Neurodevelopmental and Renal Toxicity of Thimerosal-Containing Vaccines: a Two-Phased Analysis of Computerized Databases.

Thomas Verstraeten, MD

Note: provisional results - may be subject to change
Overview

- Vaccine Safety Datalink and ethylmercury/thimerosal
- Study methodology
- Results phase I
- Results phase II
- Discussion & recomendations

Note: provisional results - may be subject to change
the Vaccine Safety Datalink (VSD)

• Partnership between CDC and seven Health Maintenance Organizations (HMOs)
• Large linked database including vaccination, clinic, hospital discharge and demographic data
• Initiated in 1991
• Covers estimated 2.5% of U.S. population

Note: provisional results - may be subject to change
Ethylmercury (= Thimerosal/2) content of vaccine used in VSD study population

• Diphtheria, Tetanus, and Pertussis vaccines:  
  0 or 25 micrograms/dose

• Haemophilus influenzae B vaccines:  
  0, 12.5 or 25 micrograms/dose

• Hepatitis B vaccines:  
  12.5 micrograms/dose

• Polio, Measles, Mumps, Rubella, Varicella, and Pneumococcal vaccines:  
  no thimerosal

Note: provisional results - may be subject to change
Cumulative ethylmercury (EtHg) exposure from thimerosal-containing vaccines in VSD study population:

<table>
<thead>
<tr>
<th>Age</th>
<th>Total EtHg exposure in the period</th>
<th>Cumulative EtHg at end of period</th>
<th>EPA limit (MeHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 m</td>
<td>12.5 ug</td>
<td>12.5 ug</td>
<td>11 ug</td>
</tr>
<tr>
<td>2-3 m</td>
<td>25 – 62.5 ug</td>
<td>37.5 – 75 ug</td>
<td>41 ug</td>
</tr>
<tr>
<td>4-5 m</td>
<td>25 – 62.5 ug</td>
<td>75 or 125 ug</td>
<td>80 ug</td>
</tr>
<tr>
<td>6-7 m</td>
<td>25 or 62.5 ug</td>
<td>100 – 187.5 ug</td>
<td>130 ug</td>
</tr>
</tbody>
</table>

Note: provisional results - may be subject to change
Infants in VSD exceeding EPA mercury exposure limit

Note: provisional results - may be subject to change
Overview

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- Results phase I
- Results phase II
- Discussion & recommendations

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Two-phased Study

• Phase I: Screen range of neurodevelopmental and renal disorders

• Phase II: Re-assess associations encountered in phase I

Note: provisional results - may be subject to change
Study design Phase I

• Retrospective cohort study of automated data

• Exposure: mercury from thimerosal-containing childhood vaccines at different ages

• Outcomes: range of plausible neurologic and renal disorders

Note: provisional results - may be subject to change
Study population

- Born between 1992 and 1998
- Born into one of two HMOs of VSD:
  - HMO A (follow-up through 1998)
  - HMO B (follow-up through 1999)
- Continuously enrolled first year of life
- Received at least 2 polio vaccinations by 1 year of age

Note: provisional results - may be subject to change
Study population: excluded infants

- Birthweight <2500 g (separate analyses)
- Congenital or severe perinatal disorders

Note: provisional results - may be subject to change
Exposure assessment

- Cumulative mercury exposure calculated from individual automated vaccination records (include vaccine type, manufacturer and lot number)
- Modelled as continuous variable: total ethylmercury exposure/12.5
- Exposure periods modelled:
  - 0-1 months
  - 2-3 months
  - 4-5 months
  - 6-7 months
  - 0-7 months: separate model

Note: provisional results - may be subject to change
Outcome definition

Neurologic developmental disorders

ICD9 codes & disorders

- 299: childhood psychosis (incl. autism)
- 307: specific psychopathological symptoms (incl. stammering, tics)
- 313: emotional disturbances
- 314: hyperkinetic syndrome (incl. attention deficit disorder)
- 315: specific developmental delays (incl. speech and coordination disorders)
- 317 - 319: mental retardation

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Outcome definition

Renal disorders

ICD9 codes & disorders

- 580, 581, 583: acute, chronic and unspecified glomerulonephritis
- 582: nephrotic syndrome
- 584 - 586: acute, chronic and unspecified renal failure
- 593.9: unspecified kidney and ureter disease

Note: provisional results - may be subject to change
Statistical analyses

• Proportional hazards models

• Stratified on gender, year and month of birth

• Separate for each HMOs

• Separate analysis for each disorder with n ≥50

Note: provisional results - may be subject to change
Statistical analyses

• Time in proportional hazards models
  –  = age
  – Starts at age 1
  – Ends at first of
    • Date first disenrollment
    • Date first diagnosis
    • Last day of follow-up

Note: provisional results - may be subject to change
Statistical analyses

• Additional variables in adjusted models (only available for approx 80% of children):
  – Birthweight
  – Gestational age
  – Mother’s age at delivery
  – Race and ethnicity
  – Apgar score at 5 minutes (HMO A only)

Note: provisional results - may be subject to change
Expected biases

• Health care utilization bias
  – Adjusted for by:
    • Time-varying count of well child visits in model
    • Matching on health facility (of well child visits < 1yr)
  – Checked for by using two “negative” control diagnoses:
    • Flat feet or toe deformities
    • Injury at unspecified site

• Outcome misclassification: medical chart reviews

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Overview

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• Results phase I
• Results phase II
• Discussion & recomendations

Note: provisional results - may be subject to change
Results: cohort selection

  \[\downarrow\]
  15,309 in final cohort

- HMO B: 184,723 born from 1992 through 1998
  \[\downarrow\]
  114,966 in final cohort

Note: provisional results - may be subject to change
Results: excluded children (%)

- Not continuously enrolled 1st year of life: 19.8% HMO B, 24.3% HMO A
- <2 polio vaccinations by 1 year of age: 1.6% HMO B, 2.8% HMO A
- Low birth weight: 3.8% HMO B, 2.6% HMO A
- Congenital or perinatal disorder: 12.6% HMO B, 3.1% HMO A

Note: provisional results - may be subject to change
Ethylmercury levels at different ages

Note: provisional results - may be subject to change
# Neurodevelopmental outcomes > 50 children

<table>
<thead>
<tr>
<th>ICD 9</th>
<th>Disorder</th>
<th>HMO A</th>
<th>HMO B</th>
</tr>
</thead>
<tbody>
<tr>
<td>299.0</td>
<td>Autism</td>
<td>(19)</td>
<td>150</td>
</tr>
<tr>
<td>299.8</td>
<td>Childhood psychosis</td>
<td>(11)</td>
<td>76</td>
</tr>
<tr>
<td>307.0</td>
<td>Stammering</td>
<td>54</td>
<td>75</td>
</tr>
<tr>
<td>307.2</td>
<td>Tics</td>
<td>(32)</td>
<td>121</td>
</tr>
<tr>
<td>307.4</td>
<td>Sleep disorders</td>
<td>56</td>
<td>123</td>
</tr>
<tr>
<td>307.5</td>
<td>Eating disorders</td>
<td>(5)</td>
<td>74</td>
</tr>
<tr>
<td>313</td>
<td>Emotional disturbances</td>
<td>79</td>
<td>203</td>
</tr>
<tr>
<td>314.0</td>
<td>Attention deficit disorder</td>
<td>69</td>
<td>517</td>
</tr>
<tr>
<td>315.31</td>
<td>Language delay</td>
<td>(15)</td>
<td>494</td>
</tr>
<tr>
<td>315.39</td>
<td>Speech delay</td>
<td>604</td>
<td>1448</td>
</tr>
<tr>
<td>315.4</td>
<td>Coordination disorder</td>
<td>76</td>
<td>(31)</td>
</tr>
</tbody>
</table>

Note: provisional results - may be subject to change
Renal outcomes and control diagnoses > 50 children

<table>
<thead>
<tr>
<th>ICD 9</th>
<th>Disorder</th>
<th>HMO A</th>
<th>HMO B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any renal disorder</td>
<td>24</td>
<td>197</td>
</tr>
<tr>
<td>5939</td>
<td>Unspecified kidney or ureter disease</td>
<td>14</td>
<td>80</td>
</tr>
<tr>
<td>734, 735</td>
<td>Flat feet or toe deformities</td>
<td>86</td>
<td>848</td>
</tr>
<tr>
<td>959.9</td>
<td>Injury at unspecified site</td>
<td>112</td>
<td>2428</td>
</tr>
</tbody>
</table>

Note: provisional results - may be subject to change
Summary of descriptive analyses

- Exposure varies by HMO and time
- Incidence of outcomes vary by HMO and time

= > Difficult to interpret crude results

= > Need to account for:
  - temporal trends: by stratification (matching)
  - differences between 2 HMOs: separate analyses

Note: provisional results - may be subject to change
(Unadjusted) relative risks by increase of 12.5 ug ethylmercury – HMO A

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0-1 m</th>
<th>2-3 m</th>
<th>4-5 m</th>
<th>6-7 m</th>
<th>0-7 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any neurodevelopmental disorder</td>
<td>1.07</td>
<td>1.07</td>
<td>1.05</td>
<td>0.99</td>
<td>1.02</td>
</tr>
<tr>
<td>Stammering</td>
<td>0.82</td>
<td>1.58</td>
<td>1.35</td>
<td>1.21</td>
<td><strong>1.26</strong> *</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>0.77</td>
<td>1.05</td>
<td><strong>1.43</strong> *</td>
<td>1.05</td>
<td>1.09</td>
</tr>
<tr>
<td>Emotional disturbances</td>
<td>1.52</td>
<td>0.96</td>
<td>1.02</td>
<td>0.97</td>
<td>1.03</td>
</tr>
<tr>
<td>Attention deficit disorder</td>
<td>1.32</td>
<td>0.91</td>
<td>0.91</td>
<td>0.91</td>
<td>0.92</td>
</tr>
<tr>
<td>Speech delay</td>
<td>0.99</td>
<td>1.10</td>
<td>1.05</td>
<td>0.99</td>
<td>1.02</td>
</tr>
<tr>
<td>Coordination disorder</td>
<td>0.65</td>
<td>1.41</td>
<td>1.28</td>
<td>0.97</td>
<td>1.06</td>
</tr>
<tr>
<td>Flat feet or toe deformities</td>
<td>0.55  *</td>
<td>0.98</td>
<td>1.14</td>
<td>0.94</td>
<td>0.97</td>
</tr>
<tr>
<td>Injury at unspecified site</td>
<td>1.09</td>
<td>1.00</td>
<td>0.90</td>
<td>1.09</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*: p<0.05  **: p<0.01

Note: provisional results - may be subject to change
(Unadjusted) relative risks by increase of 12.5 ug ethylmercury – HMO B

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0-1 m</th>
<th>2-3 m</th>
<th>4-5 m</th>
<th>6-7 m</th>
<th>0-7 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any neurodevelopmental disorder</td>
<td>1.02</td>
<td><strong>1.06</strong></td>
<td>1.03</td>
<td><strong>1.07</strong></td>
<td><strong>1.05</strong></td>
</tr>
<tr>
<td>Autism</td>
<td>0.99</td>
<td>1.08</td>
<td>0.92</td>
<td>0.97</td>
<td>0.98</td>
</tr>
<tr>
<td>Childhood psychosis</td>
<td>0.79</td>
<td>1.00</td>
<td>1.07</td>
<td>1.13</td>
<td>1.06</td>
</tr>
<tr>
<td>Stammering</td>
<td>0.97</td>
<td>1.17</td>
<td>1.21</td>
<td><strong>1.27</strong></td>
<td><strong>1.21</strong></td>
</tr>
<tr>
<td>Tics</td>
<td>1.13</td>
<td>1.01</td>
<td><strong>1.21</strong></td>
<td><strong>1.18</strong></td>
<td><strong>1.14</strong></td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>0.87</td>
<td>1.07</td>
<td>0.95</td>
<td>1.06</td>
<td>1.02</td>
</tr>
<tr>
<td>Eating disorders</td>
<td>0.86</td>
<td>1.04</td>
<td>1.12</td>
<td>0.98</td>
<td>1.03</td>
</tr>
<tr>
<td>Emotional disturbances</td>
<td>0.88</td>
<td>0.96</td>
<td>1.02</td>
<td>1.19</td>
<td>1.06</td>
</tr>
<tr>
<td>Attention deficit disorder</td>
<td>0.89</td>
<td><strong>1.11</strong></td>
<td><strong>1.10</strong></td>
<td>1.06</td>
<td><strong>1.08</strong></td>
</tr>
</tbody>
</table>

*: p<0.05   **: p<0.01

Note: provisional results - may be subject to change
(Unadjusted) relative risks by increase of 12.5 ug ethylmercury – HMO B(cont)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0-1 m</th>
<th>2-3 m</th>
<th>4-5 m</th>
<th>6-7 m</th>
<th>0-7 m</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Language delay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.37 **</td>
<td>1.20 **</td>
<td>1.02</td>
<td>1.07</td>
<td>1.09 **</td>
</tr>
<tr>
<td><strong>Speech delay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.10 *</td>
<td>1.06</td>
<td>1.00</td>
<td>1.06 **</td>
<td>1.05 **</td>
</tr>
<tr>
<td><strong>Any renal disorder</strong></td>
<td>0.97</td>
<td>1.03</td>
<td>1.04</td>
<td>1.05</td>
<td>1.04</td>
</tr>
<tr>
<td><strong>Unspecified kidney and ureter disease</strong></td>
<td>1.03</td>
<td>1.07</td>
<td>1.07</td>
<td>1.07</td>
<td>1.07</td>
</tr>
<tr>
<td><strong>Control diagnoses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Flat feet or toe deformities</strong></td>
<td>0.93</td>
<td>1.02</td>
<td>1.12 **</td>
<td>1.01</td>
<td>1.04 *</td>
</tr>
<tr>
<td><strong>Injury at unspecified site</strong></td>
<td>0.78 **</td>
<td>0.96</td>
<td>1.01</td>
<td>0.99</td>
<td>0.98 *</td>
</tr>
</tbody>
</table>

*: p<0.05    **: p<0.01

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### Relative risks by increase of 12.5 ug ethylmercury - summary of positive associations

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HMO A Unadjusted</th>
<th>HMO A Adjusted</th>
<th>HMO B Unadjusted</th>
<th>HMO B Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any neurodevelopmental disorder</td>
<td></td>
<td></td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Stammering</td>
<td>*</td>
<td>*</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Tics</td>
<td></td>
<td></td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional disturbances</td>
<td></td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention deficit disorder</td>
<td></td>
<td></td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>Language delay</td>
<td></td>
<td></td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Speech delay</td>
<td></td>
<td></td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Flat feet or toe deformities</td>
<td></td>
<td></td>
<td></td>
<td>*</td>
</tr>
</tbody>
</table>

*: p<0.05  **: p<0.01

Note: provisional results - may be subject to change
(Unadjusted) relative risks by increase of 12.5 ug ethylmercury – chart verified diagnoses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0-1 m</th>
<th>2-3 m</th>
<th>4-5 m</th>
<th>6-7 m</th>
<th>0-7 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speech delay – HMO A</td>
<td>1.31</td>
<td>1.10</td>
<td>1.09</td>
<td>0.97</td>
<td>1.03</td>
</tr>
<tr>
<td>Speech delay – HMO B</td>
<td>1.54 **</td>
<td>1.22</td>
<td>0.98</td>
<td>1.05</td>
<td>1.09</td>
</tr>
<tr>
<td>Autism – HMO B</td>
<td>0.88</td>
<td>1.10</td>
<td>0.94</td>
<td>0.99</td>
<td>1.00</td>
</tr>
<tr>
<td>Attention deficit disorder – HMO B</td>
<td>1.17</td>
<td>1.21</td>
<td>1.07</td>
<td>1.17</td>
<td>1.15 *</td>
</tr>
</tbody>
</table>

*: p<0.05   **: p<0.01
(Unadjusted) relative risks by increase of 12.5 ug ethylmercury – low birth weight children

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0-1 m</th>
<th>2-3 m</th>
<th>4-5 m</th>
<th>6-7 m</th>
<th>0-7 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any neurodevelopmental disorder – HMO A</td>
<td>0.31</td>
<td>1.26</td>
<td>1.33</td>
<td>0.99</td>
<td>0.96</td>
</tr>
<tr>
<td>Any neurodevelopmental disorder – HMO B</td>
<td>0.70</td>
<td>0.97</td>
<td>1.03</td>
<td>1.04</td>
<td>1.00</td>
</tr>
<tr>
<td>Language delay – HMO B</td>
<td>0.84</td>
<td>1.27</td>
<td>0.81</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td>Speech delay – HMO B</td>
<td>0.85</td>
<td>0.98</td>
<td>1.10</td>
<td>0.99</td>
<td>1.02</td>
</tr>
</tbody>
</table>

*: p<0.05    **: p<0.01

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Overview

• Vaccine Safety Datalink and thimerosal
• Study methodology
• Results phase I
• Results phase II
• Discussion & recomendations

Note: provisional results - may be subject to change
Phase II : study design

• Identical to phase I
  – Retrospective cohort
  – Cohort selection (same in- & exclusion criteria)
  – Exposure assessment
  – Statistical models

• Different from phase I
  – Focused analyses on outcomes of interest
    ⇒ Limited number of risk estimations

Note: provisional results - may be subject to change
Results: cohort selection

• HMO C: 30,000 born from 1991 through 1997

17, 547 in final cohort

Note: provisional results - may be subject to change
HMO C vs phase I: excluded children (%)

- Not continuously enrolled: 19.8% (HMO C), 24.3% (HMO B), 28.1% (HMO A)
- 1st year of life: 3.9% (HMO C), 1.6% (HMO B), 2.8% (HMO A)
- <2 polio vaccinations by 1 year of age: 3.8% (HMO C), 2.8% (HMO B), 3.9% (HMO A)
- Low birth weight: 3.8% (HMO C), 2.6% (HMO B), 3.8% (HMO A)
- Congenital or perinatal disorder: 12.6% (HMO C), 3.1% (HMO B), 5.7% (HMO A)

Note: provisional results - may be subject to change
HMO C vs phase I: exposure

Note: provisional results - may be subject to change
## HMO C: outcomes

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Cases</th>
<th>Mean age* (phase I)</th>
<th>% boys (phase I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tics</td>
<td>17</td>
<td>42 (44)</td>
<td>59 (67)</td>
</tr>
<tr>
<td>ADD</td>
<td>80</td>
<td>49 (49)</td>
<td>81 (80)</td>
</tr>
<tr>
<td>Speech delay</td>
<td>792</td>
<td>24 (33)</td>
<td>74 (71)</td>
</tr>
</tbody>
</table>

Note: provisional results - may be subject to change
(Unadjusted) relative risks by increase of 12.5 ug ethylmercury – HMO C

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0-1 m</th>
<th>2-3 m</th>
<th>4-5 m</th>
<th>6-7 m</th>
<th>0-7 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention deficit disorder</td>
<td>0.89</td>
<td>0.96</td>
<td>0.88</td>
<td>1.08</td>
<td>0.99</td>
</tr>
<tr>
<td>Speech or language disorders</td>
<td>0.94</td>
<td>0.93</td>
<td>0.96</td>
<td>1.01</td>
<td>0.98</td>
</tr>
<tr>
<td>Confirmed by chart review</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention deficit disorder</td>
<td>1.29</td>
<td>0.74</td>
<td>0.84</td>
<td>1.10</td>
<td>1.00</td>
</tr>
<tr>
<td>Speech or language disorders</td>
<td>1.07</td>
<td>0.92</td>
<td>0.97</td>
<td>1.01</td>
<td>0.98</td>
</tr>
<tr>
<td>LBW children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speech or language disorders</td>
<td>0.84</td>
<td>0.84</td>
<td>1.10</td>
<td>1.10</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*: p<0.05  **: p<0.01
Note: provisional results - may be subject to change
Overview

• Vaccine Safety Datalink and thimerosal
• Study methodology
• Results phase I
• Results phase II
• Discussion & recomendations

Note: provisional results - may be subject to change
Limitations of using (administrative) computerized databases

- Misclassification exposure: HepB birthdose
- Misclassification outcome: ICD9 and Costar codes
- Unknown: medical care utilization factors
- Only conditions that come to medical attention

Note: provisional results - may be subject to change
Discrepancy between Phases I and II

- HMO B biased (health care utilization bias)
- Differences in exposure → differences in power
- Differences in ascertainment
  - Over-ascertainment at HMO C → diluted T effect
  - Under-ascertainment at HMO B → bias more likely
- Population susceptibility differences

Note: provisional results - may be subject to change
# Thimerosal or other effect: DTP separate vs combined

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any neurodevelopmental disorder</td>
<td><strong>1.29</strong></td>
<td>1.07 – 1.55</td>
</tr>
<tr>
<td>Autism</td>
<td>0.71</td>
<td>0.23 – 2.25</td>
</tr>
<tr>
<td>Stammering</td>
<td>3.03</td>
<td>0.96 – 9.57</td>
</tr>
<tr>
<td>Tics</td>
<td>1.70</td>
<td>0.56 – 5.16</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>1.62</td>
<td>0.73 – 3.61</td>
</tr>
<tr>
<td>Emotional disturbances</td>
<td>1.43</td>
<td>0.50 – 4.13</td>
</tr>
<tr>
<td>Attention deficit disorder</td>
<td>1.39</td>
<td>0.71 – 2.70</td>
</tr>
<tr>
<td>Language delay</td>
<td>1.26</td>
<td>0.82 – 1.92</td>
</tr>
<tr>
<td><strong>Speech delay</strong></td>
<td><strong>1.27</strong></td>
<td>1.00 – 1.62</td>
</tr>
<tr>
<td>Flat feet or toe deformities</td>
<td>1.27</td>
<td>0.85 – 1.91</td>
</tr>
</tbody>
</table>

Note: provisional results - may be subject to change
Arguments for & against true thimerosal effect

For
– High statistical significance of some RR estimates
– Biologically plausible
– Dose response
– Consistent in DTP-Hib analyses

• Against
– Not consistent between HMOs A and B
– Not consistent between phases
– Low RR estimates
– Not found in LBW children
– One “negative” control diagnosis positive

Note: provisional results - may be subject to change
Conclusion

• Phase I analysis found several significant associations between thimerosal and neurodevelopmental disorders

• Analysis in a smaller, independent dataset does not confirm results for speech or language delay, and ADD

Note: provisional results - may be subject to change
Acknowledgements

• Group Health Cooperative / University of Washington: Bob Davis, Patti Benson
• Northern California Kaiser: Steve Black, Henri Shinefield, Paula Ray
• Harvard Pilgrim Health Care: Tracy Lieu, Stevan deProsse
• NIP: Frank DeStefano, Robert Chen, Phil Rhodes, Katie Okorro

Note: provisional results - may be subject to change
Relative risk associated with exposure at 3 months of age: neurologic developmental disorders

Note: provisional results - may be subject to change
Relative risk associated with exposure at 3 months of age: Autism

Note: provisional results - may be subject to change
Relative risk associated with exposure at 3 months of age: stammering

Note: provisional results - may be subject to change
Relative risk associated with exposure at 3 months of age: tics

Note: provisional results - may be subject to change
Relative risk associated with exposure at 3 months of age: attention deficit disorder

Note: provisional results - may be subject to change
Relative risk associated with exposure at 3 months of age: language delay

Note: provisional results - may be subject to change
Relative risk associated with exposure at 3 months of age: speech delay

Note: provisional results - may be subject to change
Relative risk associated with exposure at 3 months of age: neurodevelopmental disorder in LBW children

Note: provisional results - may be subject to change
Safe Minds questions (on this analysis)

• Cohort size variations – manipulated?
• Congenital/perinatal exclusions
• Exposure at 6 months low
• Young cohort
• Combination of disorders
• Differences HMOs
• Emotional disturbances: grouped vs separate

Note: provisional results - may be subject to change
1. Cohort size variations

• Two main reasons:
  – Different inclusion/exclusion criteria

• Minor differences:
  – Time of exposure
  – Additional variables included in model

Note: provisional results - may be subject to change
# 2. No congenital/perinatal exclusions – HMO B

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0-1 m</th>
<th>2-3 m</th>
<th>4-5 m</th>
<th>6-7 m</th>
<th>0-7 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any neurodevelopmental disorder</td>
<td>1.01</td>
<td>1.06 **</td>
<td>1.03</td>
<td>1.07 **</td>
<td>1.05 **</td>
</tr>
<tr>
<td></td>
<td>1.02</td>
<td>1.06 **</td>
<td>1.03</td>
<td>1.07 **</td>
<td>1.05 **</td>
</tr>
<tr>
<td>Autism</td>
<td>0.95</td>
<td>1.10</td>
<td>0.94</td>
<td>1.01</td>
<td>1.01</td>
</tr>
<tr>
<td></td>
<td>0.99</td>
<td>1.08</td>
<td>0.92</td>
<td>0.97</td>
<td>0.98</td>
</tr>
<tr>
<td>Stammering</td>
<td>0.87</td>
<td>1.05</td>
<td>1.17</td>
<td>1.21 *</td>
<td>1.14 *</td>
</tr>
<tr>
<td></td>
<td>0.97</td>
<td>1.17</td>
<td>1.21</td>
<td>1.27 *</td>
<td>1.21 **</td>
</tr>
<tr>
<td>Tics</td>
<td>1.18</td>
<td>1.01</td>
<td><strong>1.18</strong></td>
<td>1.23 **</td>
<td>1.15 **</td>
</tr>
<tr>
<td></td>
<td><strong>1.13</strong></td>
<td>1.01</td>
<td><strong>1.21</strong></td>
<td><strong>1.18</strong></td>
<td><strong>1.14</strong></td>
</tr>
<tr>
<td>Attention deficit disorder</td>
<td>0.85</td>
<td>1.10 *</td>
<td>1.06</td>
<td>1.07 *</td>
<td>1.06 **</td>
</tr>
<tr>
<td></td>
<td><strong>0.89</strong></td>
<td><strong>1.11</strong></td>
<td><strong>1.10</strong></td>
<td><strong>1.06</strong></td>
<td><strong>1.08</strong></td>
</tr>
</tbody>
</table>

Note: provisional results - may be subject to change
## 2. Different degrees of excluding children – HMO I

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0-1 m</th>
<th>2-3 m</th>
<th>4-5 m</th>
<th>6-7 m</th>
<th>0-7 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any neurodevelopmental disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All children (n = 4718)</td>
<td>0.97</td>
<td>1.04 *</td>
<td>1.03</td>
<td>1.06 **</td>
<td>1.04 **</td>
</tr>
<tr>
<td>Polio &gt;1 at 1 year (n = 4648)</td>
<td>0.97</td>
<td>1.04</td>
<td>1.03</td>
<td>1.06 **</td>
<td>1.04 **</td>
</tr>
<tr>
<td>No low birth weight (n = 4159)</td>
<td>1.01</td>
<td>1.06 **</td>
<td>1.03</td>
<td>1.07 **</td>
<td>1.05 **</td>
</tr>
<tr>
<td>Study cohort (n = 2989)</td>
<td>1.02</td>
<td>1.06 **</td>
<td>1.03</td>
<td>1.07 **</td>
<td>1.05 **</td>
</tr>
<tr>
<td>Autism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All children (n = 215)</td>
<td>0.94</td>
<td>1.14</td>
<td>0.95</td>
<td>1.02</td>
<td>1.03</td>
</tr>
<tr>
<td>Polio &gt;1 at 1 year (n = 213)</td>
<td>0.94</td>
<td>1.10</td>
<td>0.94</td>
<td>1.01</td>
<td>1.00</td>
</tr>
<tr>
<td>No low birth weight (n = 196)</td>
<td>0.95</td>
<td>1.10</td>
<td>0.94</td>
<td>1.01</td>
<td>1.01</td>
</tr>
<tr>
<td>Study cohort (n = 150)</td>
<td>0.99</td>
<td>1.08</td>
<td>0.92</td>
<td>0.97</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Note: provisional results - may be subject to change
3. Exposure at 6 months low

- Indeed, because many children vaccinated a few days after six months (or other recommended times of vaccination)

- Therefore exposure measured at 1, 3, 5 and 7 months (vs 1, 2, 3 and 6 months)
4. Young cohort

• Indeed
• Vaccination history of older children less reliable
• Will improve every year

5. Combination of disorders

• No, child can be counted for different disorder
  \[\Rightarrow\text{ Sum of individual disorders} > \text{any developmental disorder}\]
6. Differences HMOs

• See discussion

7. Emotional disturbances: grouped vs separate

• Also not significant when grouped

• Grouped because of:
  – Different coding between HMOs
  – Undefined entities

Note: provisional results - may be subject to change
Mrs Redwood’s request

**Autism**: RR + 95% CI for different levels of cumulative ethylmercury exposure from thimerosal-containing vaccines in first 7 months of life at HMO A and HMO B, 1992-1999

Cumulative ethylmercury exposure (n=number of cases in category)

Note: provisional results - may be subject to change