

# Thimerosal and the Occurrence of Autism: Negative Ecological Evidence From Danish Population-Based Data

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**ABSTRACT.** *Objective.* It has been suggested that thimerosal, a mercury-containing preservative in vaccines, is a risk factor for the development of autism. We examined whether discontinuing the use of thimerosal-containing vaccines in Denmark led to a decrease in the incidence of autism.

*Design.* Analysis of data from the Danish Psychiatric Central Research Register recording all psychiatric admissions since 1971, and all outpatient contacts in psychiatric departments in Denmark since 1995.

*Patients.* All children between 2 and 10 years old who were diagnosed with autism during the period from 1971–2000.

*Outcome Measures.* Annual and age-specific incidence for first day of first recorded admission with a diagnosis of autism in children between 2 and 10 years old.

*Results.* A total of 956 children with a male-to-female ratio of 3.5:1 had been diagnosed with autism during the period from 1971–2000. There was no trend toward an increase in the incidence of autism during that period when thimerosal was used in Denmark, up through 1990. From 1991 until 2000 the incidence increased and continued to rise after the removal of thimerosal from vaccines, including increases among children born after the discontinuation of thimerosal.

*Conclusions.* The discontinuation of thimerosal-containing vaccines in Denmark in 1992 was followed by an increase in the incidence of autism. Our ecological data do not support a correlation between thimerosal-containing vaccines and the incidence of autism. *Pediatrics* 2003; 112:604–606; *autism, vaccine, thimerosal, mercury, population, epidemiology.*

ABBREVIATIONS. ICD-8, *International Classification of Diseases, Eighth Revision*; ICD-10, *International Classification of Diseases, 10th Revision*.

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There has been concern that there may be an association between thimerosal, a vaccine preservative that contains ethyl mercury, and neurodevelopmental outcomes, including autism.<sup>1,2</sup> Findings in the field of methyl mercury have been used to suggest causality. Prenatal exposure to low doses of methyl mercury has been associated with subtle neurodevelopmental abnormalities in some studies,<sup>3,4</sup> and symptoms of autism and methyl mercury intoxication have been claimed to be similar.<sup>1</sup> More research has been requested,<sup>5</sup> and a recent study of the concentrations of mercury after exposure to thimerosal-containing vaccines concluded that thimerosal poses very little risk to full-term infants.<sup>6</sup> In Denmark, thimerosal was used in childhood vaccines from the early 1950s until 1992. The objective of our study was to assess the incidence rates of autism among children between 2 and 10 years old before and after removal of thimerosal from vaccines to see if the discontinuation led to a decrease in the incidence of autism.

## PARTICIPANTS AND METHODS

For this study, the period of use of thimerosal vaccines was limited to 1961 until its discontinuation in March 1992 because information about the diagnosis of autism has only been obtainable from a nationwide computerized registration system, the Danish Psychiatric Central Research Register,<sup>7</sup> since 1969 and only children born in 1961 or later were at risk of developing autism before 10 years of age. Thimerosal was used during 1961–1970 in the diphtheria-tetanus-pertussis vaccines given in 4 doses when the child was 5, 6, 7, and 15 months old, and during 1970–1992 in the whole-cell pertussis vaccines given in 3 doses when the child was 5 weeks, 9 weeks, and 10 months old. The concentrations used in the vaccines from 1961–1970 and from 1970–1992 were 0.01% = 0.1 mg thimerosal, which equals 50  $\mu$ g ethyl mercury per mL vaccine. The amount of vaccine given was 1 mL, except for the first dose of monocomponent pertussis vaccine where it was only 0.5 mL from 1970–1992. This means that children who followed the full vaccination program during the period 1961–1970 had received a total of 400  $\mu$ g of thimerosal or 200  $\mu$ g of ethyl mercury by the age of 15 months and during the period 1970–1992 they had received a total of 250  $\mu$ g of thimerosal or 125  $\mu$ g of ethyl mercury at 10 months of age. In March 1992 the last batch of thimerosal-containing vaccine was released and distributed from Statens Serum Institut in Denmark. All vaccinations were given free of charge and acceptance of vaccinations in Denmark has always been very high; from 1979 onward data on vaccination coverage was available and coverage rates of >90% were found (information was obtained from the State Serum Institute). Whether the toxicity of methyl mercury and ethyl mercury is the same remains controversial<sup>8,9</sup> but the recommended safe intake level of methyl mercury is estimated to be 0.1  $\mu$ g/kg body weight/day by the US Environmental Protection Agency.<sup>10</sup> However, other federal regulatory agencies have recommended slightly higher levels.<sup>9</sup>

Psychiatric inpatient treatment in Denmark has been reported to the Danish Psychiatric Central Research Register since 1969, and since 1995 outpatient activities were registered as well, providing the opportunity to examine long-term trends of the occurrence of autism in a total national population. In Denmark, inpatients refer both to children who stay at the hospital overnight and to children who come to the hospital on a daily basis for evaluation and treatment. The proportion of outpatient to inpatient activities was about 4 to 6 times as many outpatients as inpatients with variations across time and age bands. We obtained information on all children who from the second birthday up to, but not including the 10th birthday were diagnosed with autism in the period from January 1, 1971 to December 31, 2000 in the Danish Psychiatric Central Research Register during which period the register is assumed to be complete. The diagnosis of autism in children <2 years of age was considered uncertain. All individuals in Denmark are assigned a unique personal identification number<sup>11</sup> which is used in all national registers. Admissions to psychiatric hospitals in Denmark are coded using this CPR-number, which eliminates the risk of double-counting of cases. The date of onset was defined as the first day of the first admission leading to a diagnosis of psychosis proto-infantis (*International Classification of Diseases, Eighth Revision* [ICD-8]: 299.00) or psychosis infantilis posterior (ICD-8: 299.01) or from 1994 onward, infantile autism (*International Classification of Diseases, 10th Revision* [ICD-10]: F84.0) or atypical autism (ICD-10: F84.1).<sup>12,13</sup>

## Statistics

Incidence rates were calculated for each year 1971–2000 using the age and gender specific number of persons in Denmark as a denominator. For each year and age band, we calculated the incidence as the number of people who at that age band and year was diagnosed with autism for the first time divided by the total number of people alive and living in Denmark at that age band and year.

## RESULTS

A total of 956 children with a male to female ratio of 3.5:1 had been diagnosed with autism during the period 1971–2000. Figure 1 shows the incidence rates according to calendar year and age band. The incidence was stable until 1990 and thereafter it increased in all age groups until 1999. Generally, rates were lower in 2000 than in 1999. Further subdivision by gender had no impact on these results (data not shown). In additional analyses we examined data using inpatients only. This was done to elucidate the contribution of the outpatient registration to the change in incidence. The same trend with an increase

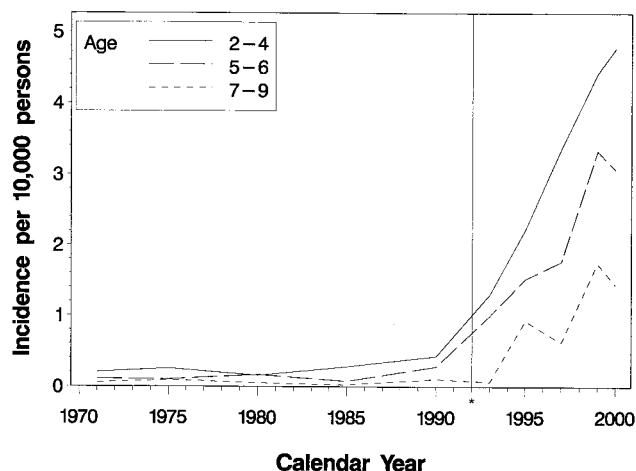


Fig 1. Incidence of autism by age and calendar year. The asterisk (\*) indicates removal of thimerosal-containing vaccines in 1992.

in the incidence rates from 1990 until the end of the study period was seen (data not shown).

There was no trend toward an increase in the incidence of autism during the period when thimerosal was used up to 1990. The incidence of autism began to increase in 1991, but continued to rise after the discontinuation of thimerosal (Fig 1), including increases among children born after 1992 (ie, the peak autism incidence in 1999 among children aged 2 to 4 and 5 to 6 years of age corresponds to children born in 1993–1997 after the introduction of thimerosal-free vaccines).

## DISCUSSION

This study investigated if the discontinuation of thimerosal-containing vaccines paralleled a decrease in the occurrence of autism. The incidence of autism remained fairly constant during the period of use of thimerosal in Denmark, and the rise in incidence beginning in 1991 continued even in the group of children born after the discontinuation of thimerosal. The amount of thimerosal used in vaccines changed during the study period with less amount of thimerosal administered in the period 1970–1992. Moreover, the thimerosal-containing vaccine was gradually phased out meaning that the incidence rates should decline gradually if thimerosal has any impact on the development of autism. However, an increase (rather than a decrease) in the incidence rates of autism was observed.

Only very few incidence studies of autism have been made, and we found similar incidence rates and the same trend of increasing rates of autism in our study compared with studies conducted in other countries.<sup>14,15</sup> The increase in the incidence of autism from 1990 on may be attributable to more attention being drawn to the syndrome of autism and to a change in the diagnostic criteria from the ICD-8 to the ICD-10 in 1994. Also, outpatient activities were included in the Danish Psychiatric Central Research Register in 1995 and because many patients with autism in former years have been treated as outpatients this may exaggerate the incidence rates, simply because a number of patients attending the child psychiatric treatment system before 1995 were recorded for the first time, and thereby counted as new cases in the incidence rates.

## CONCLUSIONS

The discontinuation of thimerosal-containing vaccines in Denmark in 1992 was followed by an increase in the incidence of autism. Our ecological data do not support correlation between thimerosal-containing vaccines and the incidence of autism. Our data cannot, of course, exclude the possibility that thimerosal at doses larger than used in Denmark may lead to neurodevelopmental damage.

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## FAT BABIES AND HEALTH

“In a recent issue an English contemporary calls attention to the mischief that is being done by the present standard that is accepted as regards healthy babies. As this paper well says, at baby shows the prize is practically always given to the fattest baby. There is a tradition current among mothers, as far as the memory of man runneth, that fat babies are just the pink of perfection. The surest index of this is that all manufacturers of artificial infant food advertise their wondrous virtues by photographs of thoroughly rounded, and at times positively obese dumplings of babies. Mothers are very proud of their young hopefuls if they are a mass of curves and dimples with deep folds at all the joints and cushions of fat that conceal their anatomy so effectively as to make them formless little masses of humanity.”

*JAMA 100 years ago. JAMA*. 2003;289:1866

*Editor's Note:* Not much change in 100 years! Will we ever win this one?

Noted by JFL, MD