Antibody responses to monovalent acellular pertussis vaccine at birth in relation to maternal dTpa pre-pregnancy

Peter McIntyre
On behalf of Nick Wood, Terry Nolan, Helen Marshall, Peter Richmond, Emma Gibbs
Outline

- What was known prior to this study?
- Rationale and study design
- Results
- Implications
What was known prior to study?

- 60% of deaths and 30% of hospitalisations <= 6 weeks
- < 10% in first 2 weeks after birth
- 4 small RCTs of neonatal acellular pertussis vaccine
Studies of acellular pertussis vaccine in first week of life

N=317  * = significant (P<0.05)

<table>
<thead>
<tr>
<th></th>
<th>Belloni et al Chiron aP (N=91)</th>
<th>Halasa et al Sanofi DTaP (N=50)</th>
<th>Knuf et al GSK aP (N=100)</th>
<th>Wood et al GSK aP (N=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertussis Ab responses in birth aP group</td>
<td>Higher*</td>
<td>Lower* (post primary and booster)</td>
<td>Higher*</td>
<td>Higher*</td>
</tr>
<tr>
<td>Concomitant antigen responses</td>
<td>Lower dip, Hep B = Higher Hib and Polio*</td>
<td>Lower Hib and Hep B</td>
<td>Lower Hib and Hep B</td>
<td></td>
</tr>
</tbody>
</table>

DTaP has “bystander effect” not seen with aP (Pediatrics 2008)
Rationale and Study design
Study rationale – in 2009

- Neonatal vaccination immunogenicity data promising
  - aP not DTaP; small studies
- Hepatitis B recommended at birth in US, Australia and many LMIC countries with good coverage
- Poor coverage for influenza vaccine in pregnancy despite long-standing recommendations
  - Nervousness about interventions in pregnancy
- Cocooning recommended – impact on next pregnancy?
Outcome measure – detectable antiPT and PRN
Correlation with protection after household exposure

- 209 RCT participants – Ab measured pre-exposure

- VE against severe (WHO) cough:
  - PT+PRN+FIM all detectable 85% (95% CI 65-93)
  - PT alone detectable 46% (95% CI 14-66)

Study Design

Maternal Tdap within 5 years of delivery
(Not in pregnancy)
N=200

- Pa at birth
- No Pa at birth

No maternal Tdap within 5 years of delivery
(N = 200)

- Pa at birth
- No Pa at birth

Eligibility: >36 weeks gestation, healthy, <120 hours after birth
Aims and endpoints

- **AIM:** Immunogenicity and safety of Pa vaccine < 120 hours after birth vs first Pa-containing vaccine at 6 weeks

- **Primary endpoint:** Detectable (>5 EL.U/ml) IgG antibody to pertactin (PRN) *and* pertussis toxin (PT) at 10 weeks

  - **Secondary endpoints:**
    - Detectable PT and PRN at 6 weeks
    - Antibody responses in mothers with Tdap < 5 years
<table>
<thead>
<tr>
<th></th>
<th>aP* and Hep B n= 221</th>
<th>Hep B only n= 219</th>
<th>Serology</th>
</tr>
</thead>
</table>
| **Birth (< 5days old)** | **Monovalent aP**  
Hepatitis B | Hepatitis B | **Maternal** |
| 6 weeks              | DTaP-HepB-Hib-IPV  
Pneumococcal Rotavirus | DTaP-HepB-Hib-IPV  
Pneumococcal Rotavirus | **Maternal** |
| 10 weeks             |                       |                    |          |
| 4 months             | DTaP-HepB-Hib-IPV  
Pneumococcal Rotavirus | DTaP-HepB-Hib-IPV  
Pneumococcal Rotavirus | **Maternal** |
| 6 months             | DTaP-HepB-Hib-IPV  
Pneumococcal | DTaP-HepB-Hib-IPV  
Pneumococcal | **Maternal** |
| 8 months             |                       |                    |          |

*GSK Pa vaccine = PT 25 mcg, FHA 25 mcg, PRN 8 mcg
Serology

- Pertussis antibodies (ELISA)
  - PT
  - PRN
  - FHA

- Hib, anti-HepB, diphtheria, tetanus
  - Infant – 8 months old

- Serology (ELISA) performed by GSK Vaccines, Belgium
  - Same laboratory as pilot study (Wood et al 2010)

- NHMRC clinical trial centre – statistical analysis
Adverse events

- Telephone contact 2 and 7 days post each vaccination
- Parental measurement of temperature and injection site reaction
  - Diary card
- Review at each visit
  - Hospitalisations
  - GP visits
Results

- Demographics
- Maternal antibody by pre-pregnancy dTpa status
- Infant antibody endpoints
  - Pertussis
  - Other antigens
### Participant demographics

|                                | aP and Hep B at birth  
<table>
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<tbody>
<tr>
<td></td>
<td>n=221</td>
<td>Hep B only n= 219</td>
</tr>
<tr>
<td>Mean birth weight (g) (range)</td>
<td>3479 (3417-3540)</td>
<td>3548 (3492-3605)</td>
</tr>
<tr>
<td>Mean gestation weeks</td>
<td>39.2 (&gt;37)</td>
<td>39.2 (&gt;37)</td>
</tr>
<tr>
<td>Male  n (%)</td>
<td>117 (52.9%)</td>
<td>116 (52.9%)</td>
</tr>
<tr>
<td>Caucasian n (%)</td>
<td>189 (86%)</td>
<td>181 (83%)</td>
</tr>
<tr>
<td>Maternal age (mean years)</td>
<td>33.6</td>
<td>33.4</td>
</tr>
<tr>
<td>Maternal Tdap &lt;5 years of pregnancy (n=96)</td>
<td>49 (22%)</td>
<td>47 (21%)</td>
</tr>
<tr>
<td>Mean months since maternal Tdap vaccine</td>
<td>21.4</td>
<td>21.2</td>
</tr>
</tbody>
</table>
Distribution of pertussis toxin antibody level according to maternal vaccine status

45% of mothers with no detectable PT at birth if no TdaP < 5 yrs

15% of mothers with no detectable PT if Tdap < 5 yrs
### Primary endpoint: @ Week 10 PT and PRN >5 EL.U/ml

<table>
<thead>
<tr>
<th></th>
<th>aP and Hep B</th>
<th>Hep B only</th>
<th>Odds ratio* (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All subjects n (%) (n=398)</strong></td>
<td>192/206 (93.2%)</td>
<td>98/193 (50.8%)</td>
<td>13.3 (7.2-24.5) p &lt;0.001</td>
</tr>
<tr>
<td>Maternal TdaP vaccine &lt; 5 years (n=90)</td>
<td>43/47 (91.5%)</td>
<td>27/44 (61.4%)</td>
<td>13.1 (7.1-24.1) p&lt;0.001</td>
</tr>
<tr>
<td>No maternal TdaP vaccine (n=308)</td>
<td>149/159 (93.7%)</td>
<td>71/149 (47.7%)</td>
<td></td>
</tr>
</tbody>
</table>

* Cochrane-Mantel-Haensel chi square test
Antibody responses to pertussis toxin (PT)

Antigen: PT

Hep B only

aP and Hep B

Birth 6 weeks 10 weeks 6 month 8 month

Anti-PT GMC (EU/ml)
## PT and PRN antibody at 6 weeks

<table>
<thead>
<tr>
<th></th>
<th>PT antibody GMC (% above detectable)</th>
<th>PRN antibody GMC (% above detectable)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pa at birth</td>
<td>Hep B</td>
</tr>
<tr>
<td>All subjects n (%)</td>
<td>7.5 (64.8%)*</td>
<td>4.8 (37.4%)</td>
</tr>
<tr>
<td>(n=410)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal dTaP &lt; 5 yrs</td>
<td>11.1 (82.2%)</td>
<td>8.6 (64.4%)</td>
</tr>
<tr>
<td>(n=91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No maternal dTaP</td>
<td>6.7 (60%)*</td>
<td>4.0 (29.4%)</td>
</tr>
<tr>
<td>(n=319)</td>
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<td></td>
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* P value <0.05 for GMC
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<th>PRN antibody GMC (% above detectable)</th>
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<td>Hep B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All subjects n (%)</td>
<td>52.8 (100%)*</td>
<td>45.2 (100%)</td>
</tr>
<tr>
<td>(n=366)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal dTaP &lt; 5 yrs</td>
<td>44.2 (100%)</td>
<td>35.4 (100%)</td>
</tr>
<tr>
<td>(n=91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No maternal dTaP</td>
<td>47.9 (100%)*</td>
<td>55.6 (100%)</td>
</tr>
<tr>
<td>(n=319)</td>
<td></td>
<td></td>
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* P value <0.05 for GMC
Summary – pertussis antibody responses

- Significantly accelerated PT responses @ 6 and 10 weeks following aP within 5 days of birth
- Maternal dTap within 5 years pre-pregnancy significantly increases % detectable Ab and GMC @ 6 and 10 weeks
- But higher mat Ab lower infant PT responses
- At 8 months, maternal status no longer significant
  - birth aP group still have significantly higher PT Ab
Concomitant antigen responses at 8 months - no change in % reaching threshold but reduced GMC

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Threshold</th>
<th>aP and Hepatitis B vaccine</th>
<th>Hepatitis B vaccine only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% &gt; threshold</td>
<td>GMC (95% CI)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>&gt;10 mIU/ml</td>
<td>150</td>
<td>99.3</td>
</tr>
<tr>
<td>Hib</td>
<td>&gt;0.15 ug/ml</td>
<td>182</td>
<td>96.7</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>&gt;0.1 IU/ml</td>
<td>181</td>
<td>99.4</td>
</tr>
<tr>
<td>Tetanus</td>
<td>&gt;0.1 IU/ml</td>
<td>181</td>
<td>100</td>
</tr>
</tbody>
</table>

Maternal dTpa status not significant except ? Hib
Safety measures following birth aP vaccine

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<thead>
<tr>
<th></th>
<th>aP and Hep B N (%)</th>
<th>Hep B only N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt;38C after birth dose</td>
<td>0 (0%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Any redness, swelling or hardness &gt;10 mm</td>
<td>12 (5%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Any medical advice sought Days 0 to 7</td>
<td>6 (3%)</td>
<td>8 (4%)</td>
</tr>
</tbody>
</table>
Implications of these results

- Clinical protection?
- Relevant in the post-maternal dTpa era?
Severe infant pertussis: evidence of significant protection after 1 dose of pertussis-containing vaccine

Maternal and Neonatal Vaccination Protects Newborn Baboons From Pertussis Infection

Jason M. Warfel,1 James F. Papin,2 Roman F. Wolf,2 Lindsey L. Zimmerman,1 and Tod J. Merkel1
1Division of Bacterial, Parasitic and Allergic Products, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, Maryland; and 2Oklahoma Baboon Research Resource, Comparative Medicine, University of Oklahoma Health Sciences Center, Oklahoma City

1 dose DTPa @ 2 days = 2 doses = maternal DTPa in protecting against pertussis challenge
SAGE statement – 2014

Supplemental Strategies: Neonatal Immunization

- Neonatal immunization not recommended at this time
  - Limited data on impact and safety
  - Lack of availability of an aP alone vaccine
  - Window period of susceptibility
- Continued evaluation recommended
  - Data from human and baboon infants receiving a single vaccine dose demonstrate protection against severe pertussis disease
  - If data supporting immunogenicity, presumptive protection, and safety become available, it may have supplementary role along with maternal vaccination
Next steps

- “Plugging pertussis immunity gap” is all about individual level protection of newborn infant
  - Limits on achievable maternal coverage
  - 17% breakthrough cases in UK case-control study\(^1\)
  - \(\sim 10\%\) of babies of immunised mothers no measurable PT @ delivery\(^2\)

- Birth aP vaccine
  - \(\uparrow\) protection if mother has low antibody + prems
  - need aP vaccine

Acknowledgements

- NHMRC Project grant funding (2009-2013)
  - NHMRC Clinical Trials Centre – statistical analysis

- GSK Vaccines for aP vaccine supply and serology

- Research nurses at each of the participating sites

- Mothers and babies who participated in the study
Questions?
Supplementary slides
Scatter plot of maternal PT in mothers with dTap < 5 yrs

2 years

Study Group
- Group 0: hepB only
- Group 1: acellular pertussis
PT antibody responses by maternal dTap status

- Hep B only and no dTap
- Hep B only and dTap < 5 years
- aP and Hep B and no dTap
- aP and Hep B and dTap < 5 years
Reverse cumulative distribution curves at week 6

Pertussis toxin

Hep B only and no dTap
aP and Hep B and no dTap
Hep B only and dTap < 5 yrs
aP and Hep B and dTap < 5 yrs
Reverse cumulative distribution curves at week 6

Pertactin

Hep B only and no dTap
aP and Hep B and no dTap
Hep B only and dTap < 5yrs
aP and Hep B and dTap < 5yrs
Concomitant antigen responses

Hepatitis B

Diphtheria

Tetanus

Hib
Pertussis hospitalisations in infants aged <12 months, Australia, July 1998 - June 2012

60% of infant hospitalizations by 10 weeks old

Source: AIHW National Hospital Morbidity Database