Review of 'Safety of Thimerosal-Containing Vaccines: a Two-Phased Study of Computerized Health Maintenance Organization Databases' (Pediatrics 2003)

- Introduction
- Review of Verstraeten findings focused on autism
- Effects of inclusion/exclusion criteria upon autism findings
- Other subanalyses of autism-thimerosal
- Chronology of autism analyses
- Discussion of other concerns
- Update on planning for Autism – Thimerosal study

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Current Funding

Agency for Healthcare Research and Quality (AHRQ): Centers for Education and Research in Therapeutics

Centers for Disease Prevention and Control: Vaccine Safety Datalink (VSD); Clinical Immunization Safety Assessment (CISA)

University of Washington School of Public Health: Teaching

Robert Davis, MD, MPH
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Pharmaceutical: Merck, GlaxoSmithKline, Wyeth, Pfizer, Amgen
Foundations: Packard, Culpepper

'Safety of Thimerosal-Containing Vaccines: a Two-Phased Study of Computerized Health Maintenance Organization Databases'
Vaccine Safety Datalink (VSD)

- Partnership between CDC and seven Health Maintenance Organizations (HMOs)

- Large linked database including vaccination, clinic, hospital discharge and demographic data

- Initiated in 1991

- Covers estimated 2.5% of U.S. population

Ethylmercury content of vaccines used in VSD study population

- Diphtheria, Tetanus, and Pertussis vaccines:

  0 or 25 micrograms/dose

- Haemophilus influenzae B vaccines:

  0, 12.5 or 25 micrograms/dose

- Hepatitis B vaccines:

  12.5 micrograms/dose

- Polio, Measles, Mumps, Rubella, Varicella, and Pneumococcal vaccines:

  no thimerosal

Cumulative ethylmercury (EtHg) exposure from thimerosal-containing vaccines in VSD study population

Age at exposure	Total Hg dose in the period	Cumulative Hg at end of period
0-1 m	12.5 ug	12.5 ug
2-3 m	25 – 62.5 ug	37.5 – 75 ug
4-5 m	25 – 62.5 ug	75 or 125 ug
6-7 m	25 – 62.5 ug	112.5 – 187.5 ug

Infants in VSD exceeding EPA mercury exposure limit
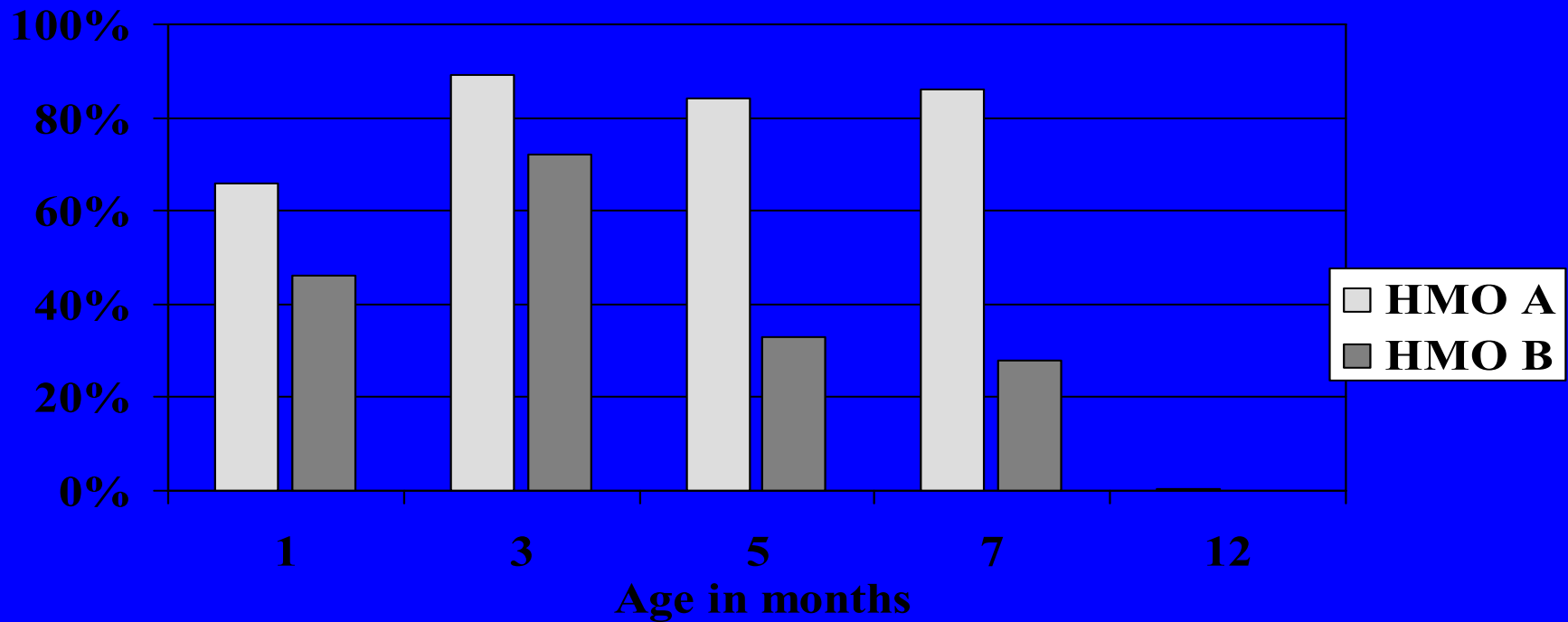
Two-phased Study

- Phase I: Screen range of neurodevelopmental and renal disorders

- Phase II: Re-assess associations encountered in phase I

Study methods

- Retrospective cohort study of automated vaccination and outcomes data

- Exposure: mercury from thimerosal-containing childhood vaccines at different ages

- Outcomes: range of plausible neurologic and renal disorders, including autism

Study population

- Born between 1992 and 1998
- Born into one of two HMOs of VSD
- Continuously enrolled first year of life
- Received at least 2 polio vaccinations by 1 year of age
- Followed until December, 2000

Study exclusions

- LBW <2500 g

- Congenital or severe perinatal disorders, or mothers with serious medical problems of pregnancy

Exposure assessment

- Cumulative mercury exposure calculated from individual automated vaccination records (including vaccine type, manufacturer and lot number)

- Total ethylmercury exposure was modeled as continuous and categorical variable

    total ethylmercury exposure/12.5 ug

- Exposure periods assessed at:

    1,3 and 7 months

Statistical analyses

- Proportional hazards models

- Separate for each HMOs

- Stratified on
  - gender, year and month of birth at HMO A
  - gender, year and month of birth, and clinic at HMO B

- Adjusted for health-care seeking behavior (restricted comparison group to children with at least 1 visit to clinic/ED at time of autism diagnosis)

Statistical analyses

- Person time began with
  - First birthday at HMO A
  - First birthday or January 1, 1995 (whichever came later) at HMO B
- Person-time censored on
  - diagnosis date or
  - last date of follow-up
- Temporary disenrollment allowed, but person time and diagnoses only used while child was enrolled

Medical record validation

- Reviewed 120 medical records of children with ICD-9 code of autism

- 81-92% showed the diagnosis was made by clinical or behavioral specialist
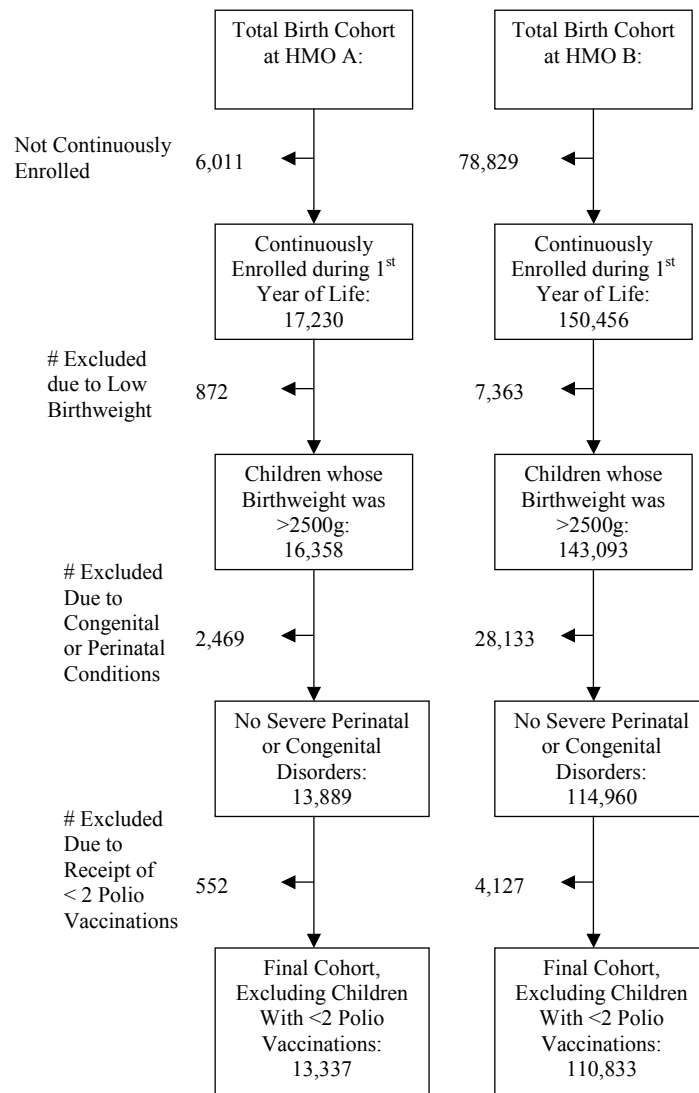
Results

Autism (299.0)

Total number   223

 HMO A   21

 HMO B   202

Mean age at diagnosis 44-49 months

Male 80%-90%

	Total Birth Cohort at HMO A:	Total Birth Cohort at HMO B:

Not Continuously Enrolled   6,011 ←   78,829 ←

	Continuously Enrolled during 1st Year of Life: 17,230	Continuously Enrolled during 1st Year of Life: 150,456

Excluded due to Low Birthweight   872 ←   7,363 ←

	Children whose Birthweight was >2500g: 16,358	Children whose Birthweight was >2500g: 143,093

Excluded Due to Congenital or Perinatal Conditions   2,469 ←   28,133 ←

	No Severe Perinatal or Congenital Disorders: 13,889	No Severe Perinatal or Congenital Disorders: 114,960

Excluded Due to Receipt of < 2 Polio Vaccinations   552 ←   4,127 ←

	Final Cohort, Excluding Children With <2 Polio Vaccinations: 13,337	Final Cohort, Excluding Children With <2 Polio Vaccinations: 110,833

Relative risk (95% CI) by 12.5 ug increase Hg exposure (HMO B)

	1 month Hg (cumulative)	3 month Hg (cumulative)	7 month Hg (cumulative)
Autism	1.16 (0.78, 1.71)	1.06 (0.88, 1.28)	1.00 (0.90, 1.09)

Relative risk for autism (95% CI) by category of Hg exposure (HMO B)

3 month cumulative Hg	RR (95% CI)	N
0-25	1.00	11
37.5-50	1.61 (0.77, 3.34)	158
>=62.5	1.38 (0.55, 3.48)	33

Relative risk for autism (95% CI) by category of Hg exposure (HMO B)

7 month cumulative Hg	RR (95% CI)	N
0 - 75	1.00	37
87 - 162.5	0.95 (0.62, 1.46)	148
>=175	0.65 (0.27, 1.52)	17

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Effect of congenital/perinatal exclusions – HMO B (based on earlier analysis; n = 150)

utcome	0-1 m	2-3 m	4-5 m	6-7 m	0-7 m
ny neurodevelopmental disorder	1.01	**1.06 ****	1.03	**1.07 ****	**1.05 ***
	1.02	***1.06 ****	*1.03*	***1.07 ****	***1.05***
utism	0.95	1.10	0.94	1.01	1.01
	0.99	*1.08*	*0.92*	*0.97*	*0.98*
ammering	0.87	1.05	1.17	**1.21 ***	**1.14**
	0.97	*1.17*	*1.21*	***1.27 ***	***1.21***
cs	1.18	1.01	**1.18 ***	**1.23 ****	**1.15**
	1.13	*1.01*	***1.21 ***	***1.18 ***	*1.14*
tention deficit disorder	0.85	1.10 *	1.06	1.07 *	1.06 *
	0.89	***1.11 ***	***1.10 ***	*1.06*	***1.08***

Effect of not excluding *any* children – (based on earlier analysis, HMO B

	0-1 m	2-3 m	4-5 m	6-7 m	0-7 m
utism					
l children (n = 215)	0.94	1.14	0.95	1.02	1.03
lio >1 at 1 year (n =213)	0.94	1.10	0.94	1.01	1.00
o low birth weight (n = 196)	0.95	1.10	0.94	1.01	1.01
udy cohort (n = 150)	0.99	1.08	0.92	0.97	0.98

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(Unadjusted) relative risks by increase of 12.5 ug ethylmercury – chart verified diagnoses

| utcome	0-1 m	2-3 m	4-5 m	6-7 m	0-7 m
peech delay – HMO A	1.31	1.10	1.09	0.97	1.03
beech delay – HMO B	**1.54 **	1.22	0.98	1.05	1.09
utism – HMO B	0.88	1.10	0.94	0.99	1.00
ttention deficit disorder – HMO B	1.17	1.21	1.07	1.17	**1.15**

*: p<0.05   **: p<0.01

Implicit adjustment for care-seeking behavior:
DTP separate vs combined (based on earlier analysis of 150 cases)

Outcome	RR	95 % CI
Autism	0.71	0.23 – 2.25
Stammering	3.03	0.96 – 9.57
Tics	1.70	0.56 – 5.16
Sleep disorders	1.62	0.73 – 3.61
Emotional disturbances	1.43	0.50 - 4.13
Attention deficit disorder	1.39	0.71 – 2.70
Language delay	1.26	0.82 – 1.92
Speech delay	**1.27 ***	1.00 – 1.62
Flat feet or toe deformities	1.27	0.85 – 1.91

Mrs Redwood's request

Autism: RR +95 %CI for different levels of cunmulative ethylmercury exposure from thimerosal-containing vaccines in first 7 months of life at HMO A and HMO B, 1992-1999
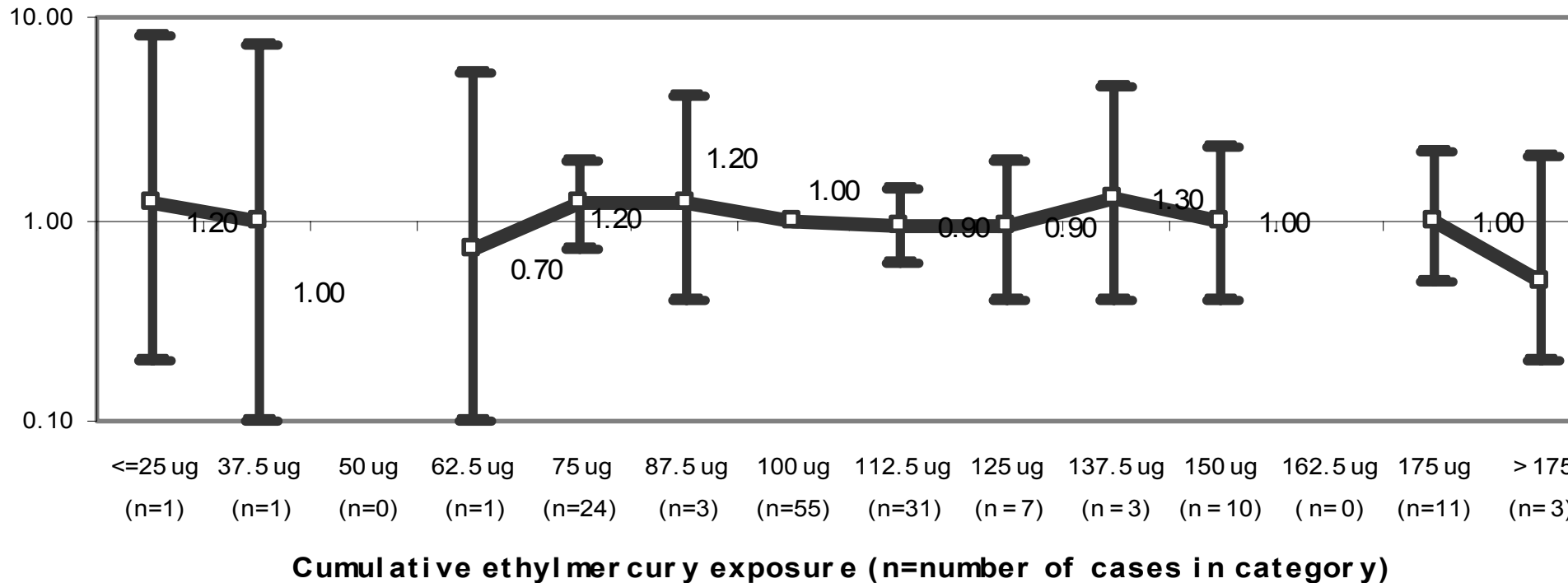
Cumulative ethylmercury exposure (n=number of cases in category)

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- Review of Verstraeten findings focused on autism
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- *Chronology of autism analyses*
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Background

- 9/99: "Thimerosal working group" identified VSD study as priority
- 9 - 10/99: Protocol developed in collaboration with thimerosal working group and VSD PIs
- 11/99 - 2/00: Data analyses
- 3 - 4/00: VSD discussions of interim results, involving FDA

Background
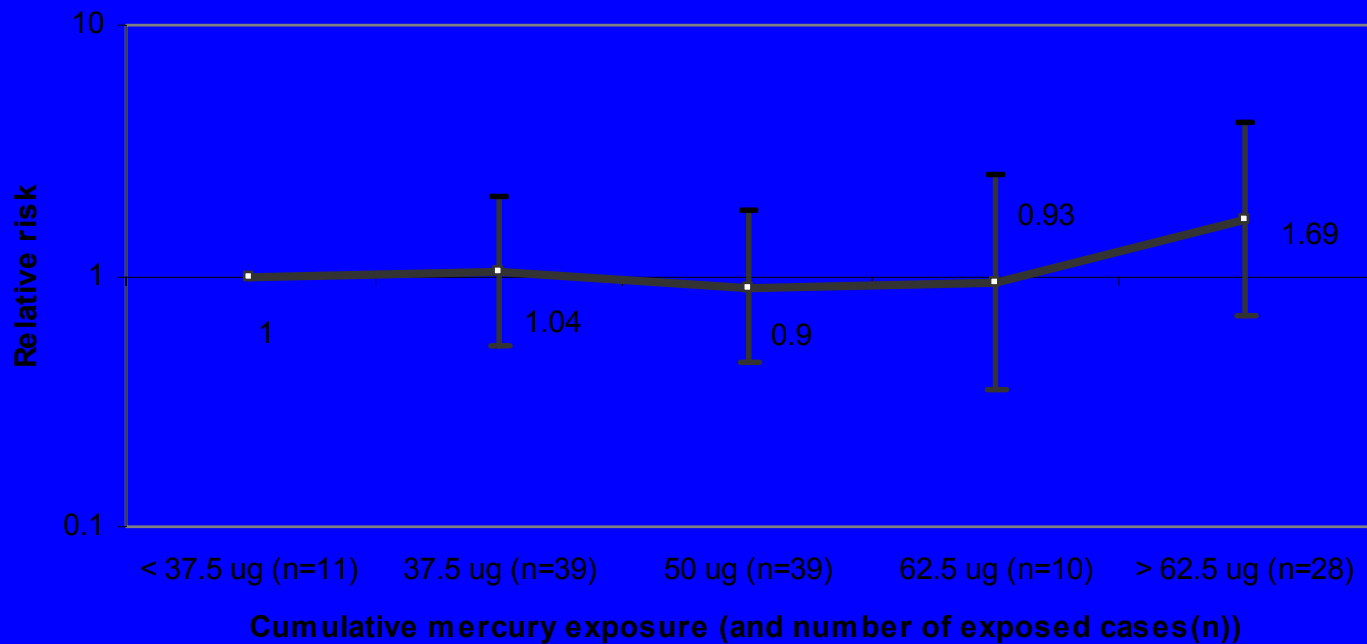
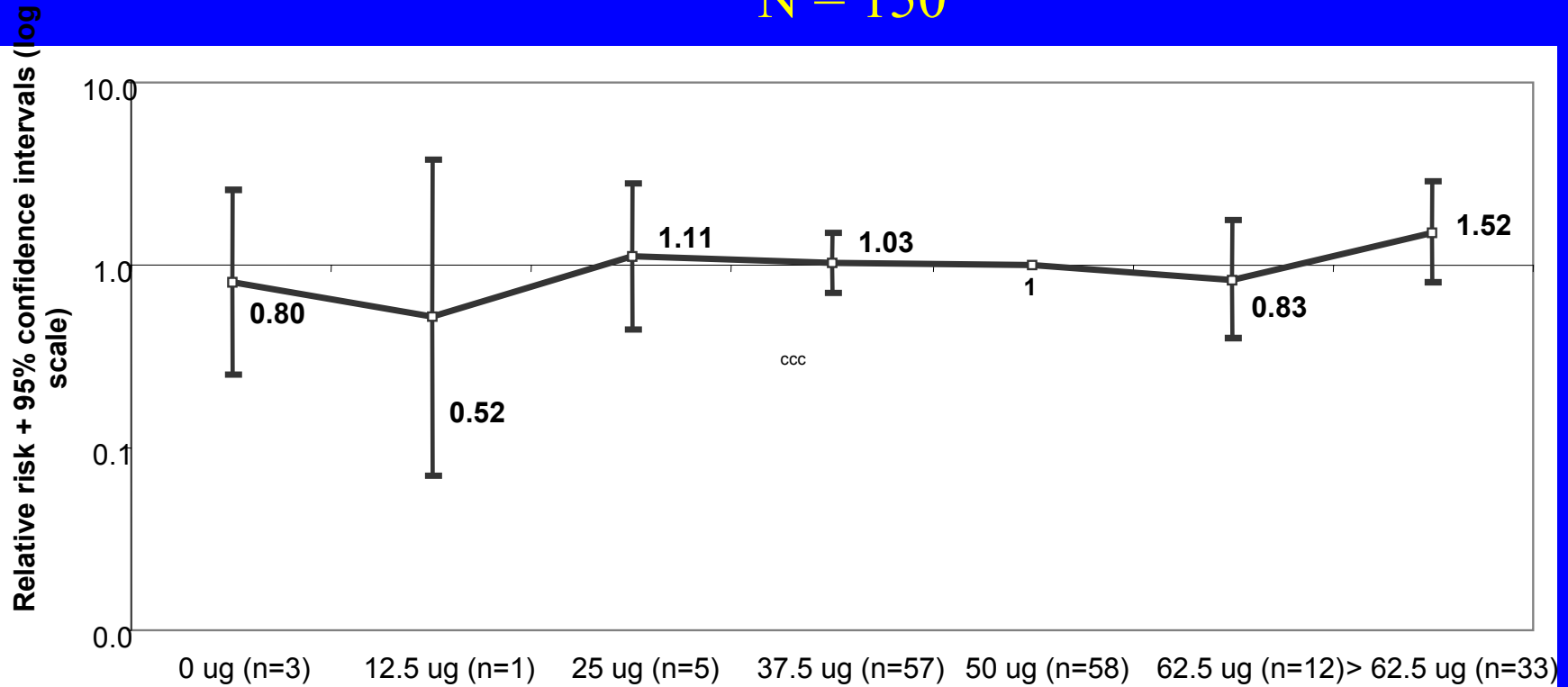February 2000

    Exposure at 3 mo

    62 cases total

    RR 2.48 at >62.5 vs <37.5; p NS (CI not given)

Relative risk associated with exposure at 3 months of age (NDD): Autism (ICD9 2990) Presented at Simpsonwood and ACIP N = 127

Trend:1.005 (0.991, 1.019), p = 0.48

Relative risk associated with exposure at 3 months of age: Autism
First presentation to IOM
N = 150

Differences in cohorts and analyses

- Major reasons:
    - Updated datasets with extended follow-up. Allowed additional cases to be identified in HMOs
    - Exclusion criteria modified, based on scientific input from IOM, CDC and VSD investigators
    - Improved adjustments for health-care seeking behavior
- Minor differences:
    - Time of exposure
    - Additional variables included in model

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Recent outside analyses of VSD data

Performed using data at RDC

- "We went to Atlanta,"…. "to the CDC, and looked at the VSD data. There is thimerosal-containing DTaP [diphtheria, tetanus and pertussis vaccine] and thimerosal-free DTaP, so we asked a question: Among children that got a minimum of either three consecutive thimerosal-containing DTaPs or three consecutive thimerosal-free DTaPs, was there a difference in the number of autism cases in the two groups? We found mega differences. More than 20 times higher. The rate of autism in the children that got more than three doses of thimerosal-containing DTaP vaccines was much, much higher. Almost all the children that have autism in that group were the ones that got the thimerosal-containing DTaP vaccine. The more thimerosal the greater the cases of autism."

Attempted replications of recent outside analyses of VSD data

Performed using data at RDC

- Limited to children born after 1997 (only children born after this date had chance of being given thimerosal-free vaccine)

- Looked at all children receiving DTPa vaccine 1/1/97-12/31/00

- Exposure: total thimerosal dose from DTPa

- Outcome: first inpt or outpt autism diagnosis

Attempted replications of recent outside analyses of VSD data
Performed using data at RDC

- Children were thus able to have 5 categories of exposure:
    - 0 ug
    - 25 ug
    - 50 ug
    - 75 ug
    - >= 100 ug

76 cases of autism

Controlled for gender

Logistic regression

Attempted replications of recent outside analyses of VSD data
Performed using data at RDC

Exposure   OR for Autism

– 0 ug   (ref)

– 25 ug   4.81 (1.48 – 15.61)

– 50 ug   4.75 (1.34 – 16.83)

– 75 ug   6.72 (2.29 – 19.76)

– >= 100 ug   18.43 (6.58 – 51.63)

– All OR are statistically significant at $p < 0.05$

Attempted replications of recent outside analyses of VSD data
Performed using data at RDC

Exposure	Age at last f/u (median)
– 0 ug	1.03 yrs
– 25 ug	1.91 yrs
– 50 ug	1.82 yrs
– 75 ug	2.20 yrs
– >= 100 ug	2.92 yrs

In other words, children with highest exposure had up to three times more 'opportunity' to be diagnosed with autism.

Attempted Replications of recent outside analyses of VSD data
Performed using data at RDC

Reanalyzed this data

- Matched cases to controls on month and year of birth. Equalized groups according to length of follow-up and ability to be diagnosed with autism

- Deleted DTaP vaccines with unknown thimerosal content

Attempted Replications of recent outside analyses of VSD data
Performed using data at RDC

Follow up corrected by controlling for age (stratifying on year and month of birth)

Exposure	OR for Autism
– 0 ug	ref
– 25 ug	1.10 (0.25-4.74)
– 50 ug	0.93 (0.18-4.70)
– 75 ug	0.75 (0.20-2.80)
– >= 100 ug	1.21 (0.28-5.34)

Thimerosal and Neurodevelopmental Disorders: Institute of Medicine Causality Assessment

- The evidence is insufficient to accept or reject a causal association (July 2001)
- Hypothesis is biologically plausible
- The IOM recommended a portfolio of additional studies
- On-going CDC studies
  - Follow-up neuropsychological testing study of children exposed to different levels of thimerosal as infants
  - Follow-up study of vaccine clinical trial participants
  - Case-control study of thimerosal and autism (planned)

Thimerosal and Autism: Next steps

– Large case-control study in final preparation stages

– Within Vaccine Safety Datalink Project

– In collaboration with Abt Associates

– External advisory board reviews protocol

– In depth examination of children with autism, along with extensive collection of data on:

  • Prenatal mercury exposures

  • Other environmental exposures

Thimerosal and Autism: Next steps

- Primary research questions:

  1. Is there an association between cumulative exposure to Thimerosal from vaccines or RhoGAM from the prenatal period up through 7 months (214 days) of age, and autistic disorder?

  2. Is the timing of children's exposure to etHG from Thimerosal in vaccines or RhoGAM related to autistic disorder?

Thimerosal and Autism: Comparison of VSD Screening Analysis and Planned Case-control Study

	Screening	**Case-control**
Design	Retro. cohort	Case-control
Population	2 HMOs	3 HMOs
Birth years	1992-1998	1994-1999
Age (years)	1-8 (~1/4 < 3)	4-10
Exposure history	Automated post-natal only	Auto, chart, interview pre and post-natal
Outcomes	AD	AD + ASD
Outcome ascer.	Auto ICD-9 code	ADOS, ADI-R
Confounding	Limited control	Detailed assess.

(Unadjusted) relative risks by increase of 12.5 ug ethylmercury – HMO B

utcome	0-1 m	2-3 m	4-5 m	6-7 m	0-7 m
hy neurodevelopmental disorder	1.02	**1.06 ****	1.03	**1.07 ****	**1.05 ***
utism	0.99	1.08	0.92	0.97	0.98
hildhood psychosis	0.79	1.00	1.07	1.13	1.06
ammering	0.97	1.17	1.21	**1.27 ***	**1.21 ***
cs	1.13	1.01	**1.21 ***	**1.18 ***	**1.14**
eep disorders	0.87	1.07	0.95	1.06	1.02
ting disorders	0.86	1.04	1.12	0.98	1.03
motional disturbances	0.88	0.96	1.02	1.19	1.06
ttention deficit disorder	0.89	**1.11 ***	**1.10 ***	1.06	**1.08 ***

*: $p < 0.05$ **: $p < 0.01$

(Unadjusted) relative risks by increase of 12.5 ug ethylmercury – HMO B(cont)

utcome	0-1 m	2-3 m	4-5 m	6-7 m	0-7 m
anguage delay	**1.37 ****	**1.20 ****	1.02	1.07	**1.09 ***
peech delay	**1.10 ***	1.06	1.00	**1.06 ****	**1.05 ***
ny renal disorder	0.97	1.03	1.04	1.05	1.04
nspecified kidney and ureter sease	1.03	1.07	1.07	1.07	1.07
ontrol diagnoses					
at feet or toe deformities	0.93	1.02	**1.12 ****	1.01	**1.04**
jury at unspecified site	0.78 **	0.96	1.01	0.99	0.98

*: p<0.05   **: p<0.01

Safe Minds questions (on this analysis)

- Cohort size variations – manipulated?
- Congenital/perinatal exclusions
- Exposure at 6 months low
- Young cohort
- Combination of disorders
- Differences HMOs
- Emotional disturbances: grouped vs separate

Limitations of using (administrative) computerized databases

- Misclassification exposure: HepB birthdose
- Misclassification outcome: ICD9 and Costar codes
- Unknown: medical care utilization factors
- Only conditions that come to medical attention

Attempted Replications of recent outside analyses of VSD data

Performed using data at RDC

Study by visiting investigator misclassified thimerosal content

Vaccines with unknown codes were assumed to have 25 ug thimerosal, but most were thimerosal free (post-1997)

Following analysis eliminated subjects with 'unknown' vaccine content

Exposure	OR for Autism
– 0 ug	(ref)
– 25 ug	6.45 (1.94 – 21.44)
– 50 ug	6.27 (1.68 – 23.35)
– 75 ug	8.45 (2.82 – 25.26)
– >= 100 ug	13.14 (4.42 – 39.06)

– All OR are statistically significant at $p < 0.05$