Association Between Thimerosal-Containing Vaccine and Autism in Denmark

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- **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

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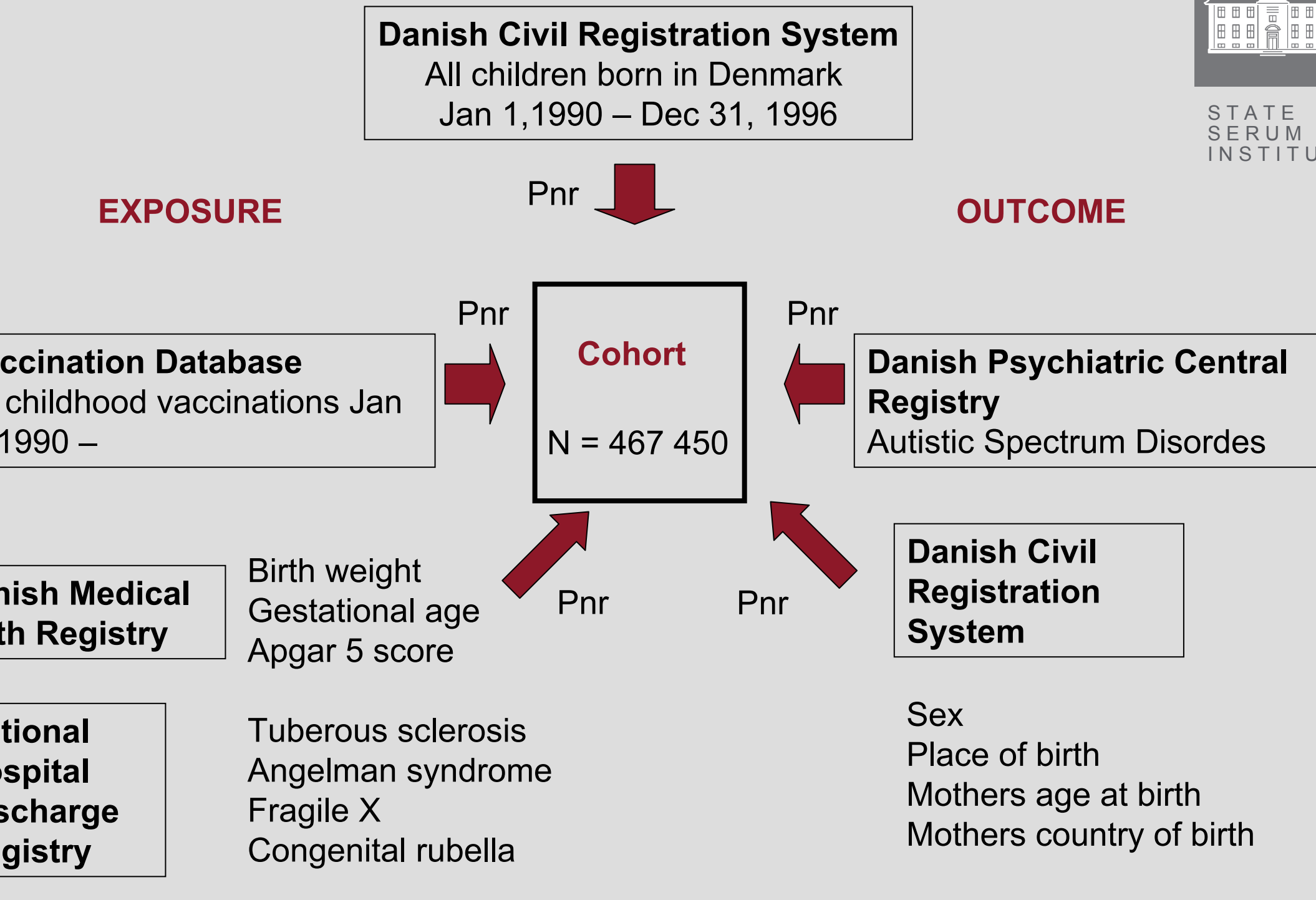
Objective

An association between thimerosal-containing vaccines and autism ?

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

A **population-based cohort study** of all children **born in Denmark from January 1, 1990 – December 31, 1996** with individual-level longitudinal information on vaccinations and autism diagnosis and **prospective follow-up from January 1, 1990 – December 31, 2000**.

Cohort Construction



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

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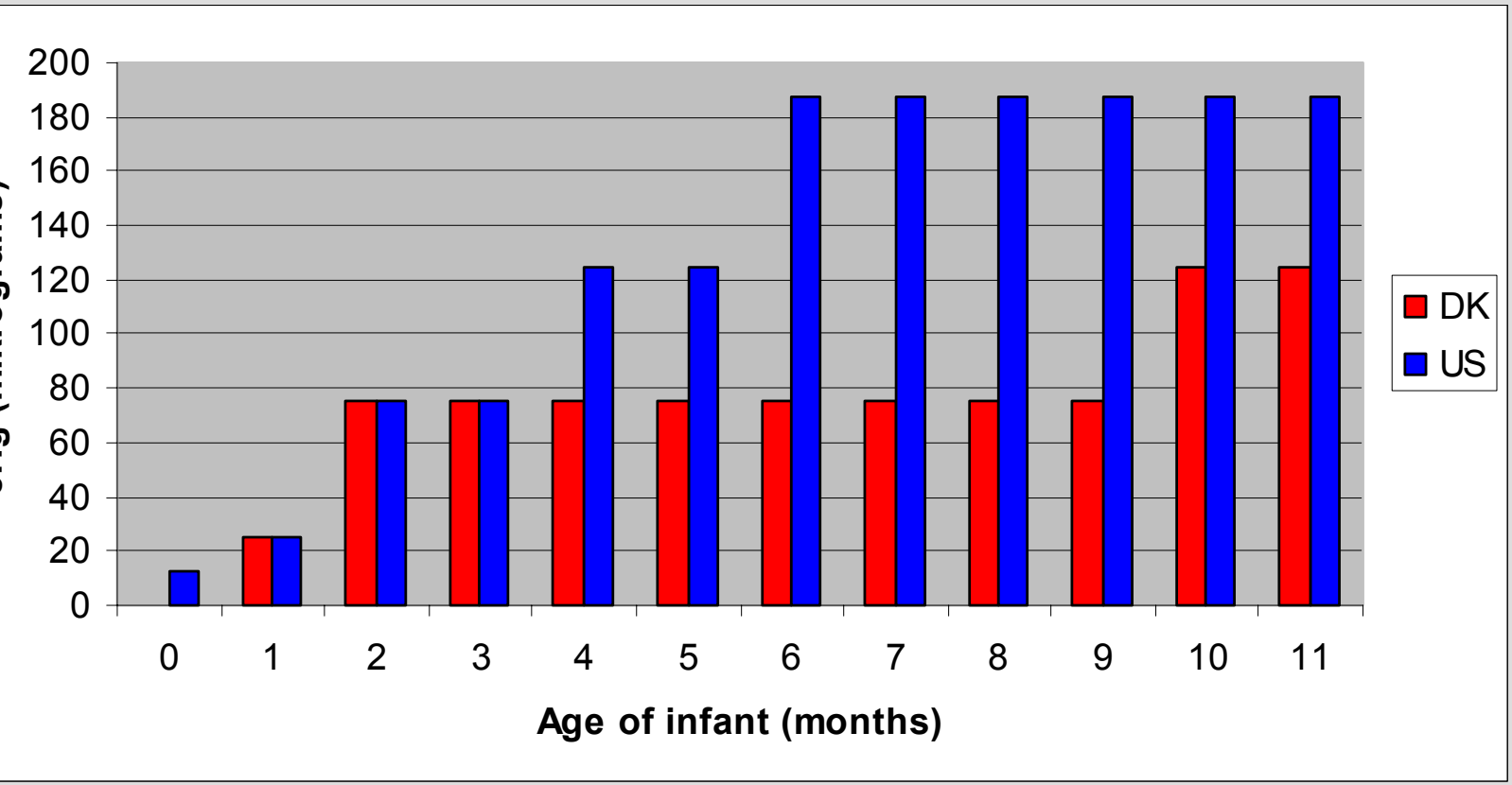
Thimerosal in the Danish schedule

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



Total amount of ethylmercury received through vaccination in the Danish schedule and in the US schedule

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Determining Thimerosal exposure

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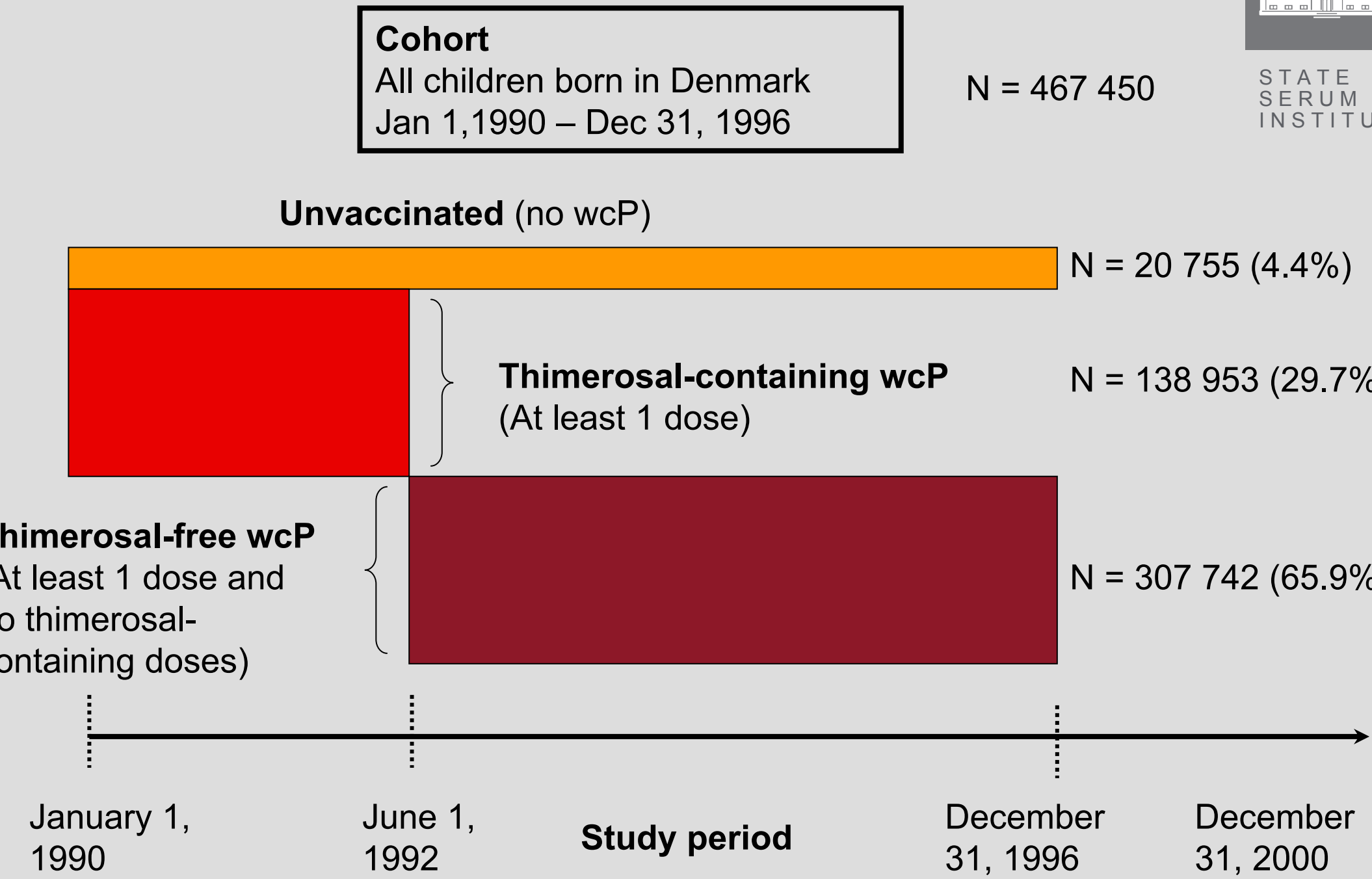

Autism diagnoses

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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
- 1995 – 2001 : Inpatients and outpatients, ICD-10

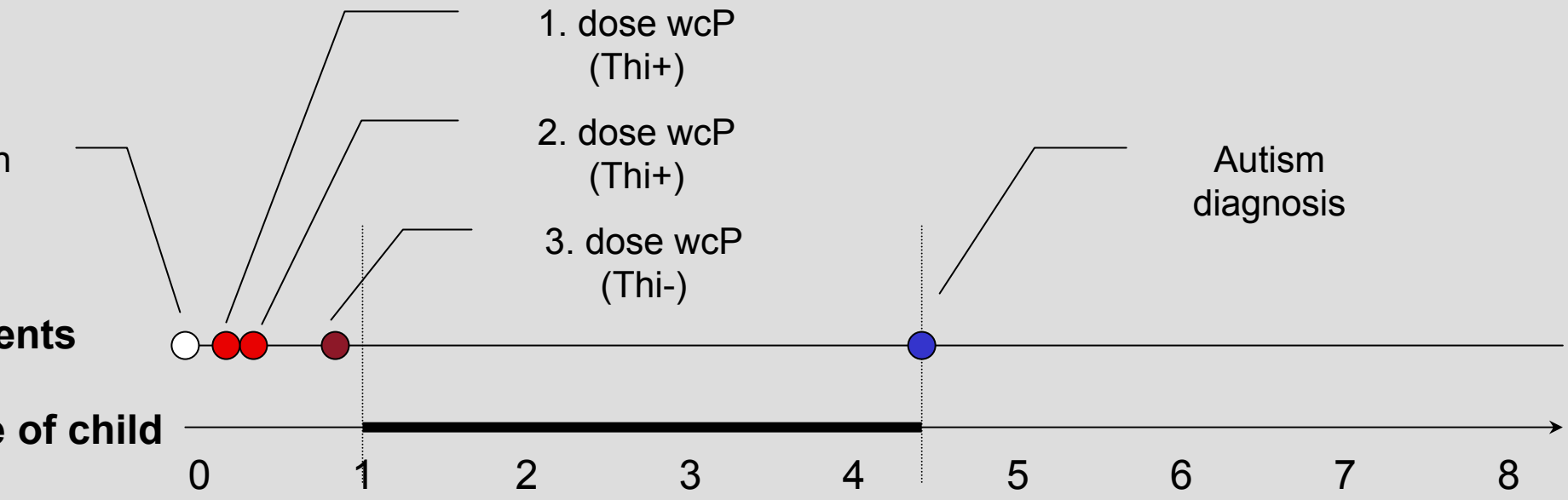
All cases ascertained using ICD-10

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

Diagnostic codes used

	ICD-8	ICD-10
Autism	(299.00)	F84.0
Other Autistic-Spectrum Disorders	(299.01 – 299.05, 299.09)	F84.1-F84.9

Methods



ism	Cases	Person-years at risk
accinated		
-		
dose		
dose	1	3½
dose		

Poisson regression

Autism	Rate ratio	95% CI
Unvaccinated		
Thi-	1	Referent
Thi+		
1.dose		
2.dose		
3.dose		

Results – Thimerosal and Autism

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	Person-years at risk	Number of cases	Rate ratio (95% CI) RR		RR
ccination					
Thimerosal-free	1,660,159	303	**1**	Referent	**1**
Thimerosal-containing	1,220,006	104	**0.85**	(0.60-1.20)	**0.85**
oses of thimerosal-ntaining vaccine					
No doses	1,660,159	303	**1**	Referent	**1**
One dose (25 µg eHg)	169.920	18	**0.99**	(0.59-1.68)	**1.01**
Two doses (75 µg eHg)	447.973	33	**0.71**	(0.46-1.09)	**0.70**
Three doses (125 µg eHg)	602.113	53	**0.96**	(0.63-1.46)	**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

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Misclassification of thimerosal exposure

Excluding children vaccinated from June 1, 1992, through December 31, 1992.

→ Autism
RR, 0.87, 95% CI (0.61-1.23)

”Skewed” cohort and homogeneity

Restricting the cohort to children born 1991-1993.

→ Autism
RR, 0.86, 95% CI (0.53-1.39)

Results – Association in subgroups

Autism

Risk factors

	RR 95% CI	RR 95% CI
Birth weight		
< 2500 g	**1.71** (1.06-2.76)	**1.10** (0.47-2.57)
2500-2999 g	**1.14** (0.82-1.59)	**0.63** (0.28-1.42)
3000-3499 g	**1** Referent	**1.00** (0.61-1.65)
3500-3999 g	**1.02** (0.79-1.32)	**0.97** (0.59-1.60)
>= 4000 g	**1.28** (0.96-1.72)	**0.77** (0.41-1.45)
Gestational age		
< 37 weeks	**0.93** (0.59-1.47)	**0.85** (0.28-2.63)
37 - 41 weeks	**1** Referent	**0.95** (0.66-1.38)
>=42 weeks	**0.82** (0.56-1.21)	**0.68** (0.26-1.74)
Sex		
Girl	**1** Referent	**0.93** (0.53-1.64)
Boy	**4.05** (3.19-5.15)	**0.83** (0.58-1.20)

Thimerosal effect in subgroups

RR, **0.85** (0.60-1.20)

(Not published)

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Study strengths and weaknesses

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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

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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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