Neonatal pertussis vaccination

Can we do it?
What can we expect?

Nick Wood
Outline

- History and epidemiology
- Newborn acellular pertussis vaccine trials
  - Immunological
  - Safety
- Specific areas of study
  - Maternal antibody influence
  - Vaccine interference
  - Cell mediated immunity
  - Immune longevity and booster response
- Expected impact
1. Sako et al  JAMA 1945; 127: 379  “the exceptionally high mortality which pertussis causes in the first half year calls for thorough investigation of the possibility of increasing the resistance of young infants to the disease by immunizing them shortly after birth...”
Pertussis hospitalisation under 1 year olds 1994 - 2008

Age at onset (weeks)

No. of hospitalised cases

Cumulative percentage of cases
Age at death - pertussis
Australia 1967 to 2009 (n=60)
The efficacy of DPT and oral poliomyelitis immunization schedules initiated from birth to 12 weeks of age

Neal Halsey¹ & Artur Galazka²
Table 5. Serum agglutinin response following immunization with adsorbed pertussis vaccine schedules initiated from one day to three months of age.

<table>
<thead>
<tr>
<th>Investigator, year, and reference</th>
<th>Vaccine type</th>
<th>Potency in units per single dose</th>
<th>Amount of organisms × 10⁸ per single dose</th>
<th>No. of infants</th>
<th>Age at immunization (weeks or days, when specified)</th>
<th>Age at antibody testing (months)</th>
<th>Percentage with agglutinins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provenzano, 1965 (118)</td>
<td>DPT</td>
<td>7</td>
<td>10,10,10</td>
<td>8</td>
<td>1, 1.2</td>
<td>3</td>
<td>25, 48</td>
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<tr>
<td>Barrett, 1962 (11)</td>
<td>DPT</td>
<td>NA</td>
<td></td>
<td>49</td>
<td>1–2 days 4–8, 8–13 13–16 4–5</td>
<td>3–4</td>
<td>(50)</td>
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<tr>
<td>Baraff, 1984 (8)</td>
<td>DPT</td>
<td>NA</td>
<td></td>
<td>10</td>
<td>3.5 days 8, 18, 26</td>
<td>9</td>
<td>105</td>
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<tr>
<td>Pstragowska, 1966 (121)</td>
<td>DPT</td>
<td>NA</td>
<td></td>
<td>13</td>
<td>8, 18, 26</td>
<td>9</td>
<td>200</td>
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<tr>
<td>Di Sant Agnese, 1949 (33)</td>
<td>DPT</td>
<td>10,20,20</td>
<td></td>
<td>103</td>
<td>6 days 5, 9</td>
<td>NA</td>
<td>23, 62</td>
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<td></td>
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<td>10,20,20</td>
<td></td>
<td>125</td>
<td>1, 5, 9</td>
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<td>54, 260</td>
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<td>DPT</td>
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<td></td>
<td>108</td>
<td>1, 5, 9</td>
<td>6</td>
<td>33, 126</td>
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<tr>
<td></td>
<td>DPT</td>
<td>10,20,20</td>
<td></td>
<td>47</td>
<td>1, 5, 9</td>
<td>12</td>
<td>34, 118</td>
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<tr>
<td>Gaisford, 1960 (51)</td>
<td>DPT</td>
<td>NA</td>
<td></td>
<td>31</td>
<td>1, 5, 9</td>
<td>3.5</td>
<td>19, 47</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>10,10,20</td>
<td></td>
<td>121</td>
<td>1, 6, 13</td>
<td>4</td>
<td>131</td>
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<tr>
<td></td>
<td>P</td>
<td>16,24,40</td>
<td></td>
<td>115</td>
<td>6, 10</td>
<td>4.5</td>
<td>63, 259</td>
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<tr>
<td>Miller, 1949 (95)</td>
<td>P</td>
<td>40,80,80</td>
<td></td>
<td>50</td>
<td>1, 4, 9</td>
<td>6</td>
<td>90, 1432</td>
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<td>Waddell, 1946 (144)</td>
<td>P</td>
<td>40,80,80</td>
<td></td>
<td>43</td>
<td>13, 17</td>
<td>6</td>
<td>95, 1740</td>
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<td></td>
<td>P</td>
<td>30,30,30</td>
<td></td>
<td>80</td>
<td>&lt;2, 8.10</td>
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<td></td>
<td>P</td>
<td>20,40,40</td>
<td></td>
<td>21</td>
<td>1, 2, 3</td>
<td>1</td>
<td>NA, 160</td>
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<tr>
<td></td>
<td>DPT</td>
<td>20,40,40</td>
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<td>4, 8.12</td>
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<td>8,12,20</td>
<td></td>
<td>1007</td>
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<td>4</td>
<td>320, 450</td>
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<td>1294</td>
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<td>6–8</td>
<td>51, 131</td>
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<td></td>
<td>P</td>
<td>20,30,30</td>
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<td>22</td>
<td>4, 8, 12</td>
<td>6</td>
<td>82, 1280</td>
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<td></td>
<td>P</td>
<td>10,10,10</td>
<td></td>
<td>25</td>
<td>4–12, 8–16, 12–20</td>
<td>6–8</td>
<td>92</td>
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<tr>
<td></td>
<td>P</td>
<td>10,10,10</td>
<td></td>
<td>7</td>
<td>4, 8, 12</td>
<td>6</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>DPT</td>
<td>20,40,40</td>
<td></td>
<td>289</td>
<td>6, 12, 18</td>
<td>7.5</td>
<td>71, 642</td>
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<td></td>
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<td>8.5–11.5U</td>
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<td>23</td>
<td>8–12</td>
<td>12–16, 16–22</td>
<td>6–9, 214</td>
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<tr>
<td></td>
<td>DPT</td>
<td>4–5.5U</td>
<td></td>
<td>19</td>
<td>8–12</td>
<td>12–16, 16–22</td>
<td>6–9, 118</td>
</tr>
<tr>
<td></td>
<td>DPT</td>
<td>≥4 NIH</td>
<td></td>
<td>67</td>
<td>6–12</td>
<td>10–18, 14–24</td>
<td>? (85)</td>
</tr>
<tr>
<td>Wyllie, 1963 (146)</td>
<td>DPT</td>
<td>≥4 NIH</td>
<td></td>
<td>31</td>
<td>6–12</td>
<td>10–18, 14–24</td>
<td>? (97)</td>
</tr>
<tr>
<td></td>
<td>DPT</td>
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<td></td>
<td>14</td>
<td>8, 14</td>
<td>4, 5</td>
<td>363</td>
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<tr>
<td></td>
<td>DPT</td>
<td>NA</td>
<td></td>
<td>44</td>
<td>8, 12, 26</td>
<td>7</td>
<td>258</td>
</tr>
</tbody>
</table>

Note: GMT indicates the age at which the antibody response was measured.
IMMUNIZATION AND ANTIBODY RESPONSE IN THE NEWBORN INFANT

I. Pertussis Inoculation within Twenty-four Hours of Birth

R. William Provenzano, M.D., † Leslie H. Wetterlow, B.S.,‡ and Charles L. Sullivan, M.D.§

Cambridge and Brighton, Massachusetts
“Can the practitioner expect an adequate antibody response to inoculations given within 24 hours of birth?”

“What type of antigen should be used – plain pertussis or combined diphtheria, tetanus and pertussis?”

“Are the untoward reactions at this age such as to make the attempt unacceptable?”
Pertussis-containing vaccine 6 to < 24 hours after birth

- **Group 1**  
P+P+P @ 3 week intervals *then* 2xDTP @ 4 week intervals
- **Group 2**  
3xDTP @1 day, 1 month, 2 months
- Boosters with DTP @ 12 and 24 months
- N= 23

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“...the immune response continued to be suppressed in 75% up to 5 months of age ....and in about 50% to the age of 15 months....these results suggest the possibility that “*immunologic paralysis*” had been induced by ..... immunization on the first day of life.....”

---

Provenzano et al

- Small sample size
- Plain pertussis vaccine – 20 000 000 000 org/ml
  - Killed by thiomersol
- Measure pertussis agglutination titres
- No safety concerns

Conclusion
- “pertussis antigen, alone or combined, be used cautiously in neonates and that immunisation should probably not be attempted under 3 weeks of age”
ACELLULAR PERTUSSIS VACCINE TRIALS

40 YEARS LATER
Pediatrics 2003

N=317 infants

J. Pediatrics 2007

J. Pediatrics 2008

PIDJ 2010
Birth Pa vaccine study methods - vary

- Pa vaccine used
  - DTPa vs Pa
  - Different antigen amounts
  - Timing of dose
- Timing of serology
  - Laboratory
- Measurement of concomitant antigen responses
- Cell mediated immunity
## Recent neonatal trials with acellular pertussis vaccines

<table>
<thead>
<tr>
<th></th>
<th>Belloni et al ITALY</th>
<th>Halasa et al USA</th>
<th>Knuf et al GERMANY</th>
<th>Wood et al AUSTRALIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccine</strong></td>
<td>Pa Chiron</td>
<td>DTPa Sanofi</td>
<td>Pa GSK</td>
<td>Pa GSK</td>
</tr>
<tr>
<td><strong>Pa antigen content</strong></td>
<td>PT 5ug PRN 2.5ug FHA 2.5ug</td>
<td>PT 10ug PRN 3 ug FHA 3 ug Fim 5 ug</td>
<td>PT 25ug PRN 8ug FHA 25ug</td>
<td>PT 25ug PRN 8ug FHA 25ug</td>
</tr>
<tr>
<td><strong>Combination vaccine</strong></td>
<td>Acelluvax DTPa Polio Hib Hep B</td>
<td>IPV Daptacel ActHib Prevnar</td>
<td>Infanrix hexa</td>
<td>Infanrix hexa Prevenar</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td>0,3,5,6,12 months</td>
<td>0,6,7,17,18 months</td>
<td>0,3,5,7 months</td>
<td>0,2,4,6,8 months</td>
</tr>
<tr>
<td><strong>Site of ELISA</strong></td>
<td>Not stated</td>
<td>Vanderbilt, US</td>
<td>GSK Belgium</td>
<td>GSK Belgium</td>
</tr>
<tr>
<td><strong>Cellular immunity measured</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Recent neonatal trials with acellular pertussis vaccines

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>Pa</td>
<td>DTPa</td>
<td>Pa</td>
<td>Pa</td>
</tr>
<tr>
<td>1 month</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 month</td>
<td></td>
<td>DTPa</td>
<td>DTPa</td>
<td>DTPa</td>
</tr>
<tr>
<td>3 month</td>
<td></td>
<td>DTPa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 month</td>
<td></td>
<td>DTPa</td>
<td>DTPa</td>
<td>DTPa</td>
</tr>
<tr>
<td>5 month</td>
<td></td>
<td>DTPa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 month</td>
<td></td>
<td>DTPa</td>
<td>DTPa</td>
<td>DTPa</td>
</tr>
<tr>
<td>7 month</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 month</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 month</td>
<td></td>
<td>DTPa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>91</td>
<td>50</td>
<td>100</td>
<td>76</td>
</tr>
</tbody>
</table>

= serology
Serology – primary response

- Pertussis antibodies
  - **PT**
  - **PRN**
  - **FHA**
  - Mother – at birth of infant
  - Infant at varying time points

- Hib, anti-HBs, dip, tetanus
  - Infant – 7 to 8 months old
    - 3 studies only (n= 257 infants)
Figure 1. Anti-pertussis antibody GMCs from birth until completion of primary vaccination (ATP cohort for immunogenicity). ○, Group aP; ○, group HBV. *95% CI on the GMC ratio between groups does not include “1.”
Antibody levels two months after 3rd dose of Pa

- Group 1 - age 4 months
- Group 2 - age 6 months
- Group 3 - age 8 months
USA

![Graph showing anti-PT GMCs (EL.U/ml) over time with P-values P=0.036 and P=0.039.](image)

- DTPa at birth
- Control

- Time points: Birth, 6 months, 7 months
Summary – primary pertussis response

- Waning of antibody from birth to 2-3 months old
- Earlier antibody responses in birth Pa group
  - 3 studies
  - PT, FHA, PRN significantly higher
- 1st dose primes and second dose increase
- Non significant difference at 7-8 months
  - 2 studies – Australia and Germany
- Contrary findings with DTPa at birth
  - ?vaccine interference
Does pre-existing maternal antibody influence pertussis antibody responses?
Fig. 3. Expected influence of maternal antibodies on infant antibody responses to subunit vaccines.
Mothers given DTPw
Compare levels at 2 months old with
Post immunisation at 7 months old

Anti-PT response post DTPa = non sig
Summary – Birth Pa trials

- Italy
  - No data
  - “no correlation was observed”

- USA
  - “no impact of maternally derived pre-existing antibodies ….. on infant responses… although pre-existing pertussis antibody levels were low”

- Germany
  - No data

- Sydney
  - lower antibody levels when combined group data
How important is baseline maternal antibody level?

<table>
<thead>
<tr>
<th>Antibody GMC EL.U/ml</th>
<th>Belloni et al ITALY</th>
<th>Halasa et al USA</th>
<th>Wood et al AUSTRALIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>4.5</td>
<td>9</td>
<td>5.1</td>
</tr>
<tr>
<td>PRN</td>
<td>4.6</td>
<td>27</td>
<td>5.5</td>
</tr>
<tr>
<td>FHA</td>
<td>16.6</td>
<td>11</td>
<td>13.6</td>
</tr>
</tbody>
</table>

Kirkland et al Clinical Infectious Disease 2009;49:584-7
Leuridan et al PIDJ 2011; 30: 608-9
Gall et al AJOG 2011;204:334.e1-5
Fig. 3. Expected influence of maternal antibodies on infant antibody responses to subunit vaccines.
Does birth pertussis vaccine interfere with primary concomitant antigen responses?
Concomitant antigen responses – birth group

<table>
<thead>
<tr>
<th></th>
<th>Belloni et al ITALY</th>
<th>Halasa et al USA</th>
<th>Knuf et al GERMANY</th>
<th>Wood et al AUSTRALIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant antigen responses</td>
<td>Not measured</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hib</td>
<td>same</td>
<td></td>
<td>LowerGMC and % &gt; 0.15ug/ml</td>
<td>Lower Group 1 only</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>same</td>
<td>Lower</td>
<td>Note: HBV was control</td>
<td>Lower Note: all given HBV</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>lower</td>
<td>Same</td>
<td></td>
<td>same</td>
</tr>
<tr>
<td>Tetanus</td>
<td>same</td>
<td>same</td>
<td>same</td>
<td>same</td>
</tr>
</tbody>
</table>

Summary – potential vaccine interference
Hepatitis B surface antibody response at age 8 months - Australia

<table>
<thead>
<tr>
<th></th>
<th>anti-HBs GMC</th>
<th>10-100 %</th>
<th>101-1000 %</th>
<th>&gt;1000 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 and 2</td>
<td>409</td>
<td>12</td>
<td>62</td>
<td>26</td>
</tr>
<tr>
<td>n=39</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Group 3</td>
<td>747.7</td>
<td>0</td>
<td>73</td>
<td>27</td>
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<tr>
<td>n=15</td>
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<td></td>
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How safe is the birth dose of pertussis vaccine?
Reactogenicity - Germany

A.

% of subjects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Group aP</th>
<th>Group HBV</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling</td>
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<tr>
<td>Drowsiness</td>
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<td></td>
<td></td>
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<tr>
<td>Fever</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of appetite</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Group aP
- Group HBV
- Grade 3
Reactogenicity - Australia

- Birth dose
  - Nil fever >38°C
  - Nil injection site reactions >10mm after birth Pa dose

Reactogenicity at 6 months age by group

![Bar chart showing reactogenicity at 6 months age by group](chart.png)
Does birth pertussis vaccine influence immune persistence and responses to booster vaccines?
Germany
- N=66
- Mean age 13.7 months and given Infanrix hexa


Table 1. Serological responses before and one month after the booster dose (ATP cohort for immunogenicity)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Time point</th>
<th>Group aP</th>
<th>Group HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>Pre</td>
<td>86.2 (68.3; 96.1)</td>
<td>12.7 (8.8; 18.2)</td>
</tr>
<tr>
<td></td>
<td>≥5 E.I.U/ml</td>
<td>100 (88.1; 100)</td>
<td>60.1 (45.5; 79.4)</td>
</tr>
<tr>
<td>FHA</td>
<td>Pre</td>
<td>100 (88.1; 100)</td>
<td>104.5 (67.5; 161.7)*</td>
</tr>
<tr>
<td></td>
<td>≥5 E.I.U/ml</td>
<td>100 (88.1; 100)</td>
<td>601.0 (451.1; 800.7)</td>
</tr>
<tr>
<td>PRN</td>
<td>Pre</td>
<td>96.6 (82.2; 99.9)</td>
<td>26.2 (17.6; 38.8)</td>
</tr>
<tr>
<td></td>
<td>≥5 E.I.U/ml</td>
<td>100 (88.1; 100)</td>
<td>409.1 (312.3; 535.8)</td>
</tr>
</tbody>
</table>

Nil significant difference in pertussis booster response between groups
Lower response to Hib in birth group
Australia

![Graph showing anti-PT GMCs (EL.U/ml) for different age groups in Australia.](image-url)

**Graph Description:**
- **Y-axis:** Anti-PT GMCs (EL.U/ml)
- **X-axis:** Age (months)
- **Legend:**
  - Group 1
  - Group 2
  - Group 3

**Key Observations:**
- Anti-PT GMCs increase with age in all groups.
- Group 1 maintains a higher level of GMCs compared to Groups 2 and 3.
- GMCs are measured at various ages: Birth, 2 months, 4 months, 6 months, 8 months, and 2 years.

**Note:** The data is specific to Australia and represents anti-PT GMCs post-immunization.
What about cell mediated immunity?
T cell immunity is important for pertussis protection

- Mouse models – Mills et al
- Pertussis – survive intracellularly
- Pa vaccines infancy = Th1 predominance > Th2

Pertussis-Specific Cell-Mediated Immunity in Infants after Vaccination with a Tricomponent Acellular Pertussis Vaccine

F. ZEPP,1* M. KNUF,1 P. HABERMEHL,1 H. J. SCHMITT,2 C. REBSCH,1 P. SCHMIDTKE,1 R. CLEMENS,3 AND M. SLAOUFI3

0019-9567/96/$04.00+0
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ncirs
NATIONAL CENTRE FOR IMMUNISATION RESEARCH & SURVEILLANCE
Cytokine response to pertussis antigens

Neonatal vaccination drives Th2 polarised memory development
Questions arising from these findings

• will Th-memory responses remain sufficiently Th2-polarised to influence injection-site responses at subsequent booster?

• will strongly Th2-polarised memory against pertussis antigens influence host responses to pathogens at infection sites?

• are the group potentially “at risk” of atopy?
Can we do it?

What can we expect from birth pertussis vaccination?
Study of the risk factors for severe childhood pertussis based on hospital surveillance data

Valérie Briand *, Isabelle Bonmarin, Daniel Lévy-Bruhl

National Institute for Public Health Surveillance, Department of Infectious Diseases,
12 rue du Val d’Oise, 94415 Saint-Maurice Cedex, France

Received 11 August 2006; received in revised form 6 July 2007; accepted 15 July 2007
Available online 2 August 2007

Table 2
Factors associated with severe pertussis in children aged 2–11 months

<table>
<thead>
<tr>
<th>Age at onset of symptoms (months)</th>
<th>Univariate analysis</th>
<th>Multivariate analysis a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR b</td>
<td>CI b</td>
</tr>
<tr>
<td>2–3</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>4–5</td>
<td>0.50</td>
<td>0.26–0.98</td>
</tr>
<tr>
<td>6–11</td>
<td>0.38</td>
<td>0.16–0.91</td>
</tr>
<tr>
<td>Number of doses of vaccine</td>
<td>OR b</td>
<td>CI b</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>1</td>
<td>0.45</td>
<td>0.23–0.85</td>
</tr>
<tr>
<td>2 or 3</td>
<td>0.08</td>
<td>0.01–0.59</td>
</tr>
</tbody>
</table>

Some evidence that 1 dose may be protective
What can we expect? – Australian hospitalisation rates

Equivalent anti-PT levels 2 months earlier with Pa at birth
Possible shift rates by 2 months
“adequate antibody response to inoculations given within 24 hours of birth?”

- Yes - given up to 5 days after birth

- What type of antigen should be used – plain pertussis or combined diphtheria, tetanus and pertussis?

- Monovalent Pa

“Are the untoward reactions at this age such as to make the attempt unacceptable?”

- No

More data needed

Current NHMRC funded multicentre trial - underway

Maternal dTpa <5 years

Pa at birth
n=110

No Pa at birth
n=110

No maternal dTpa <5 years

Pa at birth
n=110

No Pa at birth
n=110

SEROLOGY – birth, 6 weeks, 10 weeks, 6 and 8 months

CMI – 10 weeks and 8 months

N=349 to date
Safety data so far......

- Solicited adverse events days 0-2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Birth Pa (n=120)</th>
<th>No birth pa (n=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt;37.5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Redness &gt;10mm</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Grade 3 Irritability</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Grade 3 Drowsiness</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
Birth vaccination is well established

- WHO EPI schedule – OPV, BCG, Hep B
- Healthcare contact at birth
- Immunologically
  - ACTIVE antibody and CMI production
  - vs passive antibody
    - Neonatal tetanus = maternal immunisation

- ? Combination HepB-Pa vaccine – potential
- ? 5 vs 3 component Pa vaccine
- ? cost effectiveness
- ? parental and physician attitudes
Summary

- Monovalent Pa studies to date (n=317)
  - Earlier pertussis antibody
  - Concomitant antigen responses – reduced but ?significance
  - Th2 polarised responses early
  - Safe
  - No hyporesponsiveness

- Key Questions
  - Influence of maternal antibody
  - Vaccine interference and hyporesponsiveness
  - How effective?
Acknowledgements

- Peter McIntyre and NCIRS
- Foundation for Children
- GSK – Pa supply and serology testing
- NHMRC Birth Pa vaccine trial staff
  - Sydney - Rose Joyce, Carol Sheinberg, Jane Ho
  - Melbourne – Terry Nolan, Jodie McVernon, Marita Kefford
  - Adelaide – Helen Marshall, Susan Lee
  - Perth – Peter Richmond, Jenny Kent