Thiomersal and developmental problems including Autism

UK Studies

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Professor Elizabeth Miller, Head Immunisation Dept, Communicable Disease Surveillance Centre, Health Protection Agency, London UK

Nick Andrews, Deputy Head, Statistics Unit, Communicable Disease Surveillance Centre, Health Protection Agency, London UK

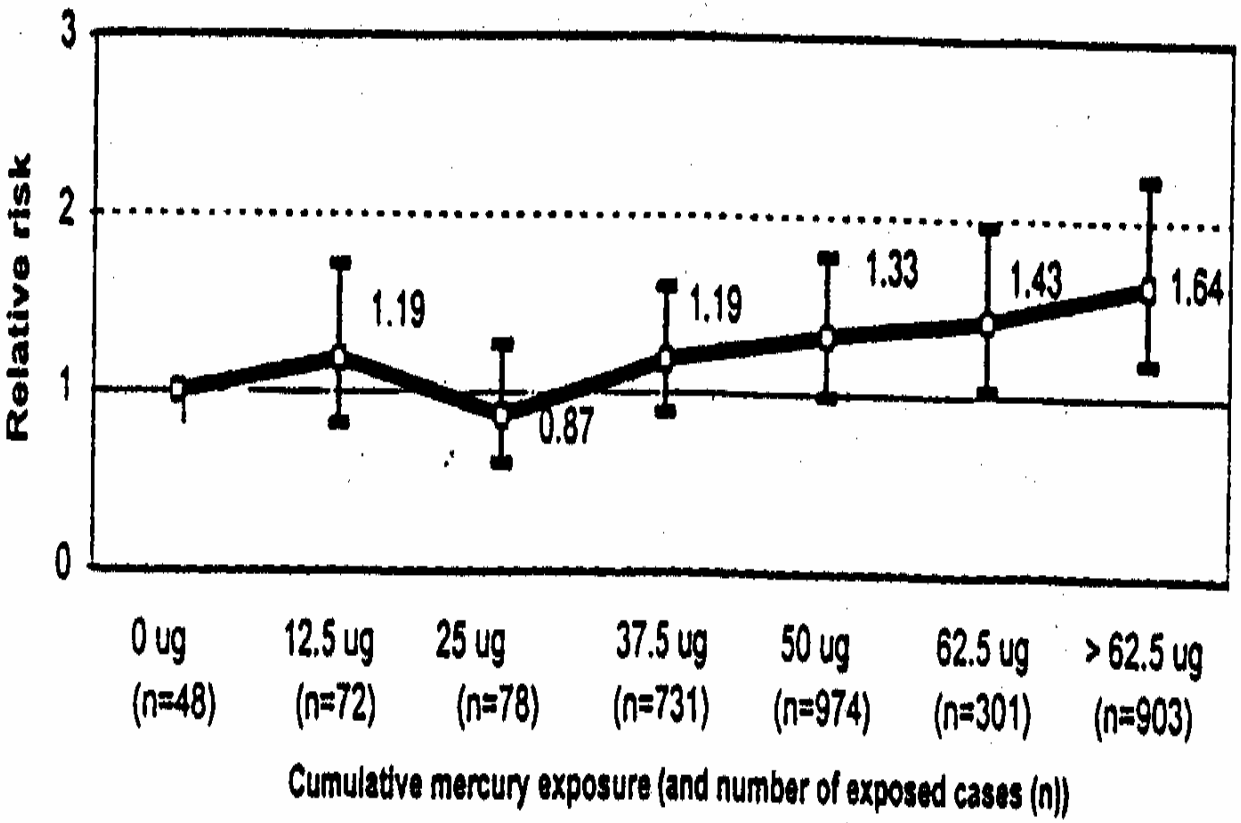
Outline

- Background
- Thiomersal Exposure in the UK
- Autism Prevalence in the Thames region
- The GPRD study
- The ALSPAC study
- Comments

Background

- 1990s: US cumulative ethyl mercury exposure via thiomersal vaccines could exceed 0.1 ug/kg/day – the most stringent safety limit set for methyl mercury.
- 1999: Thiomersal removed from vaccines in the US as a precautionary measure
- 2001: Preliminary analyses of a US Vaccine Safety Data-link study suggested an increased risk of certain developmental problems in those exposed to higher levels of thiomersal at a young age.
- WHO and UK Dept of Health commissioned two UK studies to investigate if increased thiomersal exposure from vaccines at a young age was associated with developmental problems.

Graph 2: Relative risk + 95 % *CI* of Developmental neurologic disorders after different exposure levels of thimerosal at 3 months of age, NCK &GHC, Cycle 7



Trend:
1.007/ug
$p < 0.01$

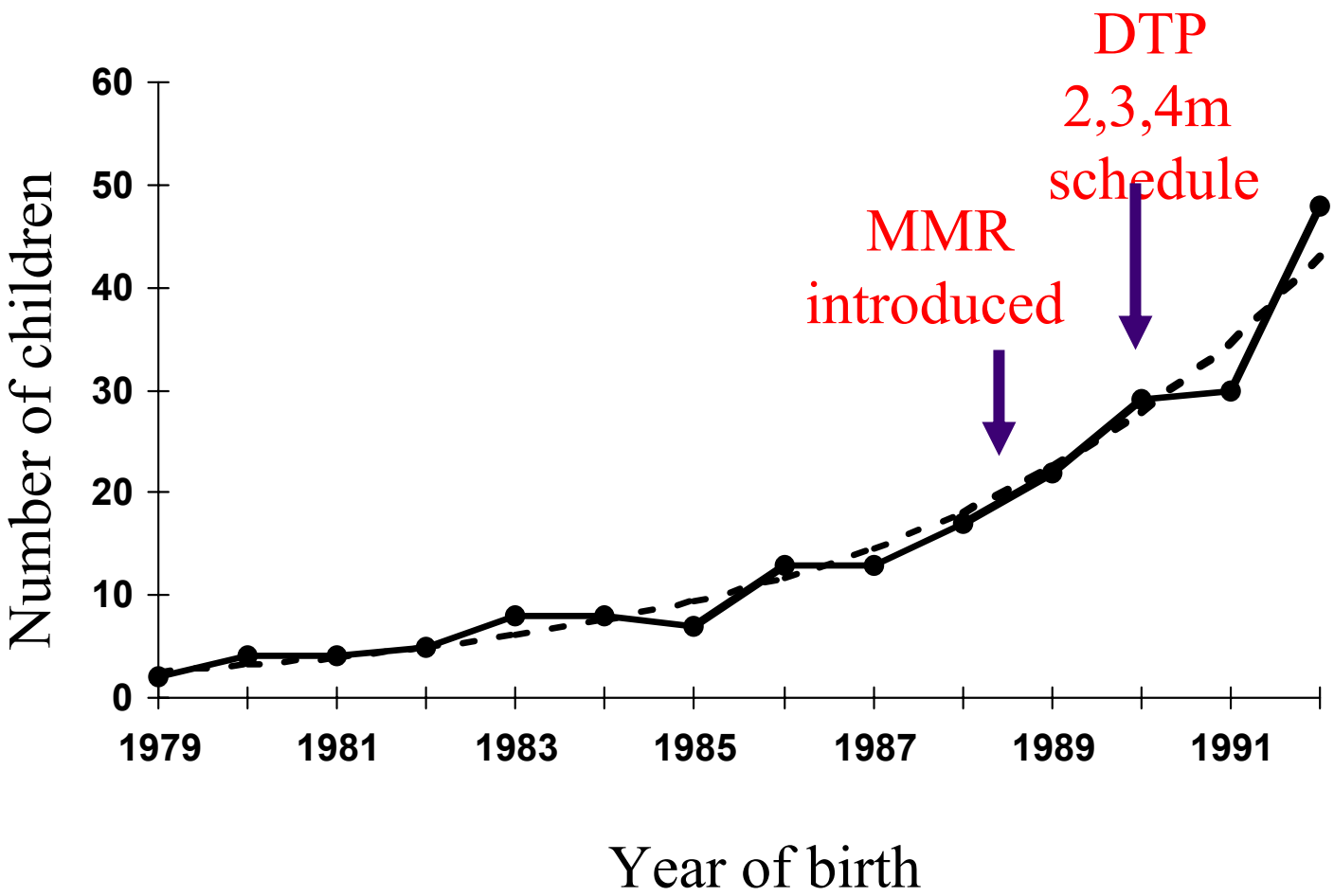
Thiomersal exposure in the UK

- Only routine vaccine with thiomersal in the UK is DTP or DT-containing vaccines with 50ug thiomersal per dose (25ug Hg)
- Vaccine scheduled at 2,3,4 months of age since 1990/91 (3,5,10 months before then)
- Similar to the E.P.I schedule
- Maximum exposure lower than US

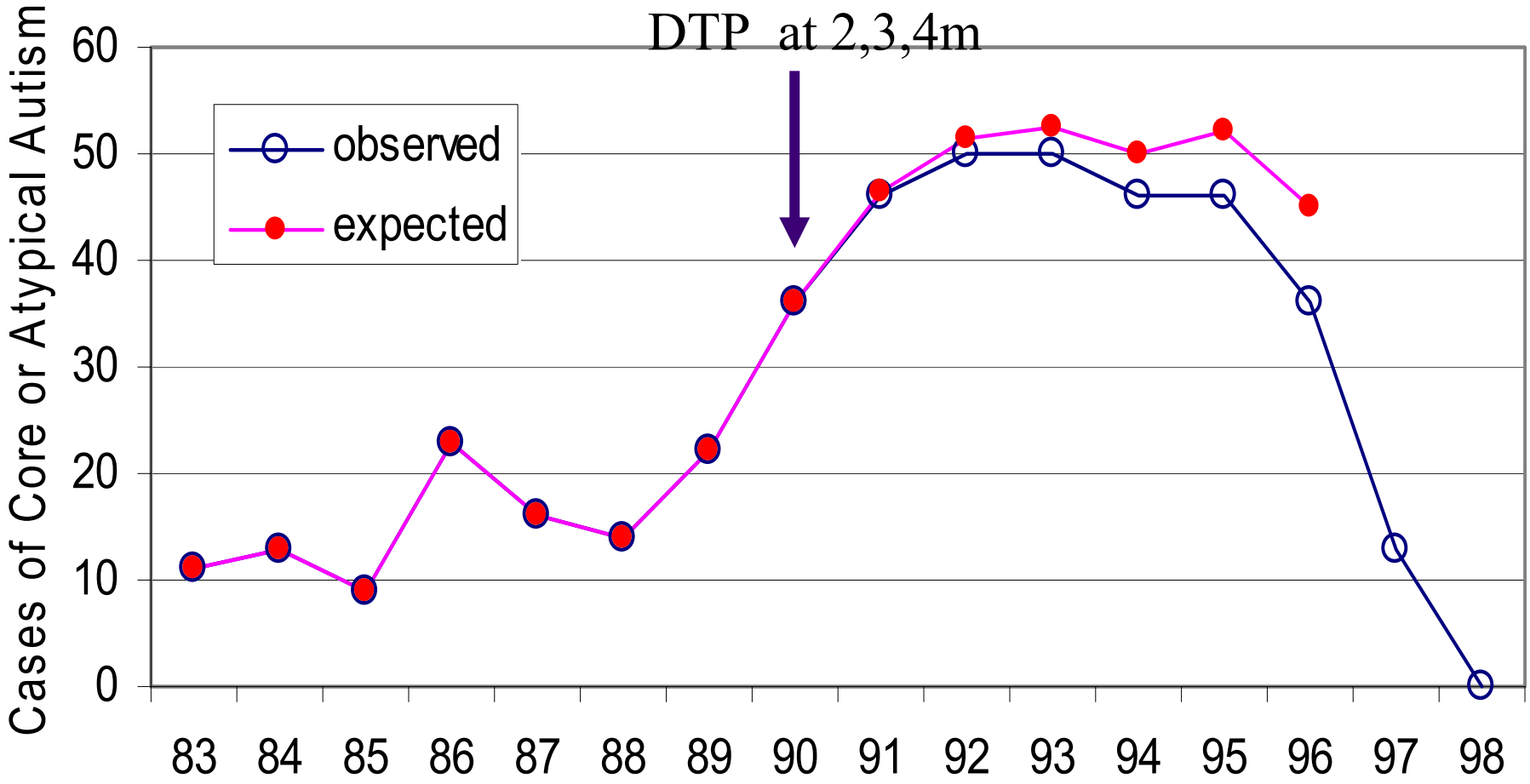
Age	UK (3,5,10m)	UK (2,3,4m)	US
3 months	25ug	50ug	75ug
4 months	25ug	75ug	125ug
6 months	50ug	75ug	187.5 ug

Autism Prevalence in the Thames region of the UK

Cases of autism diagnosed by age 5 by year of birth
1979-1992 (Lancet 1999; 353:2026-29 first North Thames study)



Cases of autism diagnosed by 10 years of age by year of birth 1983-1998. Second North Thames study. Arch Dis Child 2003;88:666-670.



Expected numbers allow for the underlying trend and delay from birth to diagnosis

The GPRD Study

- The GPRD is the General Practice Research Database
- Similarities to the US VSD data. Could examine the outcomes significant in the preliminary analysis.
- 500 General Practices (5.7% population) contribute
- Has data on patient consultations, referrals and prescribed medicines including vaccines

Selection of the GPRD cohort

- GPRD data available for the period 1988 to 1999
- Born 1988 - 1997 into a GPRD practice
- GPRD enrolled for at least 2 years
- Exact date of birth available
- Data meets “up to standard” criteria of GPRD

Exclusions

- Full Cohort N = 107152
- Exclusions
  - Date anomalies
  - Various congenital, prenatal, perinatal conditions
  - Various postnatal conditions in first 6 months
  - Outcome events in the first 6 months

Cohort for analysis = 103,043

Preterm = 2,471 Term = 100,572

One further exclusion considered was those who did not receive 3 DTP doses by one year of age

Variables causing potential confounding

- Year of Birth
- Month of Birth
- Sex
- Data on region/GP and other potential confounders such as socioeconomic status not available
- Analyses only adjusted for Sex, Year of Birth

Exposure to mercury

- Doses of DTP at 3months (93 days) giving a maximum cumulative exposure of 50 µg
- Doses of DTP at 4 months (124 days) giving a maximum cumulative exposure of 75 µg
- Age-specific exposure by 6 months

$$HgAll = \frac{(183 - \text{age at dose1}) + (183 - \text{age at dose2}) + (183 - \text{age at dose3})}{40}$$

Any doses not given or given after 183 days is set to age 183 days for the above calculation

Outcomes (ICD9 codes)

- General Developmental Delay (Developmental neurologic disorders in VSD study)*
- Behavioural Problem (3129)*
- Enuresis (7883)
- Autism (2990)
- Tics (3072)*
- ADD (314)*
- Language/Speech Delay (3153)*
- Developmental Delay unspecified (3159)*

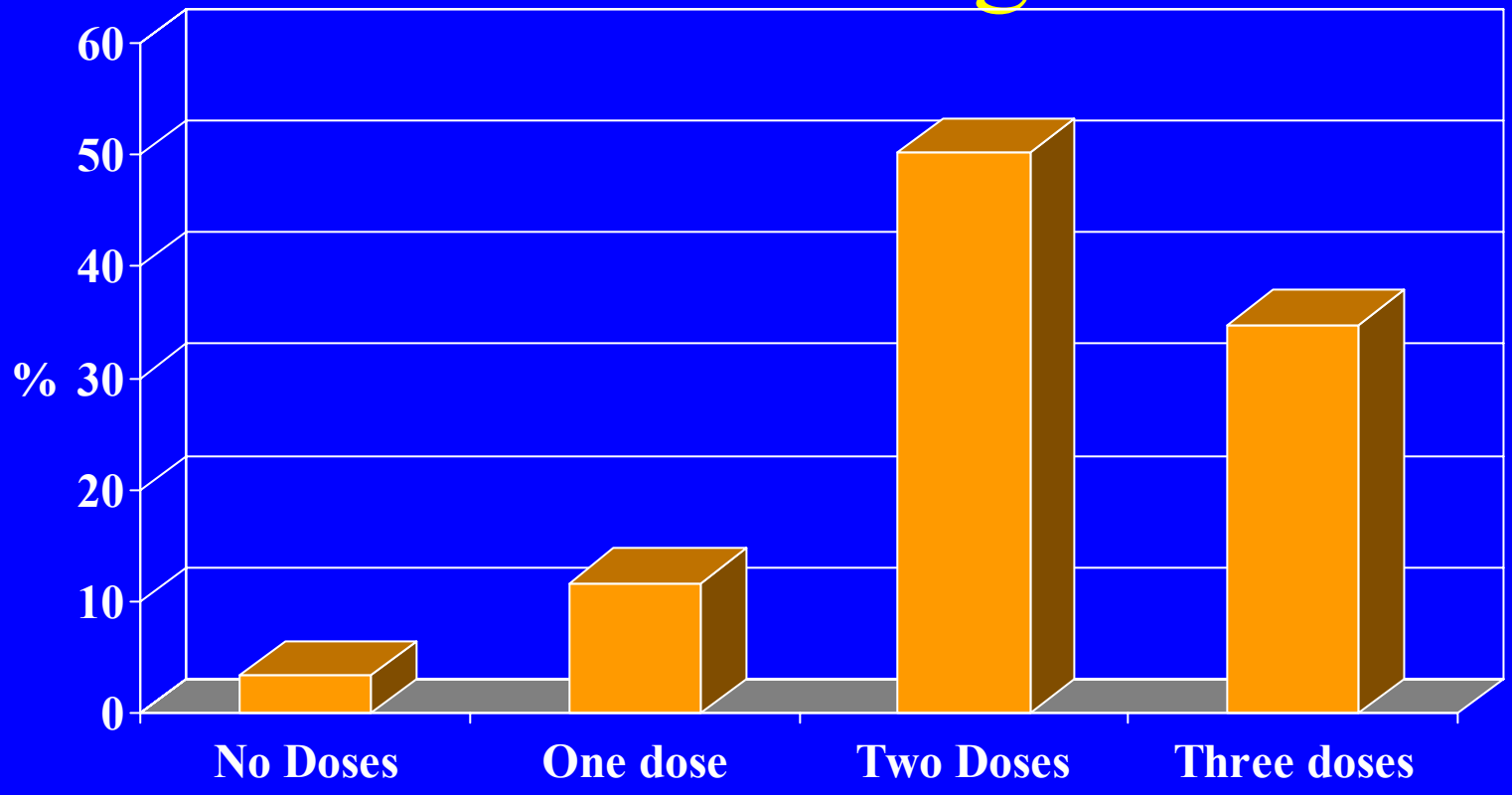
* These were significant in one or more of the preliminary analyses of the VSD study

Method of Analysis

- Cox proportional hazards survival from 183 days of age to age of event

- Censoring at age of event or last date of follow up.
- Results reported as the Hazard Ratio per DTP dose

Percentage of children receiving 0,1,2,3 doses of DTP/DT by 4 months of age



Outcome data: Age and Sex.

Outcome	N	Median Age yrs*	% Male
Unspec Delay	485	2.4	67
Lang/Speech	666	3.0	70
General DD	2035	3.6	71
ADD	222	3.7	77
Autism	104	4.4	89
Behavioural Prob	816	4.8	71
Tics	70	5.2	70
Enuresis	1312	5.6	54

*calculated to allow for censored data

Cox Regression results

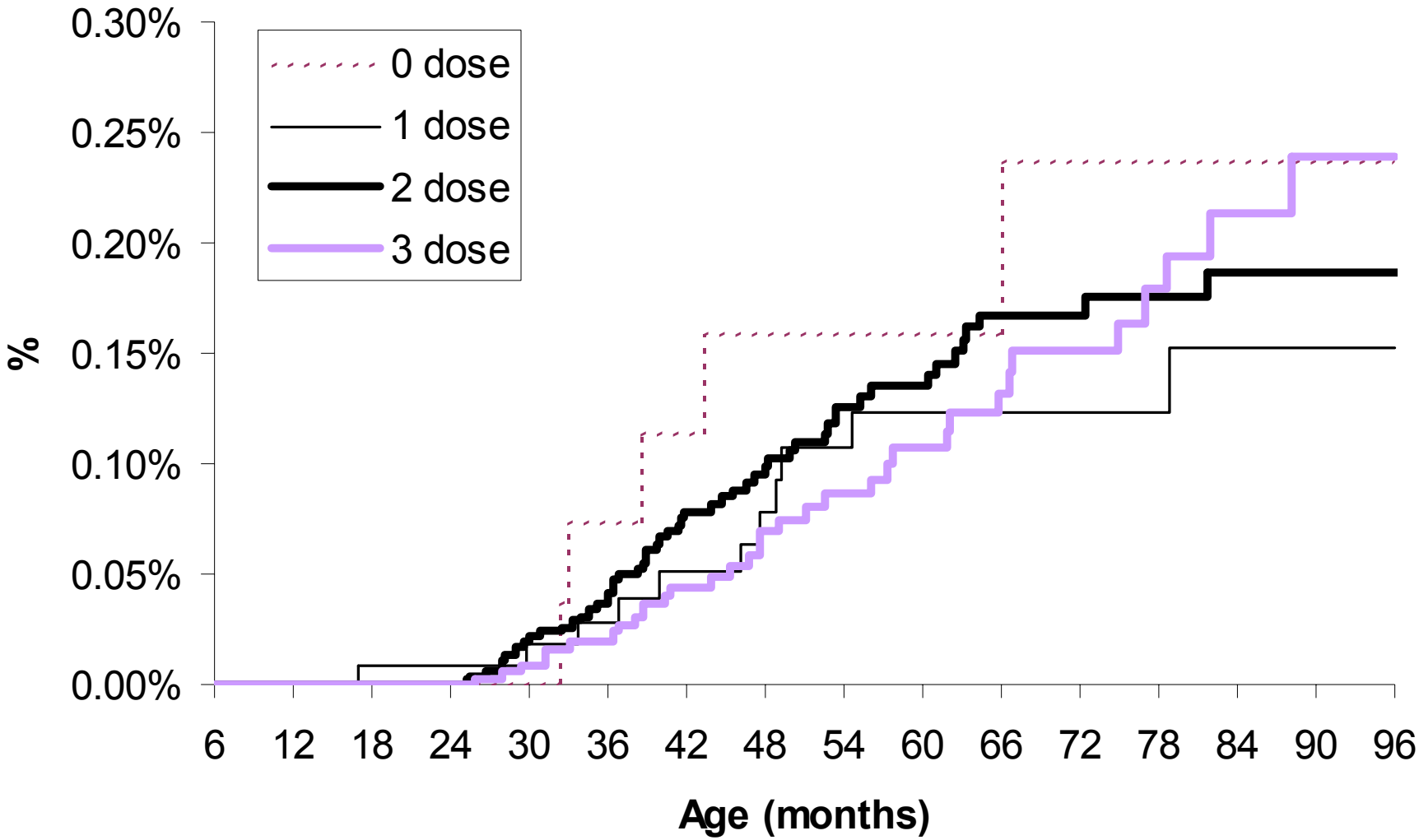
Autism Results

Exposure	HR (95% CI) per dose or unit	P-value
Doses by 3m	0.89 (0.65-1.21)	0.46
Doses by 4m	0.94 (0.73-1.21)	0.66
HgAll	0.99 (0.88-1.12)	0.89

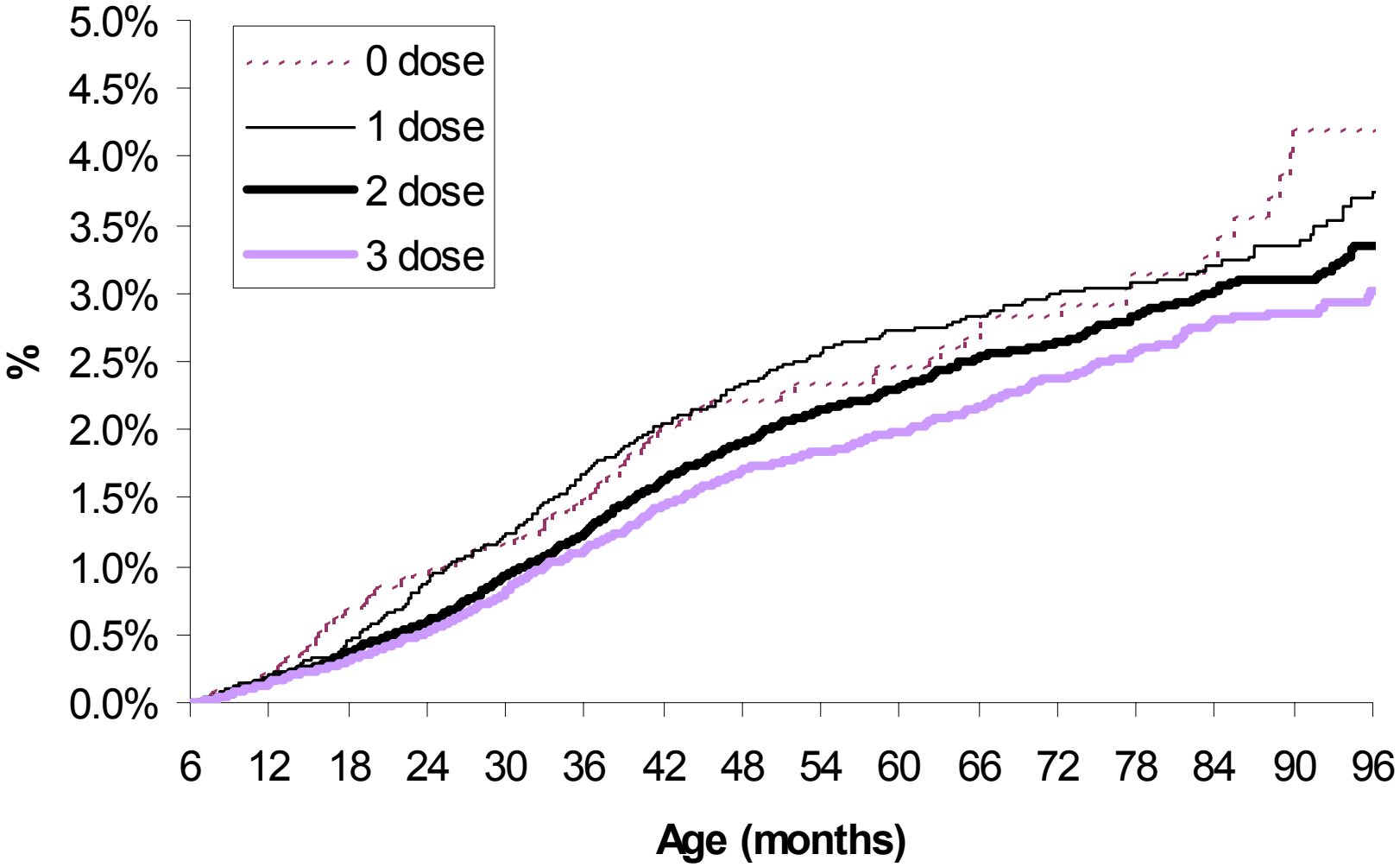
Outcome	HR (95% CI) per dose by 4 months	P-value
Autism	0.94 (0.73-1.21)	0.66
Unspec Delay	0.84 (0.75-0.94)	0.002
Lang/Speech	0.96 (0.87-1.06)	0.99
General DD	0.89 (0.84-0.94)	<0.001
ADD	0.82 (0.70-0.97)	0.02
Behavioural Prob	0.98 (0.90-1.07)	0.68
Tics	1.34 (0.96-1.85)	0.08
Tics*	1.50 (1.02-2.02)	0.04
Enuresis	1.04 (0.97-1.12)	0.25

* Result when excluding those not receiving 3 doses by the age of 366 days.

Autism: Reverse Kaplan-Meier Plot according to doses by 4 months of age



General Developmental Delay: Reverse Kaplan-Meier Plot according to doses by 4 months of age



Autism diagnosis in GPRD

- Autism diagnosis based on first mention of ICD 2990 in computerised GPRD record.
- Not validated in our study because already validated by others using GPRD to test MMR based hypotheses (Kaye et al BMJ Feb 2001, Black Et al BMJ Aug 2002).

GP Case-note validation

152 validated

122 (80%)	confirmed the child presented with the condition
11 (7%)	only parental concern
11 (7%)	incorrect coding
8 (5%)	no record of diagnosis found in notes (but was on the computer)

All dates of vaccination correct and dates of events correct or close to date in GPRD

Comments

- No evidence that increased exposure to thiomersal at a young age increases the risk of autism
- Confounding may be an issue explaining apparent protective effects for some conditions.
- Except for Tics no evidence of an increased risk
- Validation of Tics showed them to be minor and transient.

The ALSPAC study

- Avon longitudinal study of parents and children
- Enrolled women resident in Avon in the South West of England with an expected date of delivery between 1 April 1991 and 31 December 1992
- 13,617 had singleton offspring surviving to 12 months old.

- Information on childhood behaviour and development was collected in questionnaires at 6, 18, 30, 47, 81 and 91 months of age.

- Information on potential confounders comes from questionnaires given to the mother both during pregnancy and the period that followed.

- The information on immunizations was taken from the Bristol-based Child Health Surveillance Database (NHS Public Health Network).

Outcome Variables

Area	sub-areas	age (m)	outcome
Behaviour	prosocial, hyperactivity	47,81	Low 10%
	emotional symp, conduct prob		Stren/Diff
	peer prob, total difficulties		Quest
Fine Motor Devel		6,18,30	Low 10%
			R. Denver
Speech Dev	stumbles -words, diff sounds	81	yes/no
	speech worries	81	
	speech therapy	91	
Tics	Any from 18-42 months	42	yes/no
	Any at 91months	91	
Spec Educ Needs		91	yes/no
LEA statemented (due to special needs) includes autism		91	yes/no

Confounding variables considered

- Birthweight
- Gestation
- Maternal education
- Gender
- Parity
- Housing tenure
- Maternal Smoking
- Ethnicity
- Breastfeeding for 3 months

All the above were associated with vaccination ($P<0.05$)

Exposure / Analysis

- Same as the GRPD Study
- Only doses by 4 months results shown
- Other results similar
- Outcome is trend in odds ratio per DTP/DT dose.
- UOR = Unadjusted OR
- AOR = Adjusted OR (for confounders)

Example of the effect of controlling for potential confounders

* p<0.05

** p<0.01

Outcome	UOR	AOR	95%CI
Behavior at 47mn			
Prosocial	0.98	1.05	0.97, 1.15
Hyperactivity	0.88**	0.95	0.85, 1.05
Emotional symptoms	1.01	0.99	0.88, 1.11
Conduct problems	0.90*	0.94	0.85, 1.05
Peer problems	1.04	1.07	0.95, 1.21
Total difficulties	0.93	1.01	0.91, 1.12

Outcome	UOR	AOR	95%CI
Tics			
Any report (18-42m)	0.83	0.82	0.61, 1.11
Tics at 91 months	0.81	0.74*	0.57, 0.97
Special needs			
Special educat needs	0.81**	0.84*	0.73, 0.96
LEA statemented	0.81*	0.83	0.67, 1.04

* $p<0.05$

** $p<0.01$

Comments

- Unadjusted ORs sometimes show significantly protective effects of DTP/DT (as with GPRD)
- Adjusted ORs tend to be slightly higher, although some effects remain protective
- The confounding effect is usually very small. Parity was found to have the largest effect.
- This suggests that while the GPRD study could not adjust for many potential confounders this should not have led to large biases.
- No evidence of a higher risk for Tics
- FROM ALSPAC AND GPRD CONCLUDE OVERALL NO EVIDENCE OF AN INCREASED RISK OF DEVELOPMENTAL PROBLEMS FROM THIOMERSAL EXPOSURE IN VACCINES GIVEN IN INFANCY IN UK