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# Thimerosal in Vaccines

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# 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

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- ◆ Thimerosal (merthiolate ®- Eli Lilly) Ethylmercurithio-salicylic 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

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- ◆ FDAMA (1997) mandated listing and analysis of mercury-containing products  
*(21USC393 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

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- ◆ 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

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- ◆ Infants born to women who ingested high concentrations of methylmercury exhibited CNS effects
  - Minamata Bay, Japan
  - Iraq
    - » severe neurotoxicity 500-1000  $\mu\text{g/L}$
    - » Blood levels 100-200  $\mu\text{g/L}$  not associated with sx
- ◆ Population-based studies
  - Seychelle Islands
  - Faroe Islands

# Thimerosal Safety Assessment: Risk to Infants - Conclusions

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- ◆ 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

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- ◆ 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

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- ◆ Suggested limits intake of methylmercury
  - WHO
    - » adult: 3.3  $\mu\text{g}/\text{kg}/\text{wk}$
    - » pregnant woman: 0.67  $\mu\text{g}/\text{kg}/\text{wk}$
  - US
    - » EPA: 0.1  $\mu\text{g}/\text{kg}/\text{day}$  or 0.7  $\mu\text{g}/\text{kg}/\text{wk}$ 
      - ◆ dose protective of developing fetal nervous system
    - » ATSDR: 0.3  $\mu\text{g}/\text{kg}/\text{day}$  or 2.1  $\mu\text{g}/\text{kg}/\text{wk}$ 
      - ◆ adults
    - » FDA: 0.4  $\mu\text{g}/\text{kg}/\text{day}$  or 2.8  $\mu\text{g}/\text{kg}/\text{wk}$ 
      - ◆ adults

# Thimerosal Safety Assessment

## Suggested Limits on Methyl Mercury Intake in First 6 Months: Preliminary Calculations

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- ◆ 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 X average weight X 26 weeks = suggested limit
- ◆ Assume infant is as sensitive to neurotoxic effects of methyl mercury as fetus for WHO and EPA standard

	5th %	50th %	95%
WHO	<b>57</b> µg	<b>94</b> µg	<b>115</b> µg
EPA	<b>60</b> µg	<b>98</b> µg	<b>120</b> µg
ATSDR	<b>180</b> µg	<b>295</b> µg	<b>360</b> µg
FDA	<b>240</b> µg	<b>393</b> µg	<b>480</b> µg

\*Source: *Harriet Lane Handbook*

# Thimerosal Safety Assessment

## Suggested Limits on Methyl Mercury Intake in First 2 Years: Preliminary Calculations

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- ◆ 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

	5th %	50th %	95%
WHO	<b>444</b> µg	<b>544</b> µg	<b>644</b> µg
EPA	<b>464</b> µg	<b>568</b> µg	<b>673</b> µg
ATSDR	<b>1392</b> µg	<b>1703</b> µg	<b>2020</b> µg
FDA	<b>1856</b> µg	<b>2271</b> µg	<b>2693</b> µg

*\*Source: Harriet Lane Handbook*

# Caveats

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- ◆ 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

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## U.S. Licensed Vaccines Containing Thimerosal

- ◆ DTaP
- ◆ DTwP
- ◆ DT
- ◆ Td
- ◆ T
- ◆ DTP-HIB
- ◆ HIB
- ◆ Acel-Imune, Tripedia, Certiva
- ◆ All
- ◆ All
- ◆ All
- ◆ All
- ◆ Tetramune
- ◆ HIBtiter, PedvaxHIB (lyo), [ProHIBit]

# Thimerosal Safety Assessment: Exposure from Vaccines

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

- ◆ Hepatitis B
- ◆ Influenza
- ◆ Japanese encephalitis
- ◆ Meningococcal  
A/C/Y/W-135
- ◆ Pneumococcal
- ◆ Rabies
- ◆ Engerix,  
Recombivax B
- ◆ All
- ◆ JE-VAX
- ◆ Menomune (CLI)
- ◆ Pnu-Imune
- ◆ RABIE-VAX, MBPI

# Thimerosal-free U.S. Licensed Vaccines

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## Routine Use in Infants and Children

- ◆ DTaP
- ◆ HIB
- ◆ HIB-Hep B
- ◆ IPV/OPV
- ◆ MMR
- ◆ Varicella
- ◆ Rotavirus
- ◆ Hepatitis B
- ◆ Infanrix (Not for 5th dose)
- ◆ ActHIB, PedvaxHIB (liq)  
HIBtiter (single dose)
- ◆ Comvax
- ◆ All
- ◆ MMR-II
- ◆ Varivax
- ◆ Rotashield
- ◆ Recombivax B (as of  
8/27/99)

# Thimerosal-free U.S. Licensed Vaccines

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Routine use in selected populations  $\geq 2$  years

◆ Pneumococcal

◆ PNEUMOVAX

◆ Hepatitis A

◆ Havrix, Vaqta

# No U.S. Licensed Thimerosal-free Products

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- ◆ DTwP
- ◆ DT
- ◆ Td
- ◆ TT
- ◆ Influenza

# Maximum Exposure to Hg From Vaccines in U.S. Infants and Children

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## ◆ Infants ≤ 6 months

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

◆ **Total: 187.5 μg [200]**

## ◆ Children < 2 yrs (total)

- 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]**

*\*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

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## ◆ Infants $\leq$ 6 months

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

◆ **Total: 0  $\mu$ g [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  $\mu$ g [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

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◆ **Maximum Hg Exposure From Vaccines in Infants  $\leq$  6 months**

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

**Total: 187.5  $\mu$ g [200]**

◆ **Acceptable Oral Dose MeHg in Infants  $\leq$  6 months: Preliminary calc.**

	5th %	50th %	95%
WHO	57 $\mu$ g	94 $\mu$ g	115 $\mu$ g
EPA	60 $\mu$ g	98 $\mu$ g	120 $\mu$ g
ATSDR	180 $\mu$ g	295 $\mu$ g	360 $\mu$ g
FDA	240 $\mu$ g	393 $\mu$ g	480 $\mu$ g

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

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- ◆ **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  $\mu\text{g}$  [275]**

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

	5th %	50th %	95%
WHO	444 $\mu\text{g}$	544 $\mu\text{g}$	644 $\mu\text{g}$
EPA	464 $\mu\text{g}$	568 $\mu\text{g}$	673 $\mu\text{g}$
ATSDR	1392 $\mu\text{g}$	1703 $\mu\text{g}$	2020 $\mu\text{g}$
FDA	1856 $\mu\text{g}$	2271 $\mu\text{g}$	2693 $\mu\text{g}$

## Hg Exposure From Vaccines vs. Acceptable Oral Doses

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- ◆ **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

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- ◆ 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.)

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- ◆ 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

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- ◆ 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