

Thimerosal and Autism: Understanding the Controversy

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Thimerosal and autism: understanding the controversy



Vaccines, Autism and Childhood Disorders

Crucial Data That Could
Save Your Child's Life



Neil Z. Miller

bestselling author of
Vaccines: Are They Really Safe and Effective?

Foreword by
Bernard Rimland, PhD
Director, Autism Research Institute

"Neil Z. Miller is one of our greatest chroniclers of the current
issues and controversies in the exciting, offshoot vaccine program."
—Harold E. Holman, MD

<http://www.mothersing.com/> <http://thinktwice.com/vad.htm>

Google vaccines and autism: 165K hits


Autism epidemiology

- Rates higher than 25 years ago
 - Atlanta 4/1000
 - Brick township 7/1000 (Pockets?)
- Diagnostic criteria expanded: 1980, 1984, 1994
- improved identification/reporting
- Average age diagnosis is 3-6 yrs
- Average age 1st concern 18-24 mos
 - Vaccine schedule: 2, 4, 6, 12, 15 mos

Two sources of controversy

- MMR
- Thimerosal - 50% ethylHg
 - DTP 1940, DTaP 1991 (2, 4, 6, 15)
 - Hepatitis B 1986 (birth, 2, 6)
 - Hib available 1987 (2, 4, 6, 12)
 - Influenza 1945 (6 months and Q yr)

Mercury background

- Mercury
 - Organic (methyl and ethyl)  microbes
 - Inorganic (mercuric)
 - Elemental (quicksilver)
- Mercury is globally cycled
- Can of tuna 28mcg methyl Hg
- Known neurotoxin

Mercury background

- **Toxic level?: "normal" = 5-20mcg/L**
 - **Mad as a hatter: 500mcg/L air**
 - **To growing fetus (cord blood):**
 - 216mcg/L Minimata disease
 - 58 mcg/L subtle neurologic changes?
 - **Post-natal subtle CNS disease: ? level????**

Mercury background

- **1997 new EPA MethylHg guideline**
 - Set to avoid toxicity to fetus
 - Oral ingestion of methylHg
 - Assumes daily ingestion months
 - Half life of methylHg of 50days
 - 10 fold safety factor
- **EPA sets at 0.1mcg/kg/day**
- **FDA guideline is 0.4mcg/kg/day**
- **1998 FDA reviews medical Hg use**

Thimerosal background

- **Thimerosal:**
 - preservative since 1930's
 - 50% ethylmercury
- **Vaccines 12.5-25 mcg ethylmercury**
- **Child receiving all possible Hg IMZs:**
 - @ 6mos: 200 mcg (EPA 65-106mcg)
 - @ 2 years: 275 mcg
- **1999 AAP and FDA send letter to manufacturers**

Thimerosal background

- **2001 Hg removed from US vaccines**
 - Except multidose influenza, tetanus booster



- **Still used in developing countries**
 - Preservative in multidose vials
 - Without preservative need:
 - single dose vials
 - cold chain

Ethyl mercury: human PK

- **Human infant data: pilot studies**
 - **Stajich et al, 2000**
 - 15 premature and 5 term infants
 - 72 hrs post 1st hep B (12.5mcg) levels
 - Premature mean 7.4 mcg/L, term 2.2
 - 1 infant <1000g 24mcg
 - **Pichichero et al, 2002:**
 - 40 2-6 month olds
 - level checked at 3-28 days
 - No "abnormal" levels (6, range 3-20)
 - Half-life closer to 7 days (methyl =50)



**Thimerosal and autism:
does epidemiology
support causation?**

How to test this hypothesis?

- **Double blind randomized placebo controlled trial (0)**
 - What sample size needed ($p=.05$, power $.8$)?
 - Increase from 3/1000 to 4/1000: > 100K
 - Increase of 1/million: > 1 billion
- **Retrospective cohort study**
 - VAERS database (3)
 - Gradation of thimerosal exposure (4)
- **Ecological study**
 - Track change in incidence as use of thimerosal changes (6)

VAERS database cohort studies

- § **Geier MR, Geier DA.** Neurodevelopmental disorders after thimerosal-containing vaccines: a brief communication. *Exp Biol Med (Maywood)* 2003;228(6):660-664.
- § **Geier DA, Geier MR.** Thimerosal in childhood vaccines, neurodevelopmental disorders, and heart disease in the United States. *Journal of American Physicians and Surgeons* 2003;8:6-11.
- § **Geier DA, Geier MR.** An assessment of the impact of thimerosal on childhood neurodevelopmental disorders. *Pediatr Rehabil* 2003;6(2):97-102.

Geier papers: cohort data

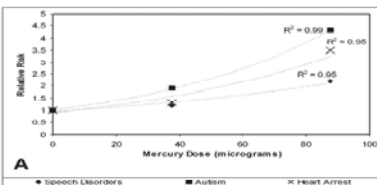
- **VAERS database**
 - Thimerosal exposed 1992-2000
 - No thimerosal 1997-2000
 - Extracted diagnoses of:
 - Autism, speech disorder, mental retardation, heart arrest
 - Control example: fever
- **Vaccines administered in US by manufacturer per CDC**

Geier papers: results/conclusions

- **Autism (8 vs 1, RR6), speech disorder (26 vs 4, RR2.2), mental retardation (37 vs 2, RR6), heart arrest (RR4)**
- **All statistically significant ($p<.05$, no CI given)**
- **Children receiving additional 75mcg at added risk**

Geier papers: conclusions

- **Data points follow exponential distribution**
- **OR of autism increased by .012 per mcg of mercury**



Geier DA, Geier MR. JAPS 2003;8:6-11.

Cases (exposed and not exposed) Not cases (exposed and not exposed)

- **Denominator**
 - Is distributed doses, not administered
 - Multidose schedule-- # of children?
 - How calculated 37.5 vs 87.5 mcg?
 - Not all cases captured

- Cases (exposed and not exposed)**
Not cases (exposed and not exposed)
- **VAERS database**
 - Passive reporting
 - Underreporting and incomplete reporting
 - Media bias
 - **Thimerosal exposure not known**
 - **Diagnoses not validated**
 - Diagnostic overlap
 - Autism young (1.7+/- 1.1)
 - **If one child misclassified or not reported, OR becomes insignificant**

- Other cohort studies**
- § **Verstraeten T**, Davis RL, DeStefano F, Lieu TA, Rhodes PH, Black SB, et al. Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases. *Pediatrics* 2003;112(5):1039-1048.
 - § **Hviid A**, Stellfeld M, Wohlfahrt J, Melbye M. Association between thimerosal-containing vaccine and autism. *JAMA* 2003;290(13):1763-1766.
 - § **Andrews N**, Miller E, Grant A, Stowe J, Osborne V, Taylor B. Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United Kingdom does not support a causal association. 2004.
 - § **Heron J**, Golding J, ALSPAC study team. Thiomersal exposure in infants and developmental disorders: a prospective cohort study does not support a causal association. 2004.

- Cohort studies (4)**
- **Verstraeten: USA, VSD database**
 - 140,887 in 3 HMOs
 - Evaluated speech delay, tics, ADD
 - Autism only at HMO B: no association (.96, .62-1.46)
 - Associations found were not consistent
 - HMO A: thim @ 3 mos and ticks - (1.89, 1.05-3.38)
 - HMO B: thim @ 3 mos and SD - (1.87, 1.08-3.23)

- Cohort studies, cont**
- **Andrews: UK, GPRD**
 - 100,572 children
 - Hazards ratio to Hg exposure
 - Association with tics (1.3, 1.06-1.69)
 - **Heron: UK, ALSPAC**
 - Data: prospective development survey
 - 12,810 children/parent pairs
 - Association: prosocial behavior
 - **Negative associations also found**

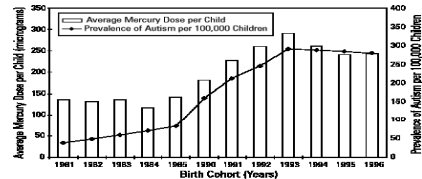
- Cohort example:**
- **Hviid: Denmark, Ntl registries**
 - 467,450 children, 1.9 million person-years
 - Thimerosal discontinued 1992
 - 125 mcg
 - Children born 1990-96 linked to vaccine and psych registry
 - **Results:**
 - Risk ratio for autism 0.85 (0.6-1.2)
 - **Other NDDs not investigated**

- Cohort studies: problems**
- **Diagnostic accuracy**
 - Verstraeten: ADD 28%, autism 92%
 - Andrews: 90% of ticks "transient"
 - **Thimerosal doses/schedules differ**
 - UK 75, Denmark 125, USA 275 mcgHg
 - **Limitations of cohort study**
 - Used best to quantify risk, not to prove its absence

Ecological studies supporting association

- § Geier DA, Geier MR. Thimerosal in childhood vaccines, neurodevelopmental disorders, and heart disease in the United States. *Journal of American Physicians and Surgeons* 2003;8(2):97-102.
- § Geier DA, Geier MR. An assessment of the impact of thimerosal on childhood neurodevelopmental disorders. *Pediatr Rehabil* 2003;6(2):97-102.
- § Geier DA, Geier MR. A comparative evaluation of the effects of MMR immunization and mercury doses from thimerosal-containing childhood vaccines on the population prevalence of autism. *Med Sci Monit* 2004;10(3):P133-P139.

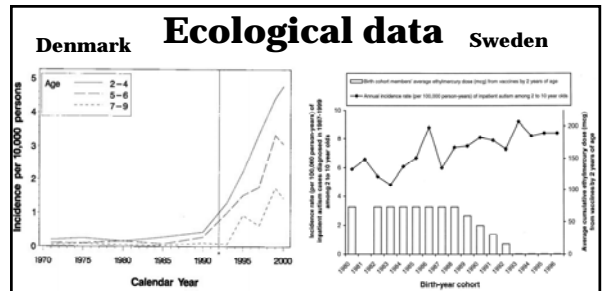
- Autism prevalence: children enrolled in USDE/# in birth cohort
 - USDE with autism: age 16 = 3.8K, age 6 = 11K
- Mercury dose: mcg Hg distributed in vaccines/ # in birth cohort
 - Calculated total Hg dose: 131-291mcg per child
 - Max in 1st 2 years is 275mcg; in 1st year is 200mcg



Geier DA, Geier MR. *Med Sci Monit* 2004;10(3):133-39

Ecological studies against an association

- § Stehr-Green P, Tull P, Stellfeld M, Mortenson PB, Simpson D. Autism and thimerosal-containing vaccines: lack of consistent evidence for an association. *Am J Prev Med* 2003;25(2):101-106.
- § Madsen K, Lauritsen M, Pedersen C, Thorsen P, Plesner A, Andersen P, et al. Thimerosal and the occurrence of autism? Negative ecological evidence from Danish population-based data. *Pediatrics* 2003;112(3):604-606.



Madsen et al, *Peds* 2003

Stehr-Green et al, *AJPM* 2003

- Thimerosal discontinued 1992
- Health system records excellent

Conclusions

- Half-life of ethylHg likely shorter than methylHg
- Hg blood levels post vaccination are not in known toxic range
- Well designed epidemiologic studies do not support an association between thimerosal and autism

Conclusions

- Consistency between well designed studies lends strength to their individual conclusions
- Thimerosal need not be removed in countries of current use
- Autism is increasing; research dollars should be directed toward areas of more promise

A word about cohort studies

- **"Epidemiology cannot exclude a rare event" can be twisted into "1/million risk"**
- **For parents, 1/million is too much for an act of commission, especially when the diseases are perceived as "gone"**

Practical advice

- **Clarify that risk is not 1/million; we have no good reason to believe that thimerosal causes autism**
- **Dispel myths that:**
 - **VPDs diseases are gone**
 - **VPDs are harmless**
 - **herd immunity is enough**
 - **alternate schedule is as protective or safe**

Thank You.

