Thimerosal in Vaccines

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Center for Biologics Evaluation and Research
Food and Drug Administration
Background:
Current Requirements for Preservatives

- Products in multidose vials shall contain a preservative CFR 610.15(a)
- Any preservative shall be sufficiently nontoxic so that the amount present in recommended dose will not be toxic to recipient and shall not denature product CFR 610.15(a)
- Definition of a preservative is not given in the CFR
- The USP definition of a preservative is widely used; Biologics need not follow USP definition
Background: Thimerosal

- Thimerosal (merthiolate ®- Eli Lilly) Ethylmercurithiosalicylic acid, sodium salt; marketed in 1930 as preservative; MW 404.8 (49.6% Hg)
- Most widely used preservative in vaccines
- Present in over 50 licensed vaccines and biologics in concentrations of 0.003% to 0.01%
- 1976 CBER review and risk assessment (memo)
  - Conclusion: No harmful effects at doses received during lifetime
- Metabolized to ethyl mercury and thiosalicylate
Background:
Current Relevance

FDAMA (1997) mandated listing and analysis of mercury-containing products
(21 USC 393 Sec. 413)

Increase in number of vaccines recommended for routine use in infants

Until additional combination vaccines for infants are licensed, infants may be exposed to increased amounts of thimerosal
Thimerosal Safety Assessment: Acute Toxicity - Thimerosal

- Cases of acute poisoning with thimerosal
  - Axton 1972: Choramphenicol with 1000x dose thimerosal as preservative
  - Fagan 1977: Tx omphaloceles in neonates
  - Matheson 1980: IVIG
  - Lowell 1996: HBIG after liver transplant
  - Pfab 1996: Thimerosal suicide attempt
- Observed effects: local necrosis, acute hemolysis, DIC, acute renal tubular necrosis, CNS: obtundation, coma, death
Chronic Toxicity:
Methylmercury

- Infants born to women who ingested high concentrations of methylmercury exhibited CNS effects
  - Minamata Bay, Japan
  - Iraq
    » severe neurotoxicity 500-1000 μg/L
    » Blood levels 100-200 μg/L not associated with sx

- Population-based studies
  - Seychelle Islands
  - Faroe Islands
Thimerosal Safety Assessment:
Risk to Infants - Conclusions

- Evidence of thimerosal toxicity
  - Local hypersensitivity reactions
  - Acute toxicity at high doses
- Use of thimerosal in vaccines may result in intake of mercury during first 6 months of life exceeding some established guidelines
- Infant exposure to Hg from vaccines may be largely avoidable by using thimerosal-free products
Thimerosal Safety Assessment: VAERS Reports

- 45 reports from 1990-1998 alleging adverse reactions due to thimerosal
- Most reports involve local hypersensitivity reactions
- Most common vaccine: Hepatitis B
- Causality cannot be inferred
Thimerosal Safety Assessment

- Suggested limits intake of methylmercury

  - WHO
    - adult: 3.3 μg/kg/wk
    - pregnant woman: 0.67 μg/kg/wk
  - US
    - EPA: 0.1 μg/kg/day or 0.7 μg/kg/wk
      - dose protective of developing fetal nervous system
    - ATSDR: 0.3 μg/kg/day or 2.1 μg/kg/wk
      - adults
    - FDA: 0.4 μg/kg/day or 2.8 μg/kg/wk
      - adults
Thimerosal Safety Assessment
Suggested Limits on Methyl Mercury Intake in First 6 Months: Preliminary Calculations

- Assume average of 5th, 50th, and 95th % weight at birth (2.5 kg, 3.3 kg, 4.1 kg) and 6 months (4.1 kg, 7.5 kg, 9.1 kg)*
  - dose/kg/week $\times$ average weight $\times$ 26 weeks = suggested limit
- Assume infant is as sensitive to neurotoxic effects of methyl mercury as fetus for WHO and EPA standard

<table>
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*Source: Harriet Lane Handbook
Thimerosal Safety Assessment
Suggested Limits on Methyl Mercury Intake in First 2 Years: Preliminary Calculations

- Assume average of 5th, 50th, and 95th % weight at birth (2.5 kg, 3.3 kg, 4.1 kg) and 2 years (10.25 kg, 12.3 kg, 14.4 kg)*
  - dose/kg/week X average weight X 104 weeks = suggested limit
- Assume infant is as sensitive to neurotoxic effects of methyl mercury as fetus for WHO and EPA standard

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*Source: Harriet Lane Handbook
Caveats

- Assumes toxicity of methylmercury is the same as ethyl mercury
- Does not factor in differences in:
  - route of administration (po vs. IM)
  - dose schedule (daily po vs intermittent IM)
  - magnitude of doses
  - pharmacokinetics
## Thimerosal Safety Assessment: Exposure from Vaccines

### U.S. Licensed Vaccines Containing Thimerosal

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Thimerosal Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP</td>
<td>Acel-Imune, Tripedia, Certiva</td>
</tr>
<tr>
<td>DTwP</td>
<td>All</td>
</tr>
<tr>
<td>DT</td>
<td>All</td>
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<tr>
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<td>All</td>
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<tr>
<td>T</td>
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</tr>
<tr>
<td>DTP-HIB</td>
<td>Tetramune</td>
</tr>
<tr>
<td>HIB</td>
<td>HIBtiter, PedvaxHIB (lyo), [ProHIBit]</td>
</tr>
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# Thimerosal Safety Assessment: Exposure from Vaccines

## U.S. Licensed Vaccines Containing Thimerosal (cont)

<table>
<thead>
<tr>
<th>Hepatitis B</th>
<th>Engerix, Recombivax B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>All</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>JE-VAX</td>
</tr>
<tr>
<td>Meningococcal A/C/Y/W-135</td>
<td>Menomune (CLI)</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>Pnu-Imune</td>
</tr>
<tr>
<td>Rabies</td>
<td>RABIE-VAX, MBPI</td>
</tr>
</tbody>
</table>
## Thimerosal-free

### U.S. Licensed Vaccines

#### Routine Use in Infants and Children

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<tr>
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<tr>
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<tr>
<td>MMR</td>
</tr>
<tr>
<td>Varicella</td>
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Thimerosal-free
U.S. Licensed Vaccines

Routine use in selected populations ≥ 2 years

- Pneumococcal
- Hepatitis A

- PNEUMOVAX
- Havrix, Vaqta
No U.S. Licensed Thimerosal-free Products

- DTwP
- DT
- Td
- TT
- Influenza
Maximum Exposure to Hg From Vaccines in U.S. Infants and Children

<table>
<thead>
<tr>
<th>Infants ≤ 6 months</th>
<th>Children &lt; 2 yrs (total)</th>
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<tr>
<td>- DTaP x 3 (75)</td>
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<tr>
<td>- HIB x 3 (75)</td>
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<td>- Hepatitis B x 3 (37.5)</td>
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<td>- [Selected populations: Influenza x 1(12.5)]</td>
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**Total: 187.5 µg [200]**  **Total: 237 µg [275]**

*Assumes two doses influenza vaccine at least one month apart beginning at age 6 months, with a third dose given 1 year later.*
Minimum Exposure to Hg From Vaccines in U.S. Infants and Children

- **Infants ≤ 6 months**
  - HIB-Hep B x 2 (0)
    » Comvax
  - DTaP x 3 (0)
    » Infanrix
  - [Selected populations: Influenza x 1(12.5)]

- **Children < 2 years (total)**
  - HIB-Hep B x 3
    » Comvax
  - DTaP x 4 (0)
    » Infanrix
  - [Selected populations Influenza x 3* (37.5)]

- **Total: 0 µg [12.5]**
- **Total: 0 µg [37.5]**

*Assumes two doses influenza vaccine at least one month apart beginning at age 6 months, with a third dose given 1 year later.*
Hg Exposure From Vaccines vs. Acceptable Oral Doses in First 6 Months of Life

- Maximum Hg Exposure From Vaccines in Infants ≤ 6 months
  - DTaP x 3 (75)
  - HIB x 3 (75)
  - Hepatitis B x 3 (37.5)
  - [Influenza x 1(12.5)]
  
  **Total: 187.5 μg [200]**

- Acceptable Oral Dose MeHg in Infants ≤ 6 months: Preliminary calc.

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### Hg Exposure From Vaccines vs. Acceptable Oral Doses in Children up to 2 years

**Maximum Hg Exposure from Vaccines in Children up to 2 years**
- DTaP x 4 (100)
- HIB x 4 (100)
- Hepatitis B x 3 (37.5)
- [Selected populations Influenza x 3* (37.5)]

**Total: 237 μg [275]**

**Acceptable Oral Dose meHg up to 2 years: Preliminary calc.**

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Hg Exposure From Vaccines vs. Acceptable Oral Doses

- For infants up to 6 months, Hg exposure from vaccines given according to U.S. recommended schedule may exceed some methylmercury exposure guidelines
  - Other exposures to Hg not included
  - Assumes maximum exposure from vaccines
  - Caveats as noted previously

- By age 2 years, Hg exposure appears to be within guidelines
Unresolved Issues in Thimerosal Safety Assessment

- Is ethyl mercury toxicity the same as methyl mercury?
- Is it appropriate to apply standards developed for chronic lifetime exposure of orally ingested methyl mercury to injections of thimerosal given over the first six months of life?
- Assuming similar toxicity, what methyl mercury standard is the most applicable for thimerosal from vaccines?
- Is there chronic toxicity from thimerosal in infants from vaccines?
Stakeholders:
Potential Issues (cont.)

- Manufacturing
  - Necessity for thimerosal in-process (e.g., detoxification)
  - Need for conducting studies for reformulations without thimerosal
  - Cost of manufacturing change

- Vaccine provider
  - Storage issues: multidose vs. single dose
  - Cost of manufacturing change
Additional Developments

- OVRR’s letter to manufacturers (7/1/99)
- Response from manufacturers
- AAP/PHS Joint Statement (7/7/99)
  - Postpone first dose of HepB vaccine if mother is known to be HepB surface antigen negative
- NVAC-sponsored Thimerosal workshop (8/11/99)
- Merck supplement approved (8/27/99) for thimerosal-free, single-dose HepB vaccine