DUKE UNIVERSITY SCHOOL OF MEDICINE

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OHRP

U.S. Department of Health and Human Services
Office for Human Research Protections

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Crossing the Line: What is Acceptable Risk?

D6: The Case of Thimerosal & Autism

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Vaccine Risks: The Case of Thimerosal and Autism

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Vaccines: 1955

- The year of the Salk Vaccine
- Release followed by 97% reduction of polio over next few years
- Triumphant moment for science– and the public

Vaccines: 2006

Vaccines in an Age of Anxiety

- Fading memory of vaccine-preventable diseases
- Rising fear of “modern“ risks
  - Food: Bacteria, toxins, genetically-modified
  - Autos: Airbags
  - Lead based paint
  - Silicon breast implants
- Result: Increasing preoccupation with vaccine safety

The Case of Thimerosal

- Water soluble powder
- Used as vaccine preservative since 1931
- Metabolized to thiosalicylate and ethylmercury

Origins of a Controversy

- 1990s: Two Conflicting Trends
  - New vaccines against 4 diseases (entailing 10-12 injections), some containing thimerosal
  - EPA lowers guidelines on safe organomercury exposure (based on fish)
- 1997-99: FDA Review: Thimerosal in vaccines in some infants exceed EPA's guidelines

The CDC/AAP Joint Statement: July 7, 1999

- "Thimerosal containing vaccines should be removed as soon as possible"
- FDA to expedite process via requesting manufacturer plans, expediting review
- Recommended temporary delay in Hepatitis B vaccine series until age 6 months
  - One of the 3 vaccine series in 1st 6 months
  - Chosen because of flexibility in schedule

Reactions

- Public: Autism and Anti-Vaccine Communities
  - Demanded immediate discontinuation of thimerosal
  - Asserted mercury in vaccines responsible for rise in autism
- Vaccinologists:
  - Saw Joint Statement as over-reaction
  - Feared disruption in Hep B vaccine program

"The policy to delay Hepatitis B immunization in infants was flawed because it elevated a theoretical risk above an actual risk"

Paul Offit, MD

Children's Hospital of Philadelphia

One Controversy, Three Notions of Risk

- Actual Risk: History of thimerosal and vaccines
- Theoretical Risk: History of organomercury poisoning
- Perceived Risk: History of public perception of “mercury poisoning”

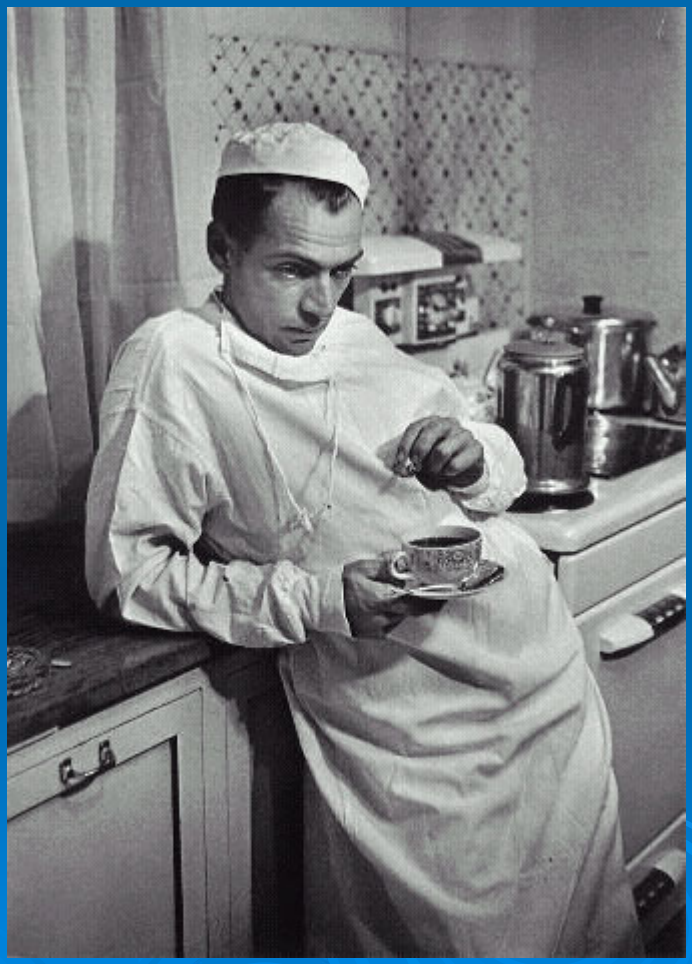
Thimerosal and Vaccines

Why was compound containing mercury introduced in vaccines?

How well was it assessed?

Background: The Problem of Vaccine Contamination

- Conditions for childhood vaccination in early 1900s: less than ideal
- Multi-dose vials
- Difficulties of maintaining hygienic technique



Major Contamination Incidents

- Columbia, SC, 1916: 26 typhoid vaccine recipents developed Staph abscesses; 4 deaths
- Queensland, Australia, 1928: 12 children dying with multiple abscesses following diphtheria immunization

Killing Bacteria before Antibiotics

- Various chemical compounds used as disinfectants, germicides, and preservatives
- Best known: Joseph Lister's carbolic acid (phenol)
- Mercury compounds also popular
  - Inorganic mercury: used as surgical scrub
  - Questionable efficacy; caused skin irritation
  - Succeeded by organomercurials after 1920

Eli Lilly and Co.: The Synthesis of Thimerosal

- Ethylmercury bound to thiosalycylate
- Patented 1928 (Trade name Merthiolate)
- 40-50x as effective in lab as phenol
- Large doses tolerated in animals

Clinical Studies

- First (and only) therapy trials: 1929 Indianapolis meningococcal epidemic
  - Not curative
  - But high doses tolerated without apparent harm
- Lilly decided to promote as preservative rather than therapy
  - Antisera, plasma, etc
  - Vaccines!

Thimerosal Enters Vaccines

- Studies at Lilly suggested effective as vaccine preservative at low (1:1000) concentrations
- Advantage over other preservatives: No adverse effect on antigenicity
- By 1940 was becoming one of Lilly's most lucrative products-- and popular vaccine preservative

The Honeymoon Ends

- AMA Council on Pharmacy: Report on organomercurials, 1948:

  "*A field in which wishful thinking is dangerous*"

Doubts about Efficacy

- Many studies in 1940s specifically challenged Lilly's in vitro efficacy data on thimerosal
- After 1980, several clusters of Strep infection linked to thimerosal-containing DTP reported
- Yet, in testing for regulatory approval, thimerosal still performed better than alternatives

First Safety Concerns

- 1960s:
  - Greater awareness of dangers of organic mercury poisoning via pollutants
- 1970s
  - Case reports of neurotoxicity from ethylmercury in large doses
  - No reports of danger at low doses.. beyond hypersensitivity

A Regulatory "No Man's Land"

- FDA's powers expanded gradually
  - 1939: Assess safety of new products
  - 1961: Assess efficacy of new products
  - Late 1960s: Assess older products
- Division of Biologics Standards (regulating vaccines) outside of FDA until 1972
- By this point, 180 products contained thimerosal…

FDA and Thimerosal after 1972

- 1974 Memo on Vaccines: Notes mercury exposure far below toxic thresholds
- 1977: Proposed rules on Skin Tests
  - Section on thimerosal notes poor efficacy data and hypersensitivity risk
  - Recommends alternatives
- 1982: Proposed rules: Mercurials in OTC products
  - Similar recommendations

Summary: Thimerosal 1930-90

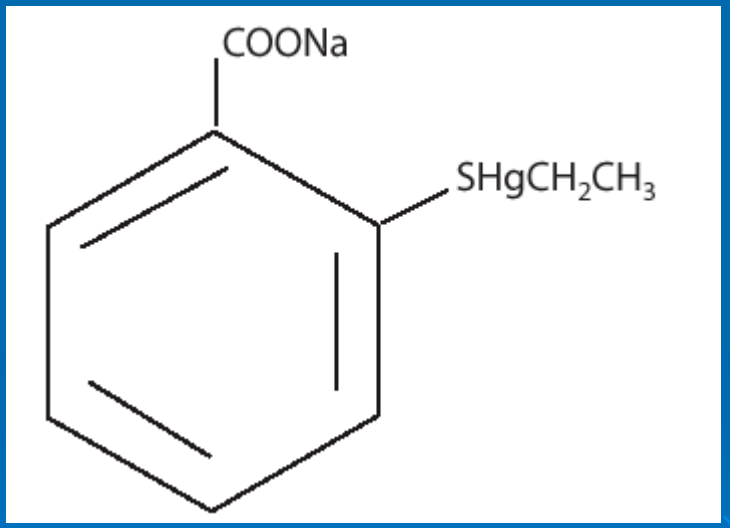
- Efficacy:
  - Defended as preservative by companies based on experience, internal data
  - But: Published laboratory data and independent evaluations often critical
- Safety:
  - Low doses (ie, vaccines) assumed to be harmless except possible hypersensitivity
  - But: no effort to assess small infants

Environmental Mercury Poisoning

How did understanding of mercury's effects on fetus and infant evolve?

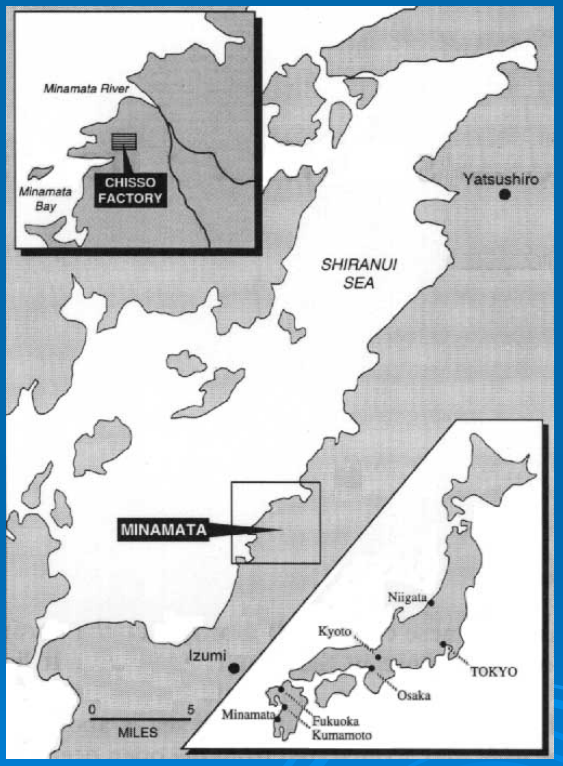
Methylmercury

- Chief form of environmental mercury
- Differs from ethylmercury by one extra carbon atom
- Analogous to ethylmercury– or not?
- Either way, most knowledge of organic mercury poisoning relates to methylmercury



Minamata Bay, Japan: 1955

- Fishing community on bay dominated by Chisso chemical plant
- Strange illness first struck fish, birds and cats in 1955, then humans
- Eventually shown to be methylmercury poisoning



Minamata Disease

Minamata Disease: Legacy

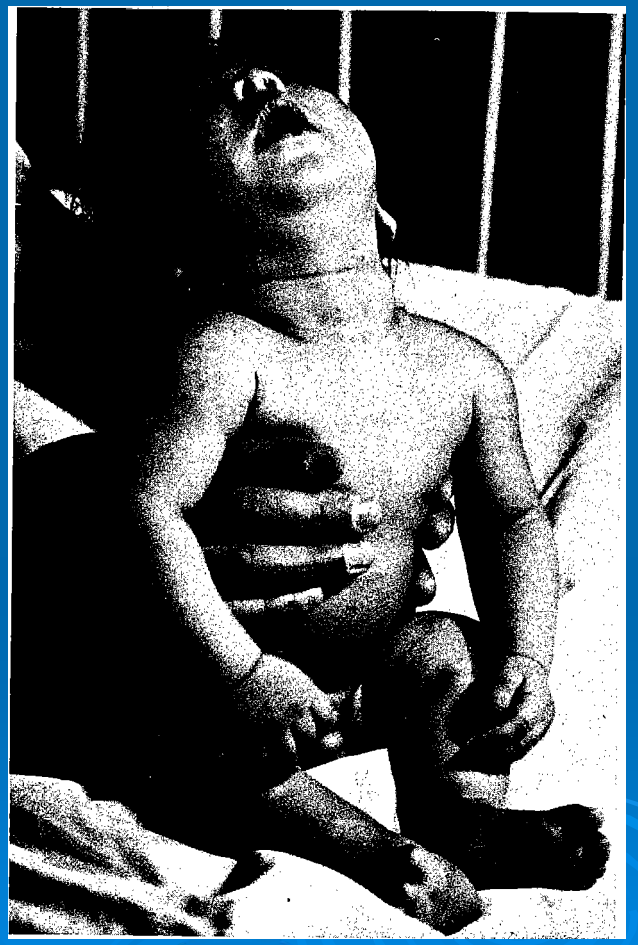
- Widely publicized in U.S. through documentary photography of W. Eugene Smith
- “Mercury poisoning” became symbol of industrial pollution and corporate greed
- Soon became concern in U.S. as studies revealed methylmercury concentrated up the food chain…

Iraq: 1972

- Source: Homemade bread contaminated by methylmercury fungicide
- Worst mercury poisoning incident in history
  - 6350 hospitalizatons
  - 459 hospital deaths
- Allowed intensive study and follow-up
- Basis for FDA calculation of acceptable daily intake in adults: 0.4 mcg/kg/day

Congenital Methylmercury Poisoning

- Described in Japan and Iraq
- Fetus more sensitive than mother
- Classic Syndrome:
  - Cerebral palsy
  - Mental retardation
  - Deaf and blind
- More subtle delays: recognized by 1980s



1990s: Two Prospective Studies

- Seychelles Islands:
  - Hg Exposure: 12 meals/week
  - Outcome: Global IQ
  - Conclusion: No effect
- Faroe Islands
  - Hg Exposures: 1-3 dinners/week, pilot whale
  - Outcome: Domain specific
  - Conclusion: language and developmental delays

Methylmercury Exposure Reference Values

Agency	Value (mcg/kg/day)	Coments
FDA (Acceptable Daily Intake)	0.4	Iraqi data, adults, 1970s
EPA (Reference Dose)	0.1	Fetus; Faroes data, 1995
ATSDR (Minimal Risk Level	0.3	Fetus: Seychelles Data, 1999

Methylmercury and the Fetus: State of knowledge in 1999

- Fetus is more sensitive than adult
- A spectrum of effects (analogous to lead)
  - Classic syndrome at high exposures
  - Subtle cognitive effects may occur at low exposures
- Many uncertainties
  - Effects of bolus vs more steady exposures
  - Analogy of methyl- versus ethyl-Hg

The FDA Investigation: 1997-99

- 1997: FDA Modernization Act includes provision to assess Hg exposure in all products, including vaccines
- 1999: FDA Team calculates minority of infants might receive 187.5 mcg Hg, exceeding EPA standard
- Series of discussions in Spring 1999, leading to Joint Statement, involving
  - American Academy of Pediatrics
  - Centers for Disease Control

The Context: Maintaining Public Trust in Vaccines

- CDC Perspective:
  - No actual evidence of harm
  - Importance of avoiding over-reaction and possibly derailing vaccine program
- AAP Perspective
  - Risk theoretical, but plausible
  - Overriding concern: public trust in vaccine system

The Rebirth of Anti-Vaccinationsim

- Pertussis Vaccine Controversy: 1974-85
  - Pertussis epidemics in UK, Japan
  - Litigation crisis and vaccine shortages in US
- Legacy
  - Vaccine injury compensation legislation in US
  - Parental “Vaccine Safety” Advocacy Groups
    - Ideology: suspicious of “experts,” public health, drug companies
    - Mobilization via internet, 1990s

Perceived Risk

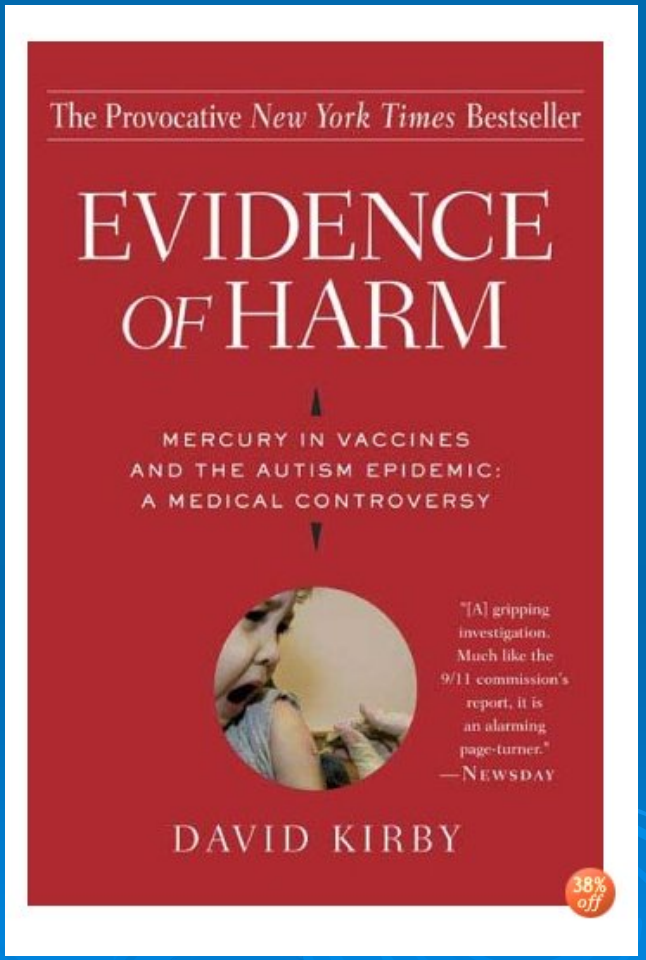
From Mercury to Autism (?)

Why Autism?

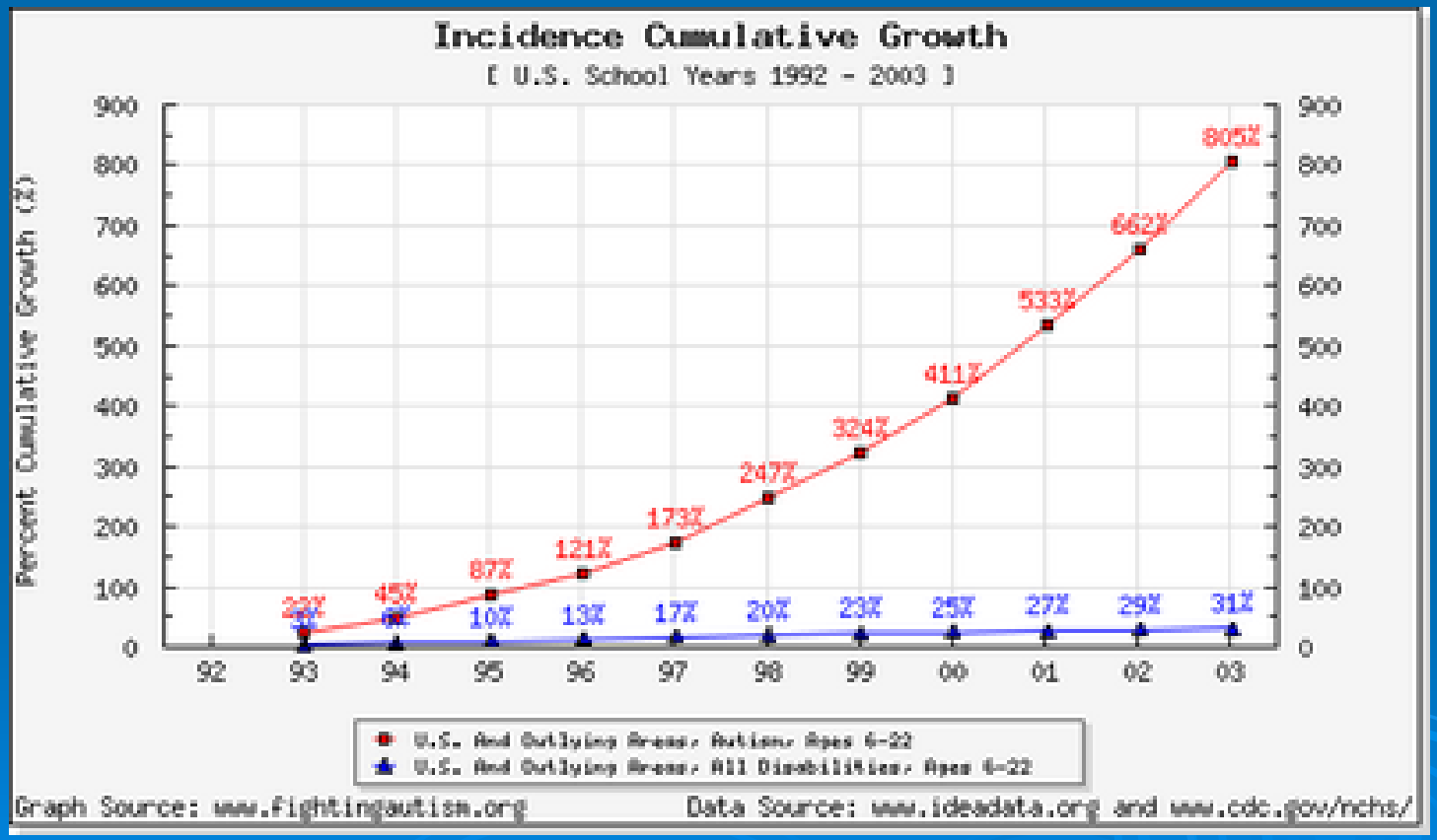
- Prior to Joint Statement, debate concerned whether thimerosal in vaccines might be linked to subtle neurological deficits (language, attention, memory)
- After Joint Statement: debate shifted to whether thimerosal caused autism
- Autism had never been described in 40-yr-old literature on congenital Hg poisoning
- What happened???

Re-framing the controversy

- Not the “anti-vaccine” groups
- But activists from the autism community



Background: An epidemic of autism?



Interpreting the “rise” of autism

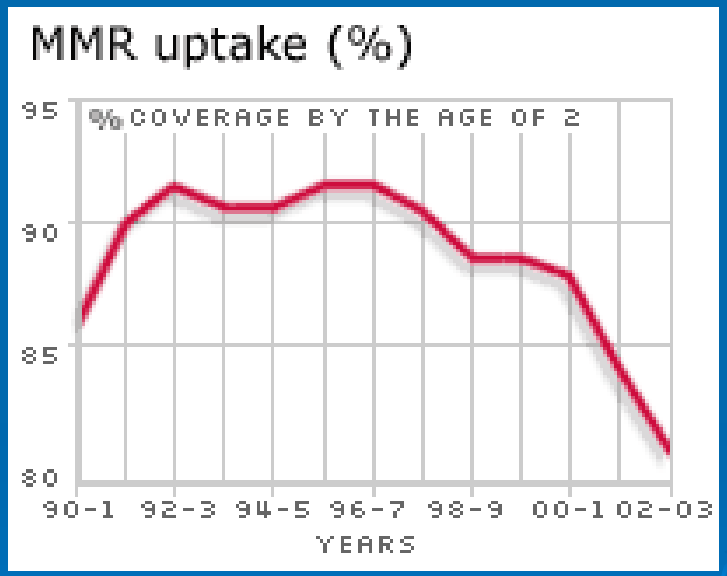
- “Mainline” autism researchers and organizations
  - Vast majority believe that expanded definition, detection explain most if not all of the trend
- “Alternative” explanations
  - But many disaffected parents reject this
  - See long lines for services, etc, as direct evidence of an “epidemic”
  - Implicate environmental cause…

Suspects in the “autism epidemic”

- Food allergy or intolerance: leading to intestinal damage, damage, and toxins affecting brain
- Environmental toxins: ie, PCBs, pollutants
- Immunological
- Vaccines!

Connecting vaccines to autism

- 1998: Lancet study describing several cases of autism following MMR
- Followed by decline in vaccination rates in UK
- Picked up by US vaccine-safety and autism parent groups

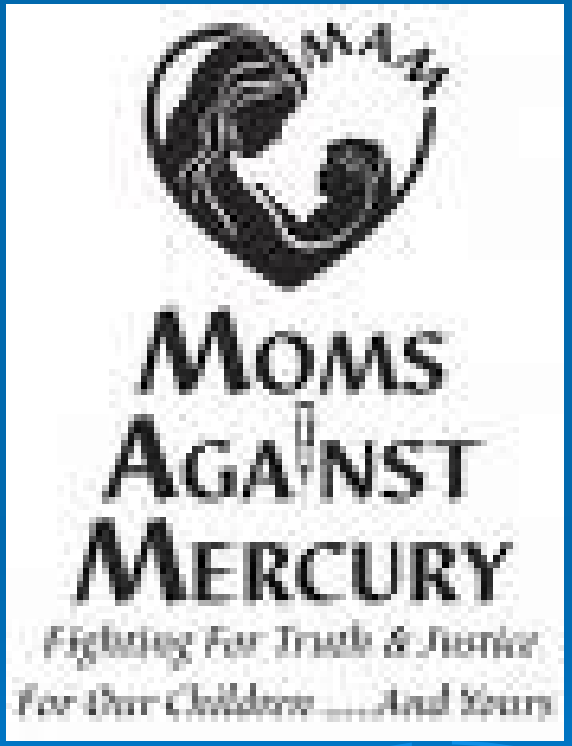


1999: A Gathering Storm

- February: Release of California DSS data documenting rise in autism cases
- MMR/Autism controversy getting headlines in US papers
- Congressman Dan Burton announces hearings on vaccines and autism
- July 9: CDC/AAP Joint Statement on Thimerosal

Linking Thimerosal and Autism: The "Mercury Moms"

- Members of "alternative autism" community
- Interpreted Joint Statement as admission of guilt
- Library research:
- Organized SafeMinds



The Story Since 1999

Politics and Polarization

Phasing Out Thimerosal

- Hepatitis B Vaccine
  - Aug 27, 1999: FDA approved thimerosal-free by Merck
  - October 1999: suspension of newborn Hep B vaccine lifted
  - December 1999: sufficient supply for all newborns in US
- By 2003, all vaccines given to infants in first 6 months free of thimerosal

Independent Evaluations

- Two IOM panels
- Conclusion of 2004 Panel: No evidence that thimerosal in vaccines led to harm
- New findings:
  - Laboratory: Ethylmercury shown to be cleared from blood faster than methylmercury
  - Epidemiological: Studies tracking autism in Scandinavian countries (who removed thimerosal in early 1990s) showed same trend as in US

Consequences on Hepatitis B Vaccine Program

- More than 90% of hospitals suspended use of thimerosal-containing vaccine for infants born to HBV negative mothers
- But contrary to guidelines, proportion of hospitals failing to vaccinate infants born to seropositive mothers rose from 1% to 7%
- Worrisome given that 90% of infants infected at birth will develop chronic HBV infection, 25% will die of liver disease as adults

Was the Joint Statement therefore wrong?

- Despite the real (though unintended) consequences for HBV vaccine coverage in newborns, this conclusion is too simplistic
- It ignores or distorts crucial aspects of the history of thimerosal and mercury…

The actual risks and benefits of thimerosal were uncertain in 1999

- True: no direct “evidence of harm”
- But no real efforts to assess safety in young infants prior to 1999
- And long history of concerns regarding efficacy as a preservative

Concerns about risks of mercury on infants were more than “theoretical”

- True: the variation between guidelines re: what constituted “safe” Hg exposure gave impression of arbitrariness
- But vaccinologists tended to miss the growing consensus that low dose Hg exposure was dangerous to infants
- Issue was taken very serious by environmental scientists

There was real potential for a major vaccine revolt in 1999

- Key points:
  - Sinister connotations for public of “mercury”
  - Existence of federal guidelines and expert opinion (among environmental scientists) affirming risk of mercury for young infants
  - It was neither possible nor ethically justifiable to withhold these concerns from the public

What Didn't Happen

- Despite the controversy– immunization rates in the U.S. have overall remained at record-high levels
- Contrast with Britain:
  - 1970s Whooping Cough epidemics
  - Recent MMR controversy
  - In both cases, controversy fueled by disagreements between "experts"
- The US has in fact maintained public trust in its vaccine system

What Next?

- Thimerosal has become problematic for many parents in any context
  - Even a single flu shot
- Still more problematic– what are the implications of the new reliance on preservative-free, single dose vials for global vaccination?

Appendix

History of Autism

Autism: A **Very** Brief History

- Hopkins child psychiatrist Leo Kanner described 11 children (1943)
- Key feature: profound "inability to relate"
  Language: literal, repetitive, devoid of meaning
- "Savant" skills
- Obsession with "sameness"

Changes in Definition

- 1950s: Kanner's "classic" syndrome
  - Profound "aloneness", obsession with sameness
  - Understood as psychogenic in origin: "Refrigerator mothers"
- 1970s: Neurodevelopmental model
  - Cause: Early abnormality in brain development
  - Genetics, not parental aloofness, the cause
- 1980-90s: "Autistic Spectrum"
  - "Infantile autism": Severe cognitive delay
  - "Higher functioning (ie, Asperger Syndrome)

Popularizing the Diagnosis

- Since 1970s, autism researchers have emphasized education and rehabilitation as key interventions
- Increasing drive to detect and treat early
  - Use of early developmental screening and autism checklists
  - 1991: Individual with Disabilities Education Act—made autism a category eligible for services