Immunising the newborn baby and what it teaches about neonatal immunity

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Immunising the newborn

- What is “normal”
  - Pregnant woman
  - Fetus and newborn

- What happens when we immunise newborns

- What this teaches us

- What we should do
Caught on the horns of a dilemma
The horns of a dilemma

- Pregnant woman does not want to mount an immune response that will reject her baby

- Fetus does not want to produce cytokines that may trigger pre-term labour

- **But** mother and fetus need to fight off infections
Pregnant woman

- Impaired response to intracellular pathogens
- $T_\text{H}1$ usually required for Listeria, herpesvirus
- T-cell responses suppressed
Fetus and newborn

- Pro-inflammatory cytokines dangerous
- Can induce rejection and pre-term labour
- Bias against $T_{H1}$ responses
- Low Toll-like receptor expression (innate immunity)
- More susceptible to microbial infection
Newborn T-cell responses to vaccines

- Newborns respond well to BCG vaccine with mature $T_H1$ response
- Respond to OPV (and IPV): low $T_H1$, high Ab’s
- Hepatitis B vaccine: low $T_H1$, high Ab’s
B cells

- Polio type 1 vaccine does not protect vs polio types 2 or 3
- Need all 3 polio strains in vaccine
- Antibody responses highly specific

T cells

- Neonatal BCG vaccine protects against TB
- Also against atypical mycobacteria + leprosy
- T cell responses less specific
Dendritic cells

- Important antigen-presenting cells
- BCG vaccine intradermal
- Improved $T_H1$ response
Toll-like receptors (TLR)

- Receptors for microbial molecules
- Innate immune response
- TLR stimulators (agonists) as adjuvants
  - Monophosphoryl lipid A and HPV vaccine
Post-natal immune response

- Initial $T_H^2$ polarisation
- Increasing $T_H^1$ response with age
- Hygiene hypothesis
Maternal IgG antibody

- Protects against infection
- Active transport across placenta
- May interfere with immunisation
Maternal measles antibody

% measles antibody +ve

Age group (months)

0-0.5, 0.5-1, 1-3, 3-6, 6-9, 9-12, 12-15
Measles vaccination and age

% seroconversion (antibody titre > 200 U/l)

Age at vaccination (months)

9 -11

12 - 14

15 - 17
Maternal hepatitis A antibody and infant response to vaccination
Exceptions

- Maternal antibody not completely protective:
  - RSV
  - Pertussis
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
Pertussis-containing vaccine 6 to < 24 hours after birth

(Provenzano et al 1965)

- Group 1  
P+P+P @ 3 week intervals

  then 2 x DTPw @ 4 week intervals, 1 month post

- Group 2  
3 x DTPw @ 1 day, 1 month, 2 months

- Boosters with DTPw  @  12 and 24 months

- N= 23
Immune response to pertussis suppressed in 75% of infants up to 5 months of age in about 50% to age 15 months. This suggests "immunologic paralysis" induced by early immunisation.
Tolerance: Burnet & Medawar
a) CBA fetus

A donor

CBA adult
(accepts A skin but rejects AU skin)

AU donor

b) Blood group A allograft

Blood group O recipient

Recipient later develops antibodies against B but not A antigens
Hepatitis B

- Mother chronic carrier (HBeAg positive)

- Risk to baby: 85-90%

- HBs antigen, **no** Ab

- Tolerance

- Immune paresis
Neonatal hepatitis B immunisation

- Hepatitis B vaccine prevents 72% (60-80%)
- Vaccine + HB-Ig prevents 86 - 92% of cases
- Overcome tolerance, although vaccine just surface antigen
- Adjuvant
Polysaccharide

- Outer capsule: sugar
- GBS, *E.coli* K1
- Hib, pneumococcus, meningococcus
- No or very poor antibody response to polysaccharide as vaccine until >18 months
Conjugate vaccines

- Hapten principle
- Conjugate polysaccharide to protein
- Use immunogenic protein (diph, tet)
Polysaccharide vs conjugate vaccines

Polysaccharide
- T cell independent
- Hyporesponsiveness
- Transient immunity

Conjugate
- T cell dependent
- Memory cells
- Lasting immunity
Pertussis – affects newborns

Paroxysmal coughing ending in a typical whoop
Pertussis deaths: US 1938-40  (N=10,730)

Sako et al  JAMA 1945; 127: 379
Can a birth dose protect against pertussis?
Pertussis birth dose study

- Nick Wood
- Peter McIntyre
- NCIRS
Study design

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N= 27 (5 doses)</td>
<td>N= 23 (4 doses)</td>
<td>N=26 (3 doses)</td>
</tr>
<tr>
<td>Birth (&lt; 5 days old)</td>
<td>Pa* Hepatitis B</td>
<td>Pa* Hepatitis B</td>
<td>Hepatitis B</td>
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<tr>
<td>1 month</td>
<td>Pa*</td>
<td></td>
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<tr>
<td>2 months</td>
<td>Infanrix Hexa</td>
<td>Infanrix Hexa</td>
<td>Infanrix Hexa</td>
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<td></td>
<td>Prevenar</td>
<td>Prevenar</td>
<td>Prevenar</td>
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<tr>
<td>4 months</td>
<td>Infanrix Hexa</td>
<td>Infanrix Hexa</td>
<td>Infanrix Hexa</td>
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<td>Prevenar</td>
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<tr>
<td></td>
<td>Prevenar</td>
<td>Prevenar</td>
<td>Prevenar</td>
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<tr>
<td>8 months</td>
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*GSK Pa vaccine = PT 25 mcg, FHA 25 mcg, PRN 8 mcg
Serology

- Pertussis antibodies
  - PT
  - PRN
  - FHA
  - Mother – at birth of infant
  - Infant at 2, 4, 6 and 8 months old

- Hib, anti-HBs, diphtheria, tetanus
  - Infant – 8 months old
Anti-PT response

*Gp 1 vs Gp 2 and 3: P<0.05  (Group 1 = Pa at birth + 1m)
Anti-FHA response

*Gp 1 vs Gp 2 and 3: P<0.05
*Gp 1 vs Gp 2 and 3: P<0.05
Antibody levels two months after 3rd dose of Pa

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

GMC ELI.U/ml

Antibody

PT
FHA
PRN
What this study adds

- Two doses Pa (birth and one month) is immunogenic by 2 months
- No hyporesponsiveness
- Could protect infants earlier
Other studies of birth dose of Pa

- Possibility of reduced response later
- Need large randomised controlled trial
- NHMRC funded, recruiting
Conclusions: neonatal vaccines

- Newborn $T_H^1$ cell response reduced
- Maternal antibodies can interfere
- Tolerance
- Dendritic cells and Toll-like receptors
- Adjuvants
- Birth dose pertussis vaccine
The future

- Further studies of neonatal vaccines
- Ways of improving the neonatal immune response: e.g. new adjuvants, new routes
- Dendritic cells and Toll-like receptors
- New vaccines: RSV, HIV
Acknowledgements

- Nick Wood
- Claire –Anne Siegrist
- Melanie Wong