Association Between Thimerosal-Containing Vaccine and Autism in Denmark


- **Funding.**
  Danish National Research Foundation
  Danish Medical Research Council

- **Employment.**
  Department of Epidemiology Research, State Serum Institute,
  - State owned
  - Control and prevention of infectious diseases
  - Research, surveillance, diagnostics, and vaccine manufacturing (law-regulated obligation, non-profit)
Introduction

Objective

An association between thimerosal-containing vaccines and autism?

More cases of autism among children vaccinated with thimerosal-containing vaccine?

Cohort Construction

Danish Civil Registration System
All children born in Denmark
Jan 1, 1990 – Dec 31, 1996

EXPOSURE

Danish Civil Registration System
Sex
Place of birth
Mothers age at birth
Mothers country of birth

Birth weight
Gestational age
Apgar 5 score

Danish Psychiatric Central Registry
Autistic Spectrum Disorders

Tuberous sclerosis
Angelman syndrome
Fragile X
Congenital rubella

Cohort
N = 467,450

OUTCOME

Danish Medical Birth Registry

Childhood vaccinations Jan 1990 –

Vaccination Database

National Hospital Discharge Registry
Vaccination database

Danish childhood vaccination program

- Voluntary
- Free of charge to the vaccinees
- Administered by general practitioners
- GP’s are reimbursed when reporting vaccinations to the National Board of Health

National Board of Health

Vaccination reports
Jan 1, 1990 -

Construction

Individual-level history of vaccinations

Vaccination database,
Jan 1, 1990 -
Dept. Epidemiology Research

Pnr, Type of vaccine, Dose, Date of vaccination
Thimerosal in the Danish schedule

Jan 1, 1970 – May 31, 1992: Whole-cell pertussis (1 dose ~ 50 µg thimerosal ~ 25 µg ethylmercury), ½ dose at 5 weeks, 1 dose at 9 weeks, and 1 dose at 10 months.

Total amount of ethylmercury received through vaccination in the Danish schedule and in the US schedule.
Determining Thimerosal exposure

**Cohort**
All children born in Denmark
Jan 1, 1990 – Dec 31, 1996

N = 467,450

**Unvaccinated (no wcP)**
N = 20,755 (4.4%)

**Thimerosal-containing wcP**
(At least 1 dose)
N = 138,953 (29.7%)

**Thimerosal-free wcP**
At least 1 dose and no thimerosal-containing doses)
N = 307,742 (65.9%)

Study period
January 1, 1990 – December 31, 2000
Autism diagnoses

Danish Psychiatric Central Register

Nationwide passive administrative registry recording contacts to psychiatric departments.

Changes in the recording throughout the study period

- 1990 – 1993: Outpatients, ICD-8
- 1994: Outpatients, ICD-10

All cases ascertained using ICD-10

Cases identified during 1990 – 1993 under ICD-8 were included if they were registered with the appropriate ICD-10 code 1994 -

<table>
<thead>
<tr>
<th></th>
<th>ICD-8</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism</td>
<td>(299.00)</td>
<td>F84.0</td>
</tr>
<tr>
<td>Other Autistic-Spectrum Disorders</td>
<td>(299.01 – 299.05, 299.09)</td>
<td>F84.1-F84.9</td>
</tr>
</tbody>
</table>
Methods

Dose

Person-years at risk

Cases

Autism diagnosis

Poisson regression

Autism

<table>
<thead>
<tr>
<th>Rate ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Thi-</td>
<td>1</td>
</tr>
<tr>
<td>Thi+</td>
<td></td>
</tr>
<tr>
<td>1.dose</td>
<td></td>
</tr>
<tr>
<td>2.dose</td>
<td></td>
</tr>
<tr>
<td>3.dose</td>
<td></td>
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Vaccinated

1. dose wcP (Thi+)

2. dose wcP (Thi+)

3. dose wcP (Thi-)
## Results – Thimerosal and Autism

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Person-years at risk</th>
<th>Number of cases</th>
<th>Rate ratio (95% CI)</th>
<th>RR</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thimerosal-free</td>
<td>1,660,159</td>
<td>303</td>
<td>1 Referent</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Thimerosal-containing</td>
<td>1,220,006</td>
<td>104</td>
<td>0.85 (0.60-1.20)</td>
<td>0.85</td>
<td>0.85</td>
</tr>
</tbody>
</table>

### Doses of thimerosal-containing vaccine

| No doses                         | 1,660,159            | 303            | 1 Referent          | 1    | 1    |
| One dose (25 µg eHg)             | 169.920              | 18             | 0.99 (0.59-1.68)    | 1.01 | 1.01 |
| Two doses (75 µg eHg)            | 447.973              | 33             | 0.71 (0.46-1.09)    | 0.70 | 0.70 |
| Three doses (125 µg eHg)         | 602.113              | 53             | 0.96 (0.63-1.46)    | 0.96 | 0.96 |

Trend (increase in RR per 25 µg eHg) | 0.98 (0.90-1.06) | 0.98 |

Adjusted for confounders

Fully adjusted
Results – Robustness

Misclassification of thimerosal exposure
Excluding children vaccinated from June 1, 1992, through December 31, 1992.

"Skewed" cohort and homogeneity
### Results – Association in subgroups

<table>
<thead>
<tr>
<th>Autism</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR 95% CI</td>
<td>RR 95% CI</td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
</tr>
<tr>
<td>&lt; 2500 g</td>
<td>1.71 (1.06-2.76)</td>
</tr>
<tr>
<td>2500-2999 g</td>
<td>1.14 (0.82-1.59)</td>
</tr>
<tr>
<td>3000-3499 g</td>
<td>1 Referent</td>
</tr>
<tr>
<td>3500-3999 g</td>
<td>1.02 (0.79-1.32)</td>
</tr>
<tr>
<td>&gt;= 4000 g</td>
<td>1.28 (0.96-1.72)</td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
</tr>
<tr>
<td>&lt; 37 weeks</td>
<td>0.93 (0.59-1.47)</td>
</tr>
<tr>
<td>37 - 41 weeks</td>
<td>1 Referent</td>
</tr>
<tr>
<td>&gt;=42 weeks</td>
<td>0.82 (0.56-1.21)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Girl</td>
<td>1 Referent</td>
</tr>
<tr>
<td>Boy</td>
<td>4.05 (3.19-5.15)</td>
</tr>
</tbody>
</table>

**Thimerosal effect in subgroups**

RR, 0.85 (0.60-1.20)

(Not published)
Study strengths and weaknesses

**Strengths**

- Large (Autism, 440 cases, Other Autistic-Spectrum Disorder, 787 cases)
- Nationwide, population-based
- All data used were collected independently and prospectively
- A comparison of children vaccinated with thimerosal-containing vaccine with children vaccinated with a thimerosal-free formulation of the same vaccine

**Weaknesses**

- Date of diagnosis instead of date of "onset of symptoms"
- No clinical information on the cases
Conclusion

Our results are not compatible with the hypothesis of a causal association between thimerosal-containing vaccine and autism (or other autistic-spectrum disorder).
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