

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?

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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

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Thimerosal Exposure

Ethyl mercury thiosalicylate

IM injection

Spaced intermittent exposure

Infant exposure

Risk to infant

Measure levels directly

MeHg Exposure/Guidelines

Methyl mercury in food

Oral intake – food

Continuing exposure to reach steady state distribution

Maternal and fetal exposure

Risk from fetal exposure – most sensitive to damage

Extrapolate from maternal hair levels to fetal exposure and effects

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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

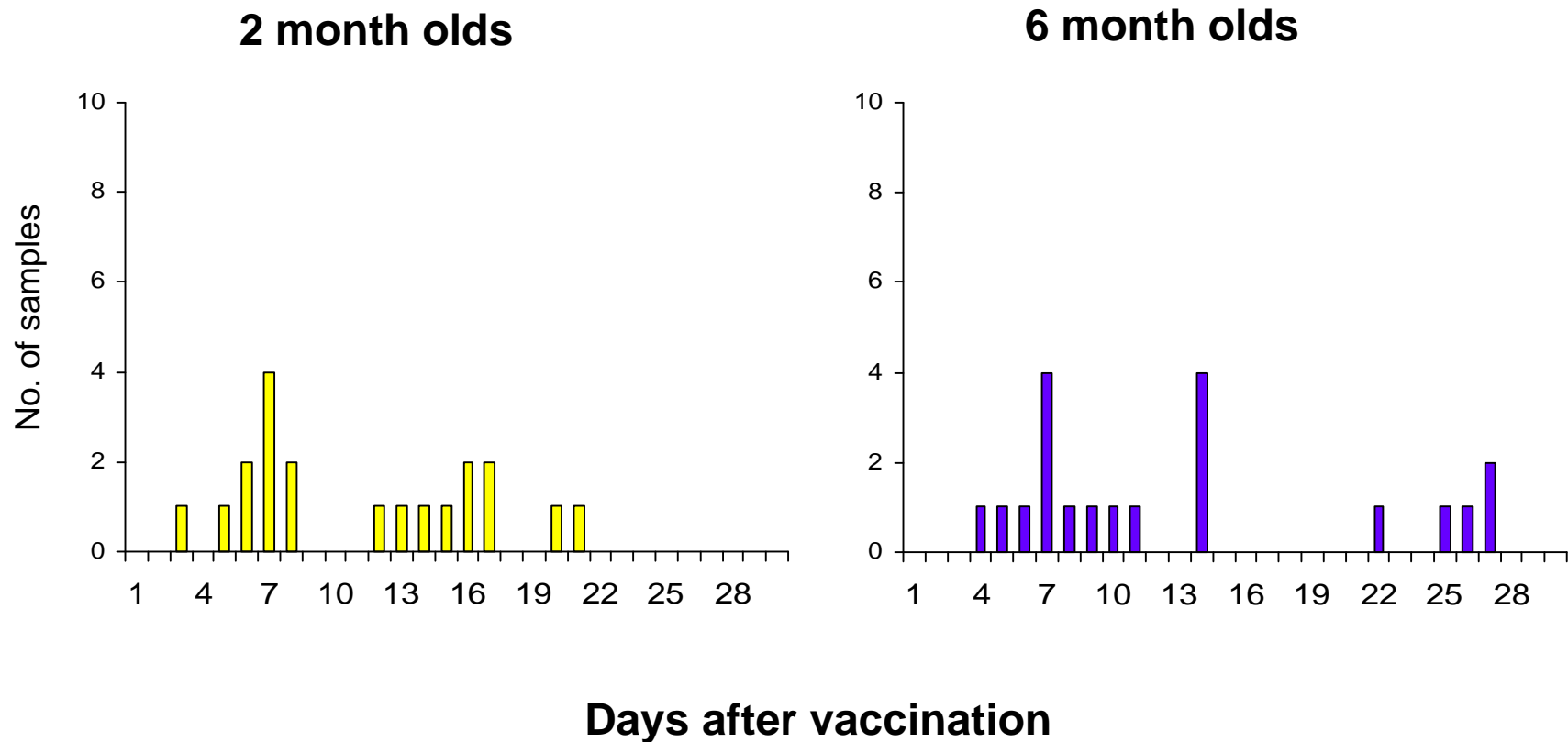
M.E. Pichichero MD, T.W. Clarkson PhD, J. LoPriato MD*, J. Treanor MD
Univ. Rochester Vaccine Evaluation Unit, *Naval Medical Center

- **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



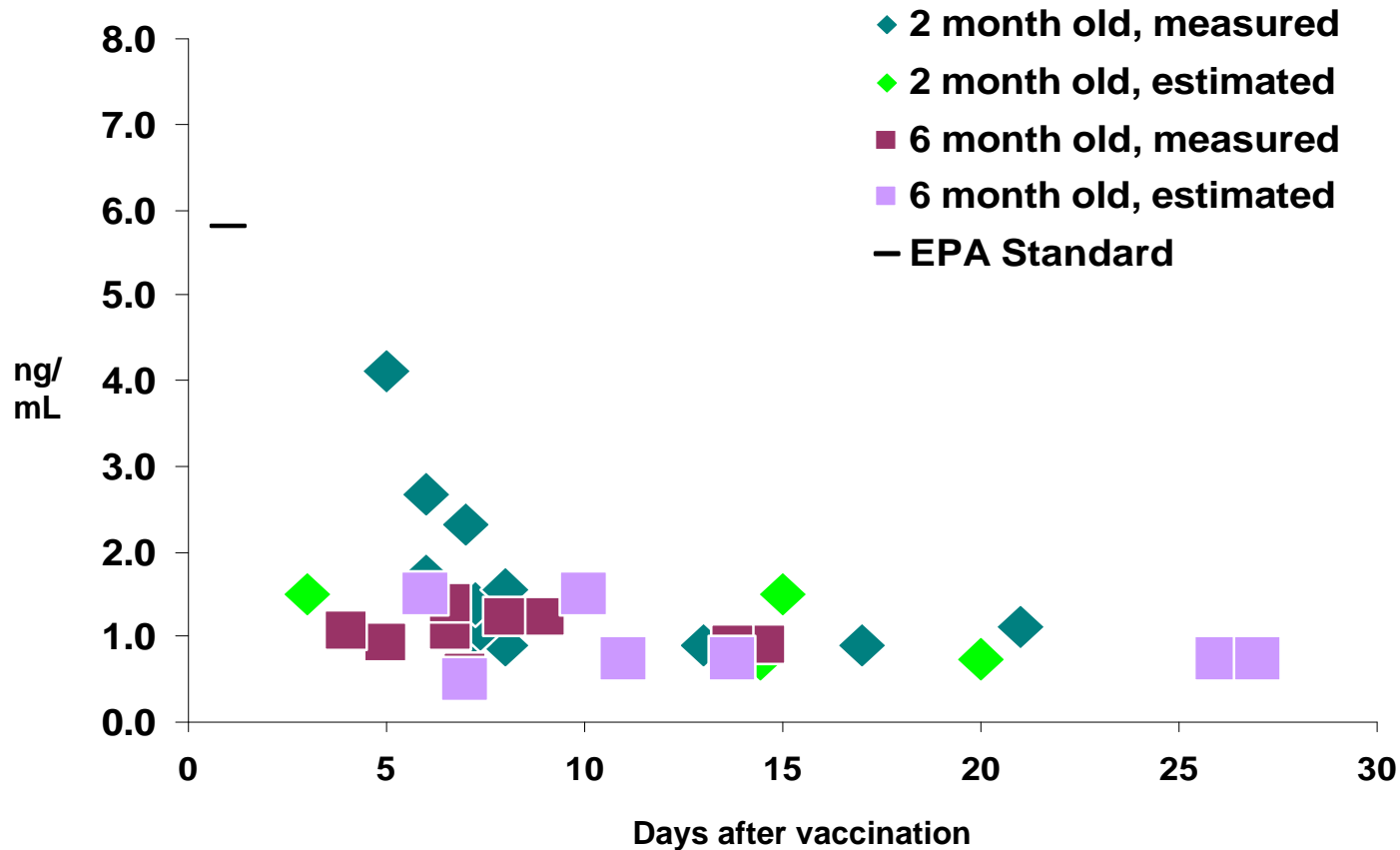
Mercury Exposure in Infants

	2 month olds	6 month olds
Number of subjects	20	20
Total Hg exposure (μg) Mean (<i>Max – Min</i>)	45.6 (62.5 - 37.5)	111.3 (175 - 87.5)
Body Weight (kg) Mean (<i>Max – Min</i>)	5.3 (6.4 - 4.0)	8.1 (10.6 - 6.7)

Mercury Levels in Infants

	2 month olds	6 month olds
Blood Hg (ng/mL) # / Undetect. Mean (<i>Max – Min</i>)	16 / 4 1.5 (4.11 - <0.75)	16 / 7 0.98 (0.98 - <0.05)
Urine Hg (ng/mL) # / Undetect. Mean (<i>Max – Min</i>)	12 / 11 0.82 [0.76] (<1.5 - <0.45)	15 / 12 0.67 (<1.5 - <0.44)
Stool Hg (ng/g dry wt) #/Undetect. Mean (<i>Max – Min</i>)	12 / 0 82 (141 – 23)	10 / 0 58 (102 – 29)

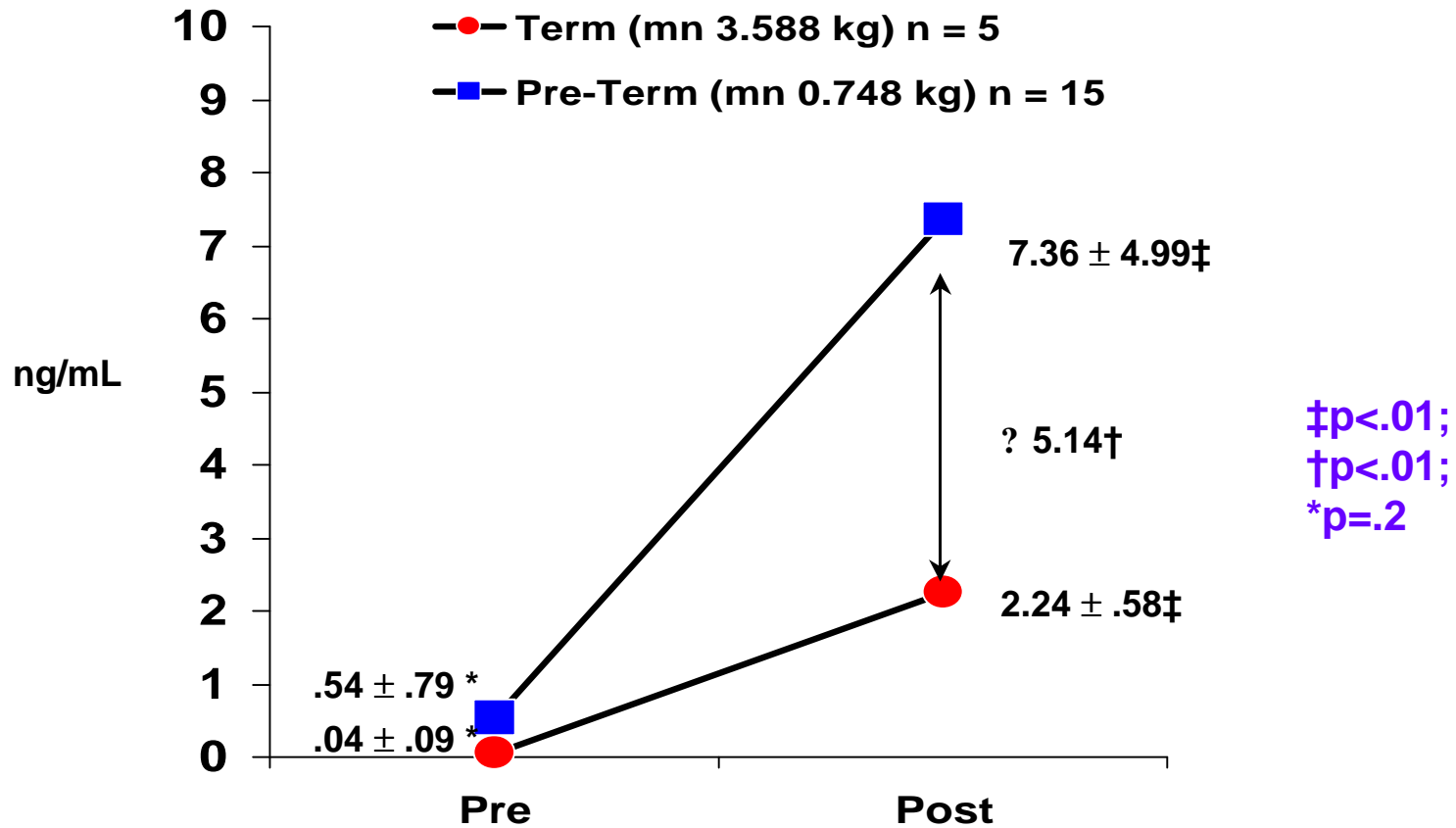
Blood Mercury by Time of Sampling



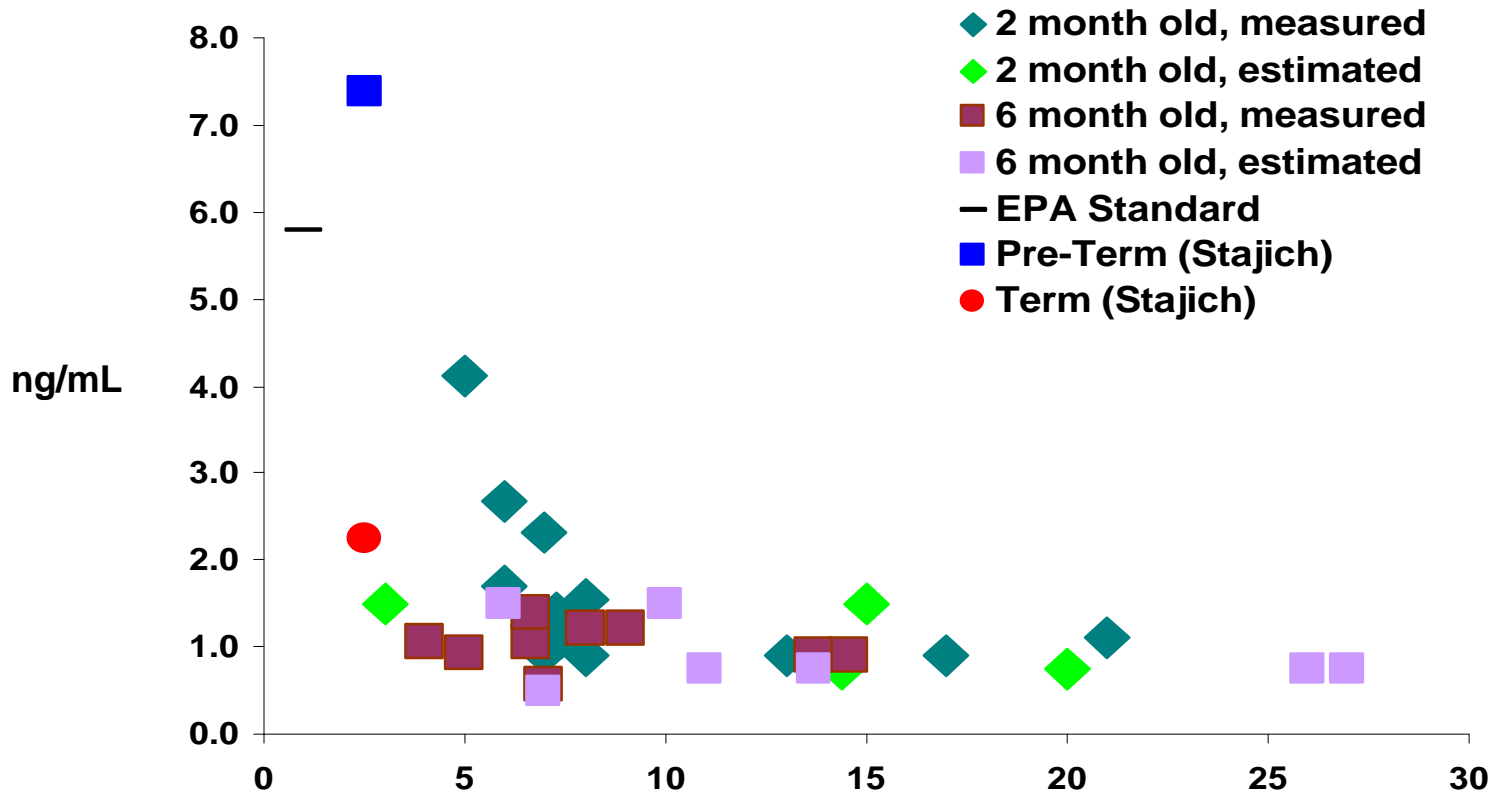
Estimated Hg = samples with undetectable Hg assigned a value of the lower limit of detection (depends on sample volume, ranges between 1.50 and 0.50 ng/mL)

Blood Mercury Levels in Infants Given Hepatitis B Vaccine at Birth

Stajich *et al. Journal of Pediatrics* 2000;136:679-81.

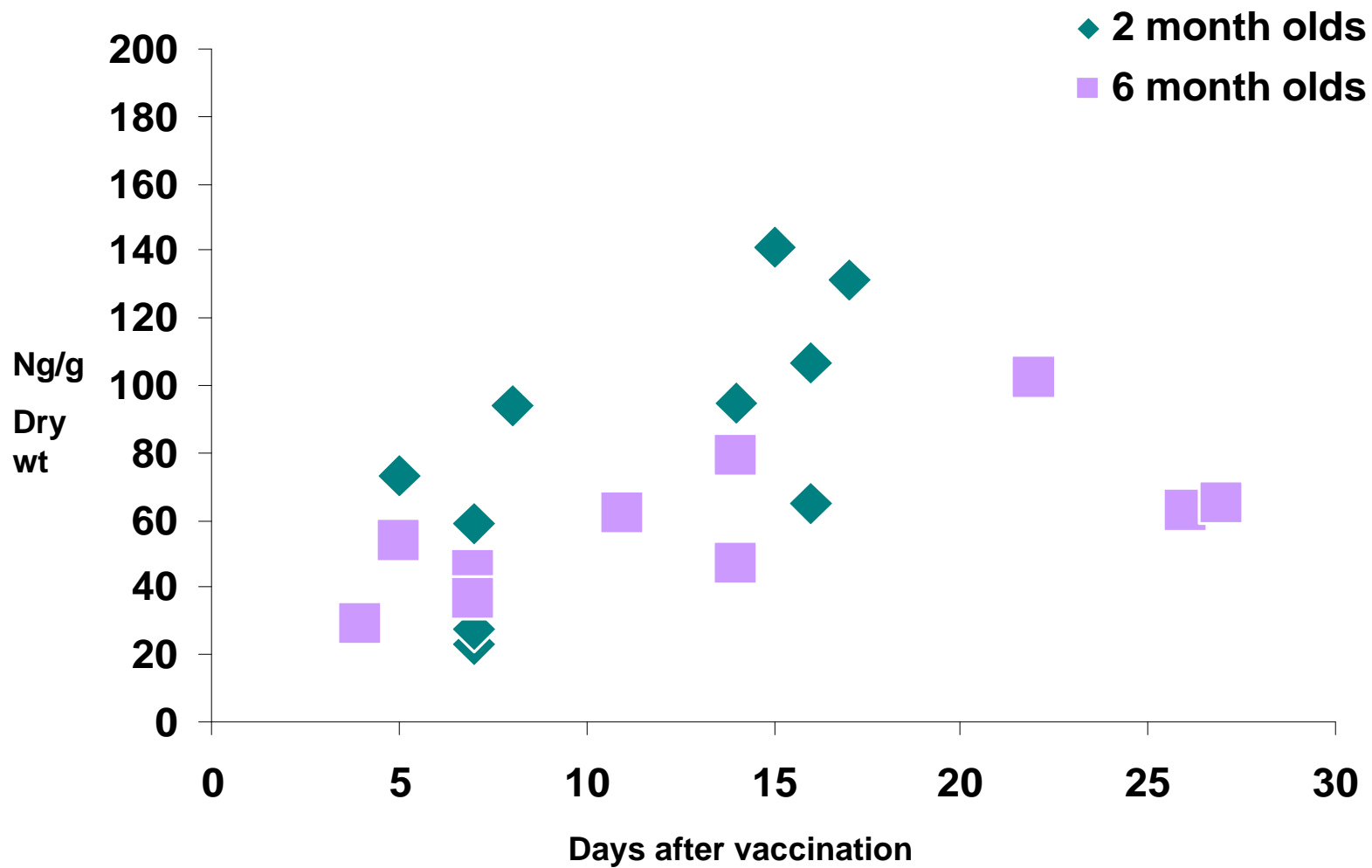


Blood Mercury by Time of Sampling

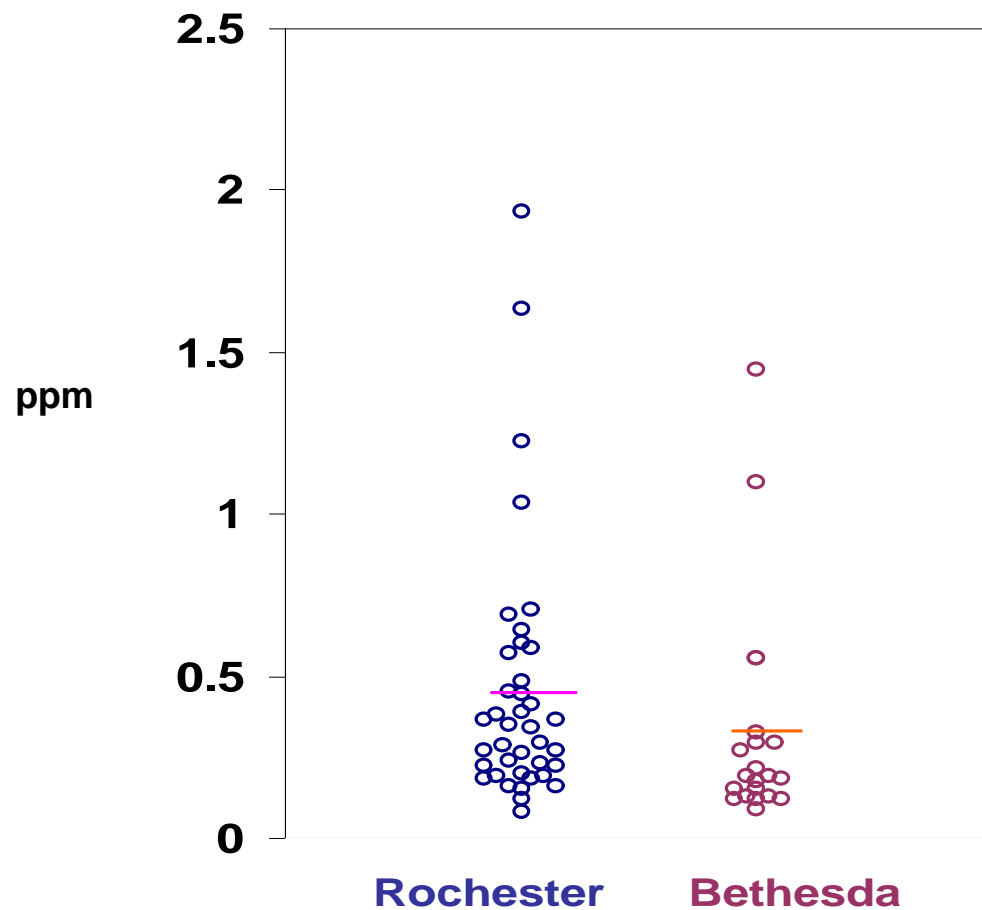


Estimated Hg = samples with undetectable Hg assigned a value of the lower limit of detection (depends on sample volume, ranges between 1.50 and 0.50 ng/mL)

Stool Mercury Levels



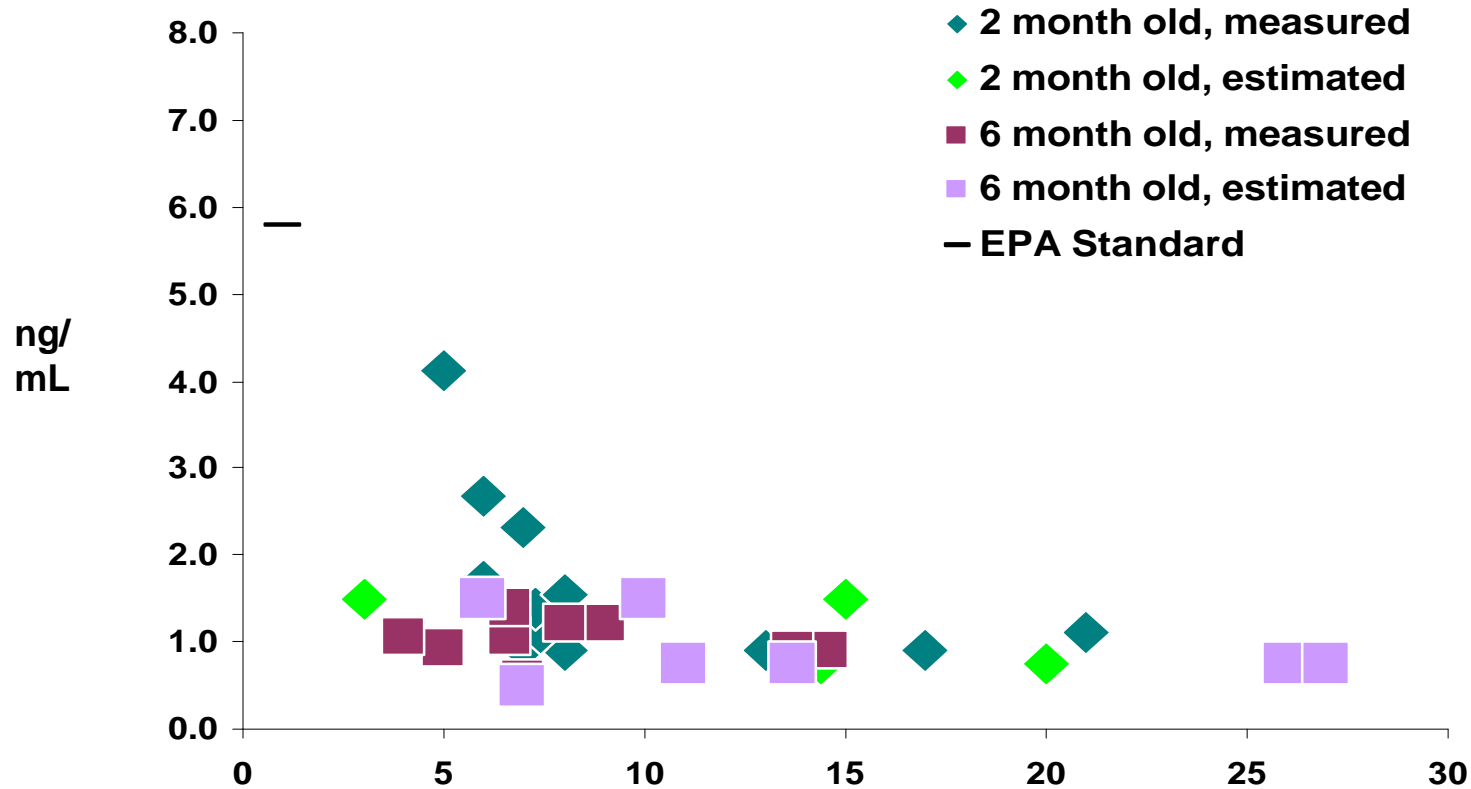
Mercury in Maternal Hair Samples



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

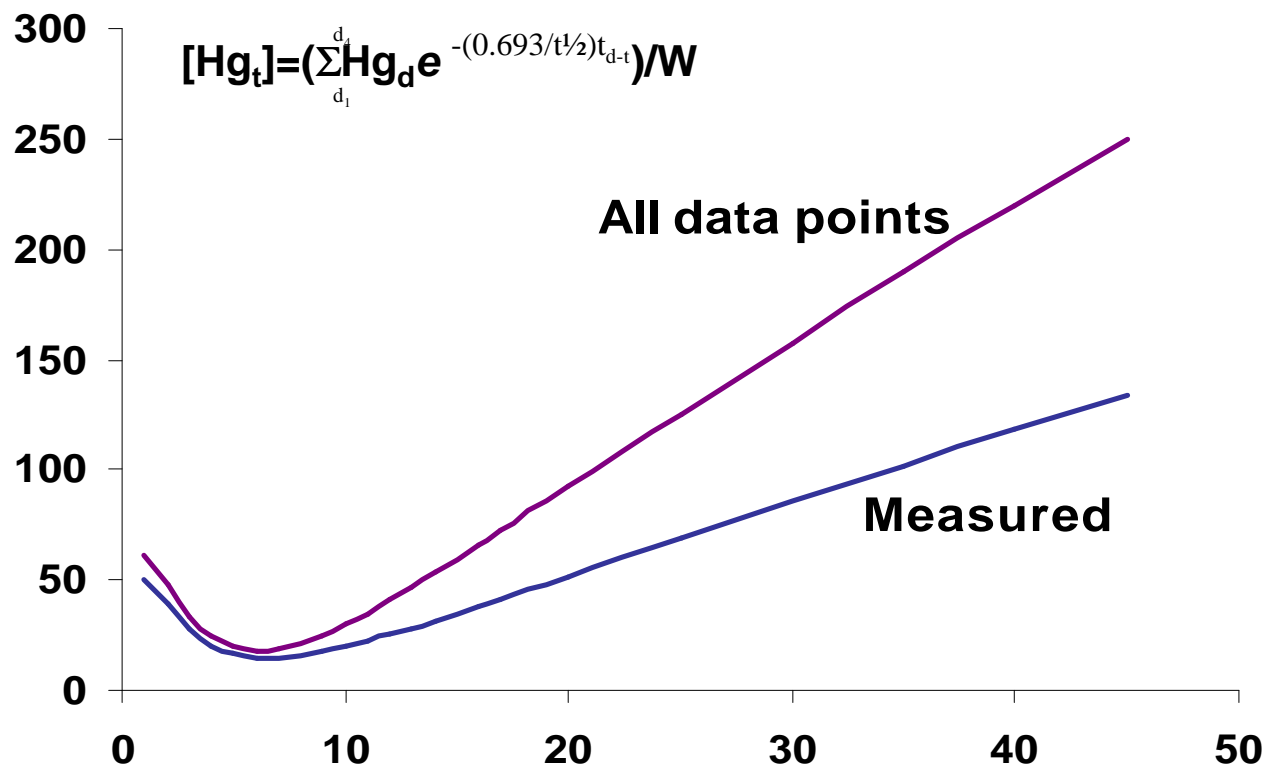


Estimated Hg = samples with undetectable Hg assigned a value of the lower limit of detection (depends on sample volume, ranges between 1.50 and 0.50 ng/mL)

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 $T_{1/2}$ on Predicted Levels of Blood Mercury



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:**
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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:**
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