NIAID Studies on Thimerosal

- Scientific Questions
- Pilot clinical study and data
- Follow-up to clinical study
- Ongoing studies in primates
NIAID Studies on Thimerosal

Scientific Questions

• Are the guidelines developed for methyl mercury (MeHg) appropriate for assessing the safety of thimerosal (sodium ethyl mercuri-thiosalicylate)?

• How are the distribution, metabolism, and excretion of thimerosal and MeHg related?
NIAID Studies on Thimerosal

Research Question -- Possibilities

• Thimerosal and MeHg are equivalent

• Thimerosal and MeHg are similar; MeHg guidelines offer additional/less margin of safety

• Thimerosal and MeHg are significantly different in distribution, metabolism, and excretion
# NIAID Studies on Thimerosal

<table>
<thead>
<tr>
<th>Thimerosal Exposure</th>
<th>MeHg Exposure/Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl mercury thiosalicylate</td>
<td>Methyl mercury in food</td>
</tr>
<tr>
<td>IM injection</td>
<td>Oral intake – food</td>
</tr>
<tr>
<td>Spaced intermittent exposure</td>
<td>Continuing exposure to reach steady state distribution</td>
</tr>
<tr>
<td>Infant exposure</td>
<td>Maternal and fetal exposure</td>
</tr>
<tr>
<td>Risk to infant</td>
<td>Risk from fetal exposure – most sensitive to damage</td>
</tr>
<tr>
<td>Measure levels directly</td>
<td>Extrapolate from maternal hair levels to fetal exposure and effects</td>
</tr>
</tbody>
</table>
NIAID Studies on Thimerosal

Research Studies

• Evaluation of mercury in Infants after thimerosal-containing vaccines (Univ. Rochester)

• Evaluation of mercury pharmacokinetics and tissue distribution in infant macaques after thimerosal and vaccines compared to MeHg (Univ. Washington)
Evaluation Of Mercury in Infants after Thimerosal - Containing Vaccines

M.E. Pichichero MD, T.W. Clarkson PhD, J. LoPriato MD*, J. Treanor MD
Univ. Rochester Vaccine Evaluation Unit, *Naval Medical Center

- **Subjects:**
  20 two-month old infants and 20 six-month old infants from Rochester NY (thimerosal vaccines); 20 control infants from Bethesda MD (no thimerosal)

- **Vaccines:**
  Tripedia (25 ug Hg per dose), Engerix (12.5 ug Hg per dose), Hib Titer (25 ug Hg per dose)
Evaluation Of Mercury in Infants after Thimerosal - Containing Vaccines

- **Sampling:**
  Whole blood, urine, and stool samples obtained at varying times within 30 days of vaccination, some vaccine, formula, breast milk, and maternal hair also tested.

- **Assay:**
  Mercury determined by atomic absorption

- **Non-detectable mercury:**
  Assigned a value at the lowest limit of detection for calculations
Sampling Times for 2 month old and 6 month old visits

2 month olds

6 month olds

Days after vaccination

National Institute of Allergy and Infectious Diseases

IOM – July 16, 2001
## Mercury Exposure in Infants

<table>
<thead>
<tr>
<th></th>
<th>2 month olds</th>
<th>6 month olds</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of subjects</strong></td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td><strong>Total Hg exposure (µg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (Max – Min)</td>
<td>45.6</td>
<td>111.3</td>
</tr>
<tr>
<td></td>
<td>(62.5 - 37.5)</td>
<td>(175 - 87.5)</td>
</tr>
<tr>
<td><strong>Body Weight (kg)</strong></td>
<td>5.3</td>
<td>8.1</td>
</tr>
<tr>
<td>Mean (Max – Min)</td>
<td>(6.4 - 4.0)</td>
<td>(10.6 - 6.7)</td>
</tr>
</tbody>
</table>
## Mercury Levels in Infants

<table>
<thead>
<tr>
<th></th>
<th>2 month olds</th>
<th>6 month olds</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood Hg (ng/mL)</strong></td>
<td>16 / 4</td>
<td>16 / 7</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>0.98</td>
</tr>
<tr>
<td>Mean (Max – Min)</td>
<td></td>
<td>(0.98 - &lt;0.05)</td>
</tr>
<tr>
<td></td>
<td>(4.11 - &lt;0.75)</td>
<td></td>
</tr>
<tr>
<td><strong>Urine Hg (ng/mL)</strong></td>
<td>12 / 11</td>
<td>15 / 12</td>
</tr>
<tr>
<td></td>
<td>0.82 [0.76]</td>
<td>0.67</td>
</tr>
<tr>
<td>Mean (Max – Min)</td>
<td></td>
<td>(&lt;1.5 - &lt;0.44)</td>
</tr>
<tr>
<td></td>
<td>(&lt;1.5 - &lt;0.45)</td>
<td></td>
</tr>
<tr>
<td><strong>Stool Hg (ng/g dry wt)</strong></td>
<td>12 / 0</td>
<td>10 / 0</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>58</td>
</tr>
<tr>
<td>Mean (Max – Min)</td>
<td></td>
<td>(102 – 29)</td>
</tr>
<tr>
<td></td>
<td>(141 – 23)</td>
<td></td>
</tr>
</tbody>
</table>
Blood Mercury by Time of Sampling

Estimated Hg = samples with undetectable Hg assigned a value of the lower limit of detection (depends on sample volume, ranges between 1.50 and 0.50 ng/mL)

- 2 month old, measured
- 2 month old, estimated
- 6 month old, measured
- 6 month old, estimated
- EPA Standard

National Institute of Allergy and Infectious Diseases

IOM – July 16, 2001
Blood Mercury Levels in Infants Given Hepatitis B Vaccine at Birth


- Term (mn 3.588 kg) n = 5
- Pre-Term (mn 0.748 kg) n = 15

†p<.01; ‡p<.01; *p=.2
Blood Mercury by Time of Sampling

Estimated Hg = samples with undetectable Hg assigned a value of the lower limit of detection (depends on sample volume, ranges between 1.50 and 0.50 ng/mL)
Mercury in Maternal Hair Samples
Mercury Measures: Other Samples

- Hg was not detectable in blood (<1.50 - <.50 ng/mL) in 14/15 children in Bethesda (non-thimerosal control group), the single detectable sample had a value of 0.98 ng/mL

- Mercury content of vaccine vials (2) was exactly as certified

- Levels of mercury in 8 samples of formula and maternal milk were all less than 0.50 ng/mL
Blood Mercury by Time of Sampling

Estimated Hg = samples with undetectable Hg assigned a value of the lower limit of detection (depends on sample volume, ranges between 1.50 and 0.50 ng/mL)
Comparison of Observed and Predicted Blood Mercury Levels: Assumptions

- Assume 8% body weight is blood volume, 5% of mercury dose distributed to blood
- Assume single compartment model with first-order kinetics
- Assign lower detection limit to samples with undetectable mercury
- Predict blood levels based on exposure, body weight, and time since vaccination, using different half-lives of mercury
- Determine half life that leads to lowest total difference between observed and expected blood levels
Effect of Varying Assumed $T_{\frac{1}{2}}$ on Predicted Levels of Blood Mercury

$$[\text{Hg}_t] = \left( \sum_{d_i} \text{Hg}_d e^{-\left(0.693/t_{\frac{1}{2}}\right)t_{d_i}} \right)/W$$

All data points

Measured
Summary

- Blood mercury levels in full term infants within 30 days of receiving routine immunization with vaccines containing thimerosal were below EPA safety guidelines.

- Blood mercury levels in these infants were lower than predicted using a 45 day half life for mercury.

- Mercury was detected in the stools of infants receiving vaccines containing thimerosal.
Conclusions

• Since levels of blood mercury were uniformly below safety guidelines, results suggest that thimerosal administered at 2 months of age does not pose undue risk of mercury toxicity in full-term infants.

• The blood half life of mercury administered parenterally as thimerosal in infants appears to be shorter than the half life of methyl mercury in adults, possibly as short as 6 - 8 days.

• Infants excrete significant amounts of mercury in stool, unlike animal models of MeHg. This possibly accounts for the relatively short apparent half-life of ethyl mercury in this study.
Follow-Up Studies in Infants

- Confirm blood levels and excretion in feces in infants receiving routine immunizations containing thimerosal
- Collect blood, urine, feces, maternal hair, breast milk and/or formula samples
- Expand pharmacokinetics studies to include pre-vaccination samples and longitudinal samples from infants
Pharmacokinetics Study in Infant Macaques

• Do exposures to thimerosal and MeHg result in the same levels of mercury in brain, blood, and other tissues?

• Study Design:
  – Infant macaques ~ 1 wk old
  – Weekly thimerosal (IM) plus infant vaccines for 4 wks
  – Sample blood, urine, feces, CSF
  – Monitor development, behavior
  – Collect blood, brain, CSF, kidney, liver, etc at 1, 3, or 6 days after end of exposure
Pharmacokinetics Study in Infant Macaques

• Current Status
  – Tested infant formula and food for Hg levels – Low
  – Analyzed brain tissues from normal infant macaque for Hg levels – Low/not detected
  – Beginning to breed females this summer
NIAID Studies on Thimerosal

• Univ. Rochester Study:
  Michael E. Pichichero MD, Thomas Clarkson PhD, John
  Treanor MD, Joseph LoPriato MD (Navy Medical Center)
  funded by NIH contract N01 AI45248, DMID, NIAID

• Univ. Washington Study:
  Thomas Burbacher, PhD, Danny Shen, PhD, Thomas
  Clarkson PhD (Rochester)
  Funded by NIH grant R01 ES03745 NIEHS and NIAID

• NIAID:
  Carole Heilman PhD, Sarah Landry MS, Polly Sager PhD