Risk Assessment of Thimerosal in Childhood Vaccines

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IOM Workshop July 16, 2001
Objectives

• Background
• Review CBER’s risk assessment of thimerosal in childhood vaccines 1998-1999
  – Preceding risk management decisions
  – Qualitative not quantitative
• Uncertainties/Research gaps
Background: AAP/USPHS Joint Statement June 7, 1999

“...The recognition that some children could be exposed to a cumulative level of mercury over the first six months of life that exceeds one of the federal guidelines on methyl mercury now requires a weighing of two different types of risks when vaccinating infants... [T]he Public Health Service, the American Academy of Pediatrics, and vaccine manufacturers agree that thimerosal-containing vaccines should be removed as soon as possible...”
Background: AAP/USPHS Joint Statement June 7, 1999 (cont’d)

Key Actions

• Formal request to manufacturers
• Public workshop
• Expedited FDA review of manufacturers’ supplements
• Risk communication
• Monitoring immunization practices, coverage, and vaccine-preventable disease levels
• Studies to better understand risks and benefits of this safety assessment
Background

• General concern over health effects of human exposure to mercury
  – EPA: *Mercury Study Report to Congress 12/97*
  – ATSDR: *Toxicological Profile for Mercury 3/99*
  – FDA: *FDAMA* 1997

• Increase in number of vaccines recommended for routine use in infants
  – Potential increased exposure of infants to mercury from thimerosal in vaccines

*Food and Drug Administration Modernization Act*
FDAMA 1997: Study of Mercury Compounds in Drugs and Food*

a. List and Analysis
   – Manufacturer call-for-data 12/98, 4/99
   – Federal Register 11/19/99
b. Study the effect of Hg in nasal sprays
c. Study of Mercury Sales
   – Adverse effects on health of children and other sensitive populations resulting from exposure to, or ingestion or inhalation of, Hg

*[21 USC 393 Sec. 413]*
# Recommended Childhood Immunization Schedule: 1988

<table>
<thead>
<tr>
<th>Age Vaccine</th>
<th>2 mos</th>
<th>4 mos</th>
<th>6 mos</th>
<th>15 mos</th>
<th>18 mos</th>
<th>4-6 yrs</th>
<th>14-16 yrs</th>
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<tbody>
<tr>
<td>Diphtheria, Tetanus, Pertussis</td>
<td>DTP</td>
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<td>Oral polio vaccine</td>
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<td>Measles, Mumps, Rubella</td>
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<td>MMR</td>
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<tr>
<td>H. influenzae type b</td>
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<td>Hib (PRP-D)</td>
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</tbody>
</table>

*1988 AAP Committee on Infectious Diseases (Red Book)*
### Recommended Childhood Immunization Schedule
#### United States, January - December 1999

Vaccines are listed under routinely recommended ages. Bars indicate range of recommended ages for immunization. Any dose not given at the recommended age should be given as a "catch-up" immunization at any subsequent visit when indicated and feasible. Ovals indicate vaccines to be given if previously recommended doses were missed or given earlier than the recommended minimum age.

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccine</th>
<th>Birth</th>
<th>1 mo</th>
<th>2 mos</th>
<th>4 mos</th>
<th>6 mos</th>
<th>12 mos</th>
<th>15 mos</th>
<th>18 mos</th>
<th>4-6 yrs</th>
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<td>Polio</td>
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Approved by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP).
Preservatives in Vaccines: Regulations*

- “Products in multi-dose containers shall contain a preservative” with certain exceptions
- “... shall be sufficiently non-toxic so that the amount present in the recommended dose of the product will not be toxic to the recipient…”

*[21 CFR: 610.15 (a)]
Preservatives in Vaccines: U.S. Pharmacopeia*

Antimicrobial preservatives are:
- Used mainly in multi-dose containers to inhibit the growth of microorganisms that may be introduced inadvertently during or subsequent to the manufacturing process.
- Should not be used solely to reduce the viable microbial count as a substitute for good manufacturing practice."

*[USP XXII, pp. 1478 - 79]*
Thimerosal Risk Assessment

• Hazard identification
  – Relevant biologic and chemical info
  – Published literature
  – VAERS Reports

• Dose-response assessment
  – Attempt to quantify dosage
  – Comparison with methylmercury

• Exposure assessment
  – Magnitude, duration, and route of exposure

• Risk characterization
  – Integration of above with estimate of risk to public health
  – Define areas of uncertainty

Hazard Identification: Thimerosal

- Thimerosal (Merthiolate®-Lilly; Thiomersal) first marketed in 1930 and promoted as preservative
- 49.6% Hg by weight
- Metabolized to ethylmercury and thiosalicylate
- 1976 CBER review and risk assessment (memo)
  - Use evaluated in adults
  - Conclusion: No harmful effects at doses received during lifetime
Thimerosal

C$_9$H$_9$NaO$_2$S, mol. wt. = 404.81

Also called:
• Ethyl[2-mercaptobenzoato(2-)-O,S]-mercurate(1-) sodium
• Ethyl (sodium o-mercaptobenzoato)mercury
• Sodium ethylmercurithiosalicylate
• Thiomersal
• Merfamin
• Merthiolate
• Mertorgan
• Merzonin
Hazard Identification: Animal Studies of Thimerosal

• Powell 1931
  – Adult rabbits, rats, mice, dogs and guinea pigs
  – Single doses of 15 mg/kg to 300 mg/kg IV, IP; Observed 7d
  – Max tolerated doses 20 mg TM/kg (rabbits); 45 mg/kg (rats)
  – Histopathology on brain not reported

• Mason 1971
  – Adult rats
  – Dosing twice weekly, ~ 8.6 to 286µg TM/kg/day SQ for 12 mo; sacrificed at 12, 18 mo
  – No histopathology performed on brain/kidney

• Blair 1975
  – Adult squirrel monkeys
  – ~1 and 6 µg TM/kg/day Intranasally for ~190 days
  – No histopathological changes observed in brain or kidney
  – For high dose only, mercury concentrations in brain significantly raised over control
# Hazard Identification: Thimerosal in Humans (High Doses)

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Description</th>
<th>N</th>
<th>Dose Hg</th>
<th>Toxicity</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powell 1931</td>
<td>Therapeutic use</td>
<td>22</td>
<td>Max 26.7 mg Hg/kg</td>
<td>Phlebitis</td>
<td>No clinical toxicity/1-62 d</td>
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<tr>
<td>Kinsella 1941</td>
<td>Tx endocarditis</td>
<td>9</td>
<td>unknown</td>
<td>Unspecified Hg poisoning in 1</td>
<td>Autopsy</td>
</tr>
<tr>
<td>Axton 1972</td>
<td>Antibiotic with TM at 1000x</td>
<td>6</td>
<td>21-105 mg Hg/kg</td>
<td>Local necrosis, ARF, DIC</td>
<td>Death 5/6</td>
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<tr>
<td>Fagan 1977</td>
<td>Topical Tx omphaloceles</td>
<td>6</td>
<td>unspecified</td>
<td>High Hg levels in tissues</td>
<td>Death due to unspecified causes</td>
</tr>
<tr>
<td>Matheson 1980</td>
<td>Replacement IG</td>
<td>1</td>
<td>Chronic use for 15 yrs</td>
<td>Acrodynia</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Rohyans 1984</td>
<td>Irrigation of tymp tube in 18 mo</td>
<td>1</td>
<td>58 mg Hg/kg</td>
<td>Renal/hep/cardiac failure/coma</td>
<td>Death</td>
</tr>
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<td>Lowell 1996</td>
<td>HBIG after liver transplant</td>
<td>1</td>
<td>0.17 mg Hg/kg</td>
<td>BL 0.104 µg/L</td>
<td>Recovery</td>
</tr>
<tr>
<td>Pfab 1996</td>
<td>Suicide attempt</td>
<td>1</td>
<td>41.5 mg Hg/kg</td>
<td>Gastritis, coma, resp failure,</td>
<td>Recovery</td>
</tr>
</tbody>
</table>
Hazard Identification

Thimerosal in Humans: Low dose

• Delayed-type local hypersensitivity reactions
  – Thiosalicylate vs. ethyl mercury as major determinant
  – Clinical significance controversial
Hazard identification: VAERS Reports

- Passive surveillance system
- Useful for
  - Detecting unrecognized adverse events
  - Monitoring known reactions
  - Identifying possible risk factors
  - Vaccine lot surveillance
- Limitations include
  - Reported diagnoses are not verified
  - Lack of consistent diagnostic criteria
  - Wide range in data quality
  - Underreporting
  - Inadequate denominator data
  - No unvaccinated control group
  - Usually not possible to assess whether a vaccine caused the reported adverse event
Hazard identification: VAERS Reports

• In July 1998 (1990-1998) queried symptom and comment text fields for thimerosal, thiomersal, merthiolate, and mercury
• 45 reports of ~90,000 total reports 1990-1998 alleging adverse reactions due to thimerosal
  – Vaccines
    • Hep B (28), Influenza (10), Td (3), DTaP (1), DTP-Hib (1), DTP + Hib (1), Hib (1)
  – Reports
    • Injection site reactions (13), rash (9), urticaria* (7), edema (5), flu like syndrome and joint aches (4) with 1 report each of anaphylaxis, “severe allergic reaction”, urticaria and wheezing (1), stridor, and malaise/agitation and reaction not specified (2)
Dose-Response Assessment

• Quantitative dose-response of thimerosal not possible due to lack of data
  – No exposure guidelines for thimerosal or ethylmercury

• Use of methylmercury exposure guidelines
Assumptions

• Toxicity of ethylmercury is similar to methylmercury
• Similar toxicokinetics
• Guidelines developed for chronic exposure are applicable to shorter time periods
• Toxicity of mercury in infants is similar to that of the fetus
Methylmercury toxicity

• Animal data
  – Methylmercury
  – Methyl vs. ethylmercury
    • Magos 1985

• Human data
  – Infants born to women who ingested high concentrations of methylmercury exhibited CNS effects
    • Minamata Bay, Japan
    • Iraq
  – Population-based studies
    • Seychelle Islands
    • Faroe Islands
    • Others
Guidelines for Methylmercury Exposure

<table>
<thead>
<tr>
<th>Agency</th>
<th>Exposure guideline</th>
<th>Terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPA</td>
<td>0.1 µg/kgbw/day</td>
<td>RfD</td>
</tr>
<tr>
<td>ATSDR</td>
<td>0.3 µg/kgbw/day</td>
<td>MRL</td>
</tr>
<tr>
<td>FDA</td>
<td>0.4 µg/kgbw/day</td>
<td>ADI</td>
</tr>
<tr>
<td>WHO</td>
<td>3.3 µg/kgbw/week</td>
<td>PTWI</td>
</tr>
</tbody>
</table>
Exposure Assessment

Maximum Exposure to Hg From Vaccines in U.S. Infants ≤ 6 months (1999)

- DTaP x 3 (75 µg)
- Hib x 3 (75 µg)
- Hepatitis B x 3 (37.5 µg)
- [Selected populations: Influenza x 1 (12.5 µg)]

Total: 187.5 µg [200]*

*Thimerosal is 49.5% Hg by weight; For vaccines containing thimerosal at 0.005%; 50 mg thimerosal/1.0 ml, 25 mg thimerosal/0.5 ml, 12.5 mg Hg/0.5 ml dose
Exposure Assessment

Minimum Exposure to Hg From Vaccines in U.S. Infants ≤ 6 months (1999)

- DTaP x 3 (0 µg)
- Hib x 3 (0 µg)
- Hepatitis B x 3 (0 µg)
- [Selected populations: Influenza x 1 (12.5 µg)]

Total: 0 µg [12.5 µg]*

*Hib-HepB (Comvax™) approved for use in infants ≥ 6 weeks born to HBsAg negative mothers
Calculated Limits for Methylmercury Intake in First 6 Months, per Weight of Infant

<table>
<thead>
<tr>
<th></th>
<th>5%</th>
<th>50%</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPA</td>
<td>65 µg</td>
<td>89 µg</td>
<td>106 µg</td>
</tr>
<tr>
<td>ATSDR</td>
<td>194 µg</td>
<td>266 µg</td>
<td>319 µg</td>
</tr>
<tr>
<td>FDA</td>
<td>259 µg</td>
<td>354 µg</td>
<td>425 µg</td>
</tr>
<tr>
<td>WHO</td>
<td>305 µg</td>
<td>417 µg</td>
<td>501 µg</td>
</tr>
</tbody>
</table>

• Assume average of 5th, 50th, and 95th % weight for girls at birth (2.36 kg, 3.23 kg, 3.81 kg) and 6 months (5.25 kg, 7.21 kg, 8.73 kg) = 3.81 kg, 5.22 kg, 6.27 kg
• Dose/kg/week X average weight X 26 weeks = suggested limit
• Assume infant is as sensitive to neurotoxic effects of methyl mercury as fetus for EPA standard
• Other exposures to mercury (environment, diet, pharmaceuticals) should be considered
Percent Distribution of 85,261 Children by Total Exposure to Hg Through Vaccinations Northern California Kaiser HMO

- ≤ 100mcg: 63.5%
- ≤ 112.5mcg: 86.8%
- ≤ 125mcg: 91.6%
# Blood Levels of Hg Following Hepatitis B Vaccination in Newborns

<table>
<thead>
<tr>
<th></th>
<th>Mean Hg Dose (µg/kg)</th>
<th>Total Hg pre-vaccine (µg/L)</th>
<th>Total Hg 1-3 d post vaccine (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 preterm</td>
<td>16.7</td>
<td>0.54</td>
<td>$7.36 \pm 4.99 \text{ (1.3 -23.9)}$</td>
</tr>
<tr>
<td>5 term</td>
<td>3.48</td>
<td>0.04</td>
<td>$2.24 \pm 0.58 \text{ (1.4-2.9)}$</td>
</tr>
</tbody>
</table>

## Infant Exposure to Mercury from Diet

<table>
<thead>
<tr>
<th>Reference</th>
<th>Source</th>
<th>Mean Total Hg (µg/L)</th>
<th>Daily Exposure (µg/kg/d)*</th>
<th>Calculated Total Hg/6mo**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gunderson 1988 Clarkson 1990 (USA)</td>
<td>Diet (&gt; 6 mo)</td>
<td>--</td>
<td>0.05</td>
<td>47 µg</td>
</tr>
<tr>
<td>Oskarrson 1996 (Sweden)</td>
<td>Breast milk</td>
<td>0.37 0.76</td>
<td>0.057 0.11</td>
<td>54 µg 104 µg</td>
</tr>
<tr>
<td>Drasch 1998 (Germany)</td>
<td>Breast milk Formula</td>
<td>0.6 51% inorg.</td>
<td>0.1</td>
<td>95 µg</td>
</tr>
<tr>
<td>Pichichero 2001 (USA)</td>
<td>Breast milk/Formula</td>
<td>0.30</td>
<td>0.046</td>
<td>44 µg</td>
</tr>
</tbody>
</table>

*Assume mean daily intake of 850 ml breast milk/formula for infant weighing 5.5 kg

**For female at 50%, assume average at birth and 6 months

= 5.22 kg X daily exposure (µg/kg/d) X 182 days
Thimerosal Risk Assessment: Risk Characterization

- No data found on harm at dose levels in vaccines, except local hypersensitivity reactions
- Inadvertent high-dose exposure to thimerosal has caused neurotoxicity and nephrotoxicity
- Use of thimerosal in vaccines may result in intake of mercury during first 6 months of life, exceeding EPA guidelines for methylmercury
- In U.S., exposure of infants to thimerosal can be reduced or eliminated using vaccines formulated without thimerosal as a preservative
Uncertainties

- Applicability of methyl Hg exposure guidelines
- Ethyl vs. methyl Hg
- Toxicokinetics
- Peak exposure vs. chronic exposure
- Developmental neurotoxicity
- Neurodevelopmental outcomes in children exposed to thimerosal in vaccines
- Genetic susceptibility
# Recommended Childhood Immunization Schedule

**United States, January - December 2001**

Vaccines are listed under routinely recommended ages. Bars indicate range of recommended ages for immunization. Any dose not given at the recommended age should be given as a "catch-up" immunization at any subsequent visit when indicated and feasible. Ovals indicate vaccines to be given if previously recommended doses were missed or given earlier than the recommended minimum age.

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccine</th>
<th>Birth</th>
<th>1 mo</th>
<th>2 mos</th>
<th>4 mos</th>
<th>6 mos</th>
<th>12 mos</th>
<th>15 mos</th>
<th>18 mos</th>
<th>24 mos</th>
<th>4-6 yrs</th>
<th>11-12 yrs</th>
<th>14-18 yrs</th>
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<td>Hepatitis B</td>
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Approved by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP).
Thimerosal and Neurodevelopmental Outcomes

Remaining Question:

How much and what kind of evidence is needed to determine whether there is an association between thimerosal and neurodevelopmental toxicity?