes the 10-14 year old cohort five years later in the 2000 registry. Yet now the number of cases for this group has fallen to 75 children, a decline of 22 cases or nearly a quarter (23%) of the original 1995 cases.

Table 1. Comparison of Case Counts for a Single Age Cohort in Two Registry Years, 1995 & 2000

Age Group	1995	2000
0-4 year olds	73	156
5-9 year olds	97	257
10-14 year olds	36	75

Since autism is considered a life long disorder, and very few cases in the registry are in older age groups who are likely to die, any case that is entered into the registry should remain there. The exceptions might be rare instances where a misdiagnosis occurs, but this situation is not common to autism. Thus, removal of these cases is probably due to administrative error. It means that these autism cases still exist, but they are not being recorded.

In order to determine the extent of the artificial removal of diagnosed cases from the registry, we calculated the number of cases removed for each year for the ten year period leading up to 2000, or from 1991 to 2000. For each of these years, we took the number of new cases added to the registry for that year, as shown on the Registry Data Set "New Both Sex" tab, and added it to the number of previous year's cases which already existed in the registry. We compared this total of new plus existing cases to the number of cases shown in the registry for that year. We did this calculation for the total number of cases in the registry for a given year, that is, all age bands combined. The results of this analysis are shown in Table 2 below.

It is easily seen that a large number of cases are regularly dropped from the registry. For several years the proportion lost amounts to one fourth of the cases (e.g., 1993). For the registry year 2000, on which the Hviid *et al* analysis is based, 23% of the cases (211 of 921) were dropped from the data set. On a cumulative basis, between 1991 and 2000, 815 cases were eliminated, more than the total number of cases remaining in the data base in 2000.

Table 2. Number of Diagnosed Cases Dropped from the Registry Each Year

Year	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
# Total Cases Reported	100	108	137	168	250	385	451	507	562	673	710
# New Cases	N/A	46	73	91	136	156	130	140	168	237	248
# New + Previous Year's Cases		146	181	228	304	406	515	591	675	799	921
# Dropped Cases*		38	44	60	54	21	64	84	113	126	211

**Represents the difference in reported cases vs real (new + previous) cases.*

As removed cases accumulate each year, for any given registry year, proportionately more of the removed cases would have fallen in the older age groups, since with each successive year, the removed case gets older. As a result, the main impact of case removal is a bias in the registry toward more accurately counting younger age cohorts while undercounting older age groups. The relative risk of the Hviid study is predicated on finding fewer cases in the older thimerosal cohort and more in the younger non-thimerosal groups. Given the problem of case elimination in the registry, their analysis is flawed and any conclusions drawn from it are greatly weakened if not invalidated.

Reanalysis using alternative methodology

An alternative method of analyzing case rate trends avoids the bias demonstrated previously of older patients being removed from the data set. This method compares cohorts of the same age but in different registry years. One registry year would be comprised only of those children who received thimerosal-containing vaccines. The other registry year would be comprised of those who only received thimerosal-free formulations. Since the average age of diagnosis is 4.7 years,[2] the most stable age group to analyze is the 5-9 year olds.

The only registry year available which is exclusively comprised of children 5-9 years old who were entirely exposed to thimerosal-free vaccines is the 2002 registry. For the thimerosal-exposed registry year, we choose the 1992 registry, because several events in Denmark affecting the population of the registry eliminated the choice of other possible registry years:

(1) Prior to 1992, records for a large clinic in Copenhagen were not included in the registry. This clinic accounted for 20% of autism cases.[5] It would therefore be preferable to choose a registry year from 1992 on.
(2) In 1993, the Danish health system changed from using ICD-8 codes to ICD-10 codes for diagnostic purposes.[5] A number of seminars were held regarding this switch, which may have inflated the diagnosis and reporting of autism cases.[5] In fact, an increase in cases can be seen in the 1993 and 1994 registry years for many age groups.[1] Therefore, it would be preferable to avoid these two years for analysis.
(3) In 1995, autism out patient records were added to the registry, which previously only contained in patient records. In a previous paper,[4] Danish researchers stated that 6.9% of the cases in the 1999 registry were in-patients and 93.1% were out patients.

The addition of out patients greatly expanded the number of records in the registry. It would be preferable to avoid the early years of changeover to the expanded data base.

In choosing 1992 as our analytic year, we would need to adjust for the absence of outpatient records in the data set. There are 38 cases of autism in the 5-9 year olds in the 1992 registry. We can estimate that the 38 cases in 1992 only represent 6.9% of the total diagnosed cases actually existing in Denmark for this age group. We can estimate the total cases by dividing 38 by 0.069, which equals 551 cases.

The 2002 registry contains 239 5-9 year olds. This is the group that received no thimerosal. The 1992 group represents 551 cases, and it received thimerosal. The 1992 group has 2.3 times the number of cases as the 2002 group, suggesting that the removal of mercury was followed by a steep decline in autism incidence.

Incidence

If we look at the 2002 registry for the 5-9 year olds, the 239 cases represent an incidence of 68 per 100,000, which equates to 1 in 1,470, or approximately 1 in 1,500, as shown in Table 3. This is 3-6 times lower than the numbers being reported in the US and UK for core autism (1 in 250 and 1 in 500 respectively) [7,8]

If we look at the estimated 551 cases for 1992 among 5-9 year olds, the rate is 204 per 100,000, which equates to an incidence of 1 in 500. This is much closer to the rates observed in the US and UK. We would expect to see a slightly lower rate in Denmark relative to the US because the Danish thimerosal dose amount and timing of administration was slightly less and later than in the US, while these practices were comparable to those in the UK.

Table 3. Number of Autism Cases and Autism Incidence for 5-9 Year Olds, 1992 vs. 2002 Registry Years

	1992 Registry 5-9 Year Olds	2002 Registry 5-9 Year Olds
# of Autism Cases*	551	239
Population of Age Group – All of Denmark*	270,164	341,804
Incidence	1 in 500	1 in 1,470

**1992 numbers are adjusted for missing outpatient records. 2002 numbers are from Registry Data Set. Population counts are from Registry Data Set.*

Volatility of the Denmark Registry Data

It has been pointed out that the Denmark registry experienced a number of key changes in the 1990s which affected the number of cases in the data set. These changes included the addition of outpatient records, conversion from ICD-8 to ICD-10 diagnoses with accompanying educational seminars, loss of diagnosed cases from the records, and the addition of records from the Copenhagen clinic.

Another example worth noting which illustrates how variable the data set can be with just minor shifts in the study population observed, can be seen through a comparison of the

Madsen *et al* (2002) MMR study[4] and the Hviid *et al* Thimerosal study[2] cohorts. Madsen *et al* used the 1999 registry and within it, examined children born in 1991-1998, a total of 8 years. The autism case count was 316, or 40 cases per year on average. Hviid *et al* used the 2000 registry and within it, examined children born in 1990-1996, a total of 7 years. The autism case count was 440, or 63 cases per year.

The increase from the 40 cases of the Madsen *et al* 1999 registry to the 63 cases of the Hviid *et al* 2000 registry is 59%, which is very large for just a single year shift. The lower count for the 1999 registry group is even more surprising given that this study sample extends into the more recent birth years (1997, 1998), when there was no thimerosal and supposedly the autism rates where going up, at least according to the *JAMA* authors.

One reason for this discrepancy, of course, is that for 3 years of the Madsen *et al* MMR study cohort (birth years 1998, 1997, 1996) the children were too young to be fully diagnosed. So the question arises as to why this age group was chosen to analyze the impact of the MMR vaccine on autism rates. The point is that depending on what birth cohorts from the registry an investigator chooses, and what registry year he or she chooses to study, very different results can be produced and significant bias can be introduced.

Conflict of interest

The authors of the *JAMA* paper work for Statens Serum Institut, which is the manufacturer and promoter of vaccines in Denmark. *JAMA* did not disclose to its readers that the authors have a financial conflict of interest in the outcome of the study, contrary to standard medical and scientific journal practice.

A more honest and productive approach to examining the Denmark registry data set would entail having independent researchers unconnected to vaccines investigate the data.

CONCLUSIONS

The Hviid *et al* finding of lower autism rates with thimerosal exposure is likely due to errors in record keeping in the registry data set. Another approach to analyzing the same data, which adjusts for lack of outpatient records, has found a 3-fold increase in autism incidence with thimerosal exposure. The Denmark autism registry has large variability in the nature of its records and utilization of the data set for epidemiological analysis is prone to bias. Use of this data to investigate the role of vaccines in autism should be conducted by researchers unconnected to vaccine manufacture or promotion.

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