VSD Studies that Utilized Iterative Analyses

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Outline of Presentation

- Brief review of VSD
- Usual VSD study procedures
- Example of “typical” VSD study: asthma
- Review of thimerosal screening analysis

Vaccine Safety Datalink

- Collaboration between CDC and managed care organizations (since 1991)
- Resource for the ongoing evaluation of vaccine safety
- Planned vaccine safety studies and timely investigations of safety concerns

Vaccine Safety Datalink

- Population
  - 8 HMOs
  - >7 million members
- Large-linked databases
  - Exposure (vaccination)
  - Outcome (ER, OPD, hosp, lab)
  - Covariates (birth, death certificates)

Research in MCOs: Caveats

- Identifiable (large) population
  - enrollment and disenrollment
- Computerized data bases
  - not developed for research
  - Dynamic
- Conditions that come to medical attention

VSD Analytic Approach

- Screening analyses (electronic data)
  - preliminary assessment of vaccine-outcome associations
- In-depth studies (chart reviews, interviews)
  - validate outcomes (and dates)
  - verify vaccination history (and dates)
  - additional risk factor or clinical information

VSD Research Process: Overview

1. Study concept
2. Mini-proposal/protocol
3. IRB review
4. Pilot study
5. Data collection and analysis
6. Initial review of preliminary findings by co-investigators
7. Present preliminary findings to all VSD investigators
8. **Present preliminary findings at scientific meetings** (sometimes to policy committees)

VSD Research Process: Overview (cont'd)

9. Draft manuscript
10. Review by co-authors
11. CDC clearance
12. Submit to journal
13. Revise/re-submit
14. Published article

Example of a "Typical" VSD Study: Vaccines and Asthma

- Objective
  - To evaluate association between infant and childhood vaccines and risk of asthma
- Design
  - Retrospective cohort study
- Main findings
  - No association with DTP, OPV, or MMR
  - Weak associations with Hib and hep B, partially accounted for by health care utilization bias

Vaccines and Asthma Study: Chronology and Release of Findings

Jan. 1997 – Mini-proposal on Asthma Studies

Fall 1997 – Publication of Kemp article and other papers on "hygiene hypothesis"

1998 -- VSD Pilot study

- Based on VSD 5% DQ chart review sample
- **Pilot findings** presented at June 1998 VSD meeting and **Sept. 1998 ICAAC**
- Limitation: incomplete ascertainment of vaccinations received outside HMO
- **Lesson**: Need to restrict to children born as HMO members to obtain complete vaccination history

Vaccines and Asthma Study: Chronology (cont'd)

1998-1999 – Revised study

- Design
  - retrospective cohort
  - electronic data
  - restricted to children born into HMO
  - algorithm to identify asthma cases
- Presentation of findings
  - May 1999 VSD meeting (prelim. findings)
    - ? Validity of "unvaccinated"
    - Sub-analysis of >1 health care visits
  - **Aug 1999 ICPE and Sept 1999 ICAAC**
    - findings same as in final paper

Vaccines and Asthma Study: Manuscript Review

Jan 1999 – first draft
Dec 1999 – draft submitted for CDC clearance
Jan 2000 – initial comments from clearance review
- caveats about Hib and Hep B findings
- add analysis of 2 DTP, 2 OPV, and MMR
- sub-analysis of more severe cases

Jul 2000 – revised and resubmitted for CDC clearance
Aug 2000 – additional questions and comments
Sept 2000 – response to additional comments
Sept 28, 2000 – manuscript cleared

Vaccines and Asthma Study: Manuscript Publication

Oct 23, 2000 – submitted to first journal
Dec 1, 2000 – not accepted by first journal
May 7, 2001 – submitted to second journal
Jul 27, 2001 – not accepted by second journal
Aug 15, 2001 – submitted to third journal
Dec 20, 2001 – accepted pending suitable revision
Jan 10 2002 – resubmitted revised manuscript
Feb 10, 2002 – accepted for publication
June 2002 – article published (PIDJ 2002;21:498-504)

Safety of Thimerosal-Containing Vaccines: A Two-Phased Study of Computerized Health Maintenance Organization Databases

REFERENCE: Pediatrics Nov. 2003

Background

- Joint PHS and AAP statement in July1999
  - Recommended reduction and/or elimination of thimerosal from vaccines
- NIH meeting August 1999
  - Recommended additional research

Vaccine Safety Datalink Analysis

- CDC analysis of U.S. HMO data to explore possible associations between thimerosal and neurodevelopmental disorders
- Intended as an initial screen of possible associations
- More detailed study to be planned if any associations were identified

Chronology

- 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: Preliminary data analyses
- 3 - 4/00: VSD discussions of preliminary findings
- 4/00: VSD annual meeting: alert NIP leadership about preliminary findings (associations with speech or language delay, any developmental delay, ?ADHD)

Chronology (cont'd)

- 4/00: Presentation of preliminary findings at EIS conference
- 4/27/00: Briefing for CDC Associate Director for Science
  - Convene review panel of CDC scientists
- 5/2/00: CDC scientific review panel
  - Evidence weak but should be explored further
  - *Recommendation to replicate in independent data set*
- **6/7-8/00: External experts review (Simpsonwood)**
  - Evidence weak but should be explored further along several lines of inquiry (including replication in an independent database, and neurodevelopmental testing study)

Chronology (cont'd)

- **6/00: Presentation to ACIP**
  - Included findings from third HMO: Did not replicate findings of associations at two VSD HMOs
- Other presentations
  - 7/00 National Immunization Conference
  - 8/00 WHO Global Vaccine Advisory Committee
    - Recommended similar analysis in U.K. GPRD
- **7/01: IOM Immunization Safety Review Committee**
  - Additional follow-up data available, findings generally similar to earlier analyses
  - Findings judged to be inconclusive
  - Recommended a portfolio of additional studies

Chronology: Manuscript

- 6/01: First draft of manuscript
- 6/01- 10/02: Revise manuscript and conduct additional analyses
  - Additional follow-up data available
  - Better address concerns about possible health care seeking bias
- 10/02-12/02: CDC Clearance process
- 12/02: Submitted to first journal
- 1/02: First declined because of length
- 1/17/03: Submitted to second journal (Pediatrics)
- 5/7/03: Manuscript accepted pending revision
- 6/27/03: Revised manuscript resubmitted
- 7/9/03: Manuscript accepted for publication
- **11/03: Article published**

VSD Thimerosal Screening Analysis: Final Results

- At one HMO cumulative exposure at 3 months resulted in a significant positive association with tics
- At second HMO, increased risks of language delay were found for cumulative exposure at 3 months and 7 months
- Significant associations found in either of the first two could not be replicated in the third HMO
- In no analyses were significant increased risks found for ADD or autism

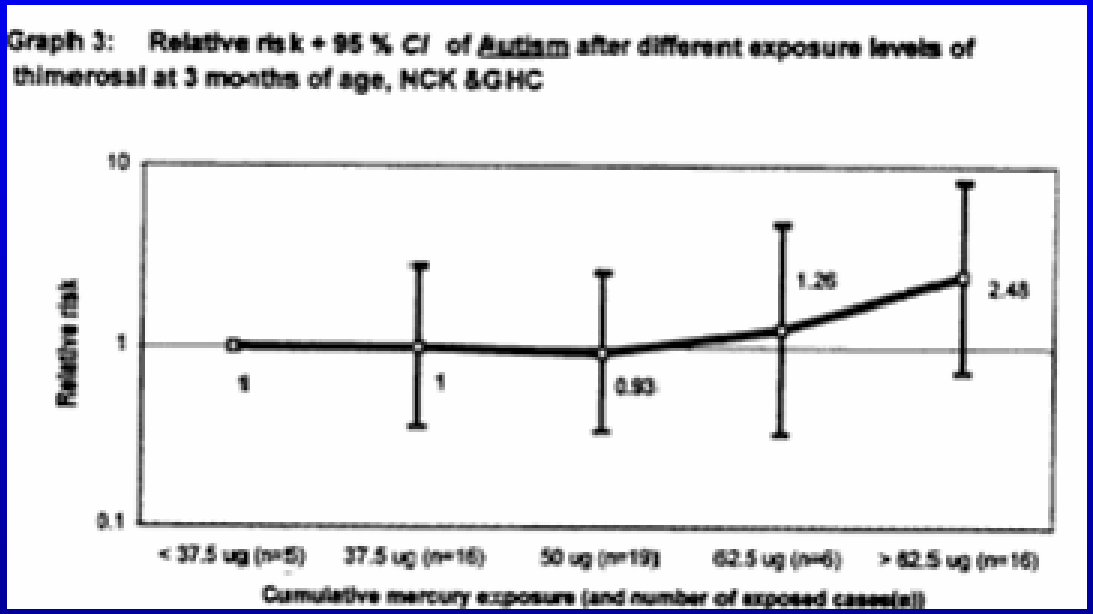
Reference: Pediatrics November 2003

VSD Thimerosal Study Iterative Analyses: Differences in cohorts and analyses

- Major methodological differences
  - Updated datasets with extended follow-up. Allowed additional cases to be identified in HMOs
  - Exclusion criteria modified, based on scientific input from IOM, CDC, VSD investigators, others
  - Improved adjustments for health-care seeking behavior
- Intent of analyses
  - Screening analysis versus completed study

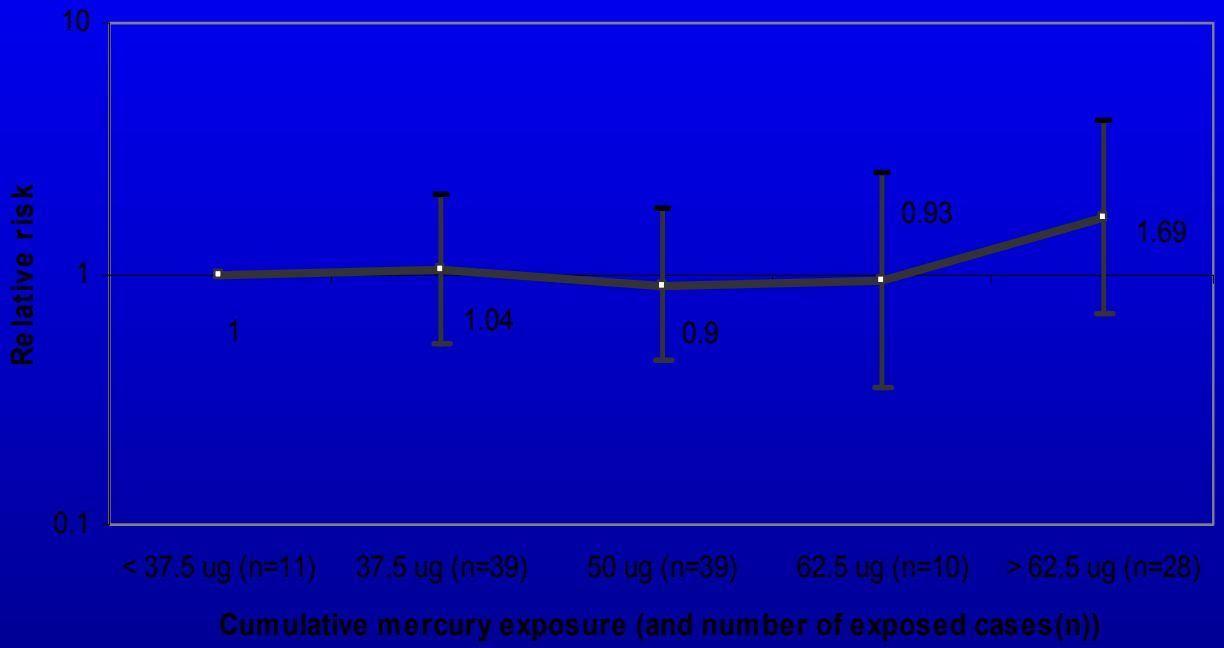
Changes in results in different iterations: Autism

VSD Thimerosal Screening Analysis Preliminary Findings: Autism (n=67) February 2000



Exposure at 3 mo
RR 2.48 at >62.5 vs <37.5; p NS

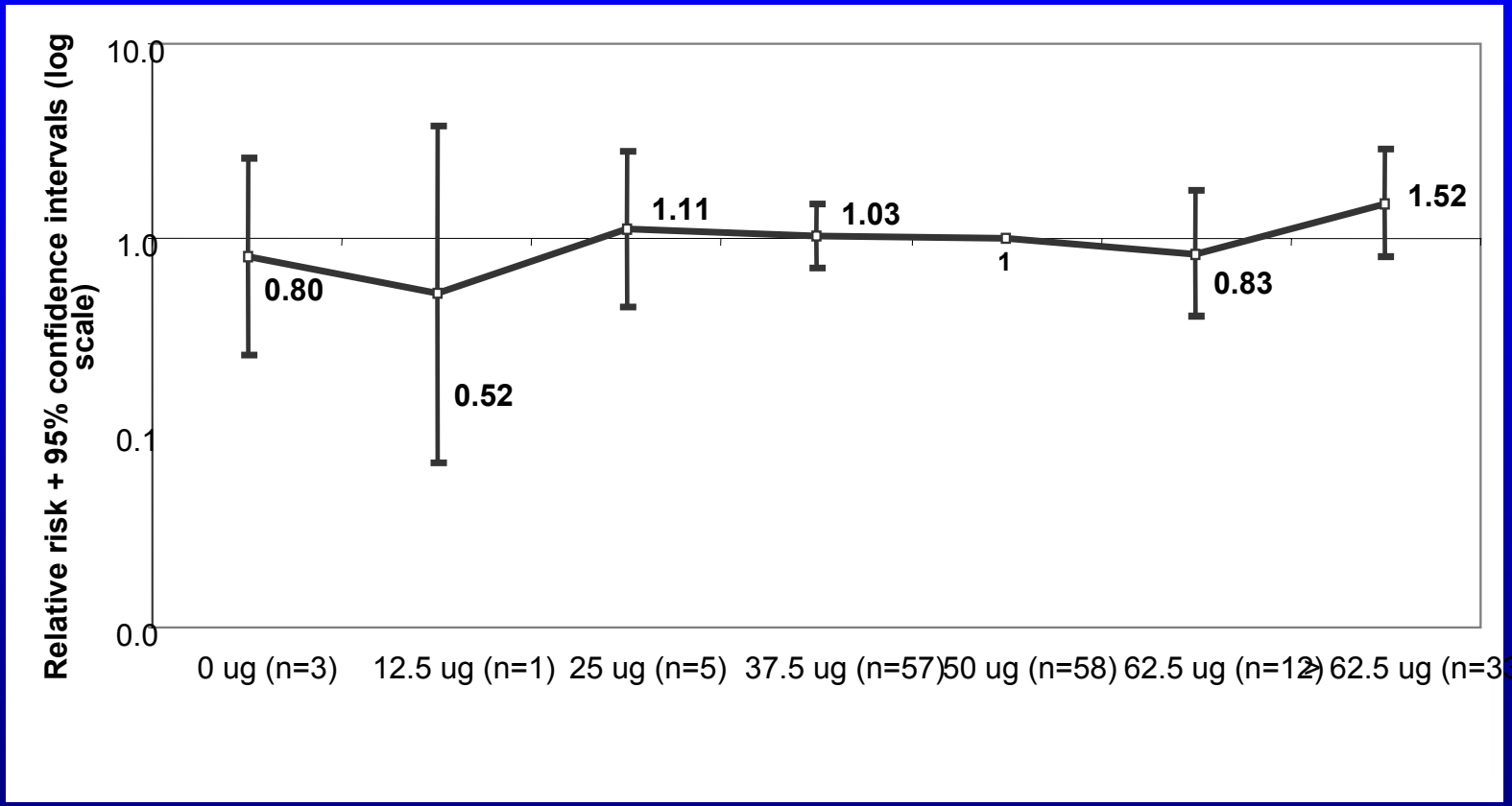
VSD Thimerosal Screening Analysis Preliminary Findings: Autism (n=127) June 2000 (Simpsonwood and ACIP)



Exposure at 3 mo

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

VSD Thimerosal Screening Analysis
Preliminary Findings: Autism (n=150)
July 2001 (IOM)



Exposure at 3 mo

VSD Thimerosal Screening Analysis
Final Results: Autism (n=202)
November 2003

Age at exposure	Cumulative Hg exposure (ug)	RR (95% CI)	P Value
3 months	0-25	1.00	0.40
	37.5-50	1.61(0.77-3.34)	
	>/=62.5	1.38 (0.55-3.48)	
7 months	0-75	1.00	0.58
	87-162.5	0.95 (0.62-1.46)	
	>/=175	0.65 (0.27-1.52)	

Linear trends n.s.

Summary of Main Differences with Different Iterations of Analyses (HMOs A&B)

	Initial 2/2000	ACIP 6/2000	IOM 7/2001	Final 11/2003
Birth years	1992-97	1992-97	1992-98	1992-99
F/U through	1997	1998	1998 - A 1999 - B	2000
Exclusions	Broader	Restricted	Restricted	Restricted
Total eligible pop.	75,540	109,993	130,275	124,170
Autism cases	N=67	N=127	N=150 (B)	N=202 (B)

VSD Thimerosal Screening Analysis: Limitations

- Limitations of data bases
  - Misclassification of outcomes: diagnosis codes
  - Only conditions that come to medical attention
  - Potential medical care utilization bias
- Limitations of results
  - Not consistent between HMOs
  - Not replicated in third HMO
  - Multiple comparisons
  - Low RR estimates (weak associations)
  - Limited ability to control for confounding

Current CDC Studies of Thimerosal and Neurodevlopmental Disorders

1. Follow-up neuropsycholocial testing study of children exposed to different levels of thimerosal as infants
2. Follow-up study of vaccine clinical trial participants
3. Case-control study of thimerosal and autism