New Belgian Immunization Guidelines for Premature Infants

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Immuneological factors I

- Premature infants are IgG deficient due to diminished transplacental transport in the 3rd trimester.
  - Less (prolonged) passive protection.
- Immature T and B cell function.
  - Less immunologic response to vaccines
Host factors

- Co-morbidity;
  - Chronic respiratory disease (BPD).
  - Growth retardation en malnutrition.

- Treatment:
  - Corticosteroids (pre- en postnatal), IVIG, transfusions.
Vaccination schedule in Flanders, Belgium.

http://www.zorg-en-gezondheid.be
Outline

- What makes the preterm infant different?
- What is recommended?
  - Are there data to support these recommendations?
    - What about safety?
      - What about efficacy?
- Are there exceptions?
- What is actually happening?
Reaction to DTaP-Vaccine

- **Gestation age:** <30w
- **N= 48**

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt; 37.5°C</td>
<td>0 %</td>
<td>33%*</td>
</tr>
<tr>
<td>Extra O2</td>
<td>40%</td>
<td>42%</td>
</tr>
<tr>
<td>Apnoe (stimulation)</td>
<td>15%</td>
<td>23%</td>
</tr>
<tr>
<td>Sepsis screening</td>
<td>0%</td>
<td>8%**</td>
</tr>
</tbody>
</table>

* *P < .05,
** All increased CRP

Ellson VJ et al., J Pediatr. Child Health 2005
Apnoe and bradycardia after vaccination in premature infants with DTaP-IPV-HBV/HIB.

53 PT; DTaP + Hib vaccinations

First or recurrent apnoe in 13%
Cardiorespiratory (CR) events after 2nd dose DTaP?

N=64
2nd dose in NIC

V1
CR+
N= 33 (51%)

V2
CR+
6 (18%)

V2
CR-
27

V1
CR-
N= 31 (48%)

V2
CR-
31

V2
CR+
0 (0%)

Outline

- What is recommended?
  - Are there data to support these recommendations?
    - How about safety?
      - How about efficacy?
- Are there exceptions?
- What is actually happening?
What after Hexavalent vaccin (3 dose schedule)? Diphtheria, HBV, Polio-1,2,3.

FT = 92, PT = 94.

All GMT are lower in PT.

**Polio-3:** GMT, PT = 486 vs. 1208 bij FT.

Pertussis after Hexavalent vaccine?

- No difference PT vs. FT.
- Equal GMT after 3 doses.

Haemophilus influenza type-B?

Anti-PRP (>= 0.15 mcg/mL) after primary and booster vaccination with **Hexavalent** vaccine.

- Lower response after 1st vaccination.
- Faster decline of immunity after primary vaccination.
- Equal (100%) response after booster (12m).

Omenaca F. et al, Pediatrics Jan 2007
Influence of gestational age on HiB immune response after primary vaccination with hexavalent vaccine.

- Primary immune response correlates with degree of prematurity.
- Cave < 28w en < 1000g.
- GA had no influence on booster reaction (12m).

Omenaca F. et al, Pediatrics Jan 2007
Influence of co-morbidity on HiB immune response.

- Prenatal steroids: no influence
- Postnatal steroids (BPD): negative?
- Bloedtransfusion: negative?
- IVIG: negative?
- Failure to thrive (< P10th op 6m): Negative +++
  - Postnatal malnutrition?

Omenaca F. et al, Pediatrics Jan 2007
DtaP-Hib-Polio-HepB vaccination - Belgian Health Council recommendation for premature infants.

- **Safety**
  - CR-monitoring at 1st dose
    - 24 - 48h of discharge
  - CR-monitoring at 2nd dose if
    - admitted in hospital for prematurity and
    - if “serious” CR-event after first dose
  - No CR-monitoring if no event after 1st dose

- **Efficacy**
  - Booster dose at **13** month instead of **15** month
Hepatitis B Vaccine

GMT HBsAb

% Seroprotected

HepB vaccination - Belgian Health Council recommendation for premature infants.

- Mother HepB surface antigen positive (carrier)
  - HepB vaccination + hyperimmune IgG
    - 300 IE IM contralateral leg
    - Within 12 hrs of birth !!

- If neonate < 2000g
  - Extra HepB vaccine dose at 4 weeks
  - Primary vaccination (2-3-4 month) +13 month)
  - Check immunity
    - 4 weeks after primary vaccination (at 5-6 month)
Immunogenicity of 7v-Pnc-vaccine (Prevenar) in preterm and term infants: Protection after primary vaccination (2, 3, 4 m)?

<table>
<thead>
<tr>
<th>Serotype</th>
<th>5 m &gt; 0.2 mcg/ml</th>
<th>5 m &gt; 0.35 mcg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PT (n=62)</td>
<td>FT (n=61)</td>
</tr>
<tr>
<td>4</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>6B</td>
<td>70</td>
<td>92</td>
</tr>
<tr>
<td>9V</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>14</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>18C</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>19F</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>23F</td>
<td>88</td>
<td>95</td>
</tr>
<tr>
<td>1*</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>5*</td>
<td>0</td>
<td>34</td>
</tr>
</tbody>
</table>

*No vaccine serotypes antibodies dependent on GA en Ab at 2 m.

1 Fisher’s exact test (double sided)

Immunogenicity of 7v-Pnc-vaccine (Prevenar) in preterm and term infants: Protection after **booster** pneumovax23 (12m)?

<table>
<thead>
<tr>
<th>Serotype</th>
<th>12 m &gt; 0.35 mcg/ml</th>
<th>After booster 13m &gt; 0.35 mcg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PT (n=62)</td>
<td>FT (n=61)</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>85</td>
</tr>
<tr>
<td>6B</td>
<td>70</td>
<td>87</td>
</tr>
<tr>
<td>9V</td>
<td>69</td>
<td>80</td>
</tr>
<tr>
<td>14</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>18C</td>
<td>44</td>
<td>75</td>
</tr>
<tr>
<td>19F</td>
<td>68</td>
<td>97</td>
</tr>
<tr>
<td>23F</td>
<td>59</td>
<td>80</td>
</tr>
<tr>
<td>1*</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>5*</td>
<td>22</td>
<td>43</td>
</tr>
</tbody>
</table>

Low protection in PT although equal reaction to CPS booster (good memory).

Pnc-7 vaccination -
Belgian Health Council recommendation
for premature infants.

- **Schedule**
  - instead of 2 + 1 booster, use 3+ 1 booster schedule
    - = *Extra Pnc-vaccine dose at age 3 month*
  - Booster not later than 12 month
Measles

- Peak during epidemic (USA): 24% < 12m old.
- Transplacental antibodies
  - At birth: PT 48%, FT 71%
  - If < 28w, At 3 month age: None
- MMR given earlier? 6 - 9 m en 2nd dose after 3 m (12m)
Early waning of maternal measles antibodies in era of measles elimination

- Transplacental antibodies
  - Vaccinated mothers
    - 3m: 29%
    - 6m: 0%
  - Natural immune
    - 3m: 60%
    - 6m: 15%

Preterm infants were excluded!

Leuridan E et al. BMJ 2010
Influence of Maternal antibodies on humoral response in Measle vaccine?

MA = maternal antibodies
NMA = no maternal antibodies

Graph showing seroprotectivity at 6, 9, and 12 months for MA and NMA groups.
Measle vaccination - Belgian Health Council recommendation for premature infants.

- No special recommendation out of an epidemic situation

- When risk of exposure (epidemic)
  - 1 extra dose at 6 month
  - 2nd dose at 12 month
  - booster dose at 10-12y
**RotaTeq: high efficacy in premature infants confirmed by intent to treat analysis (population receiving at least one dose)**

Rate reduction for hospitalisations and emergency department (ED) visits attributable to G1-G4 RVGE in premature infants vaccinated with Rotateq or placebo up to 2 years after vaccination

<table>
<thead>
<tr>
<th></th>
<th>RotaTeq (n=938)</th>
<th>Placebo (n=990)</th>
<th>Rate reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisations</td>
<td>1</td>
<td>24</td>
<td><strong>96%</strong> (76,100)</td>
</tr>
<tr>
<td>ED visits</td>
<td>0</td>
<td>10</td>
<td><strong>100%</strong> (59,100)</td>
</tr>
<tr>
<td>Combined hospitalisation + ED visits</td>
<td>1</td>
<td>14</td>
<td><strong>92%</strong> (57,100)</td>
</tr>
</tbody>
</table>

Vaccination schedule: three doses from 6 weeks of age at 4 to 10 week intervals

Intent to treat population: population receiving at least one dose

Efficacy: From 14 days after the third dose through the 1st rotavirus season

n=numbers of evaluable subjects

**Goveia MG et al. Pediatr Infect Dis J 2007;26:1099-1104.**
Rota-vaccine – precautions!

- No influence of IVIG and PC transfusions, but first dose before 3 month.
- Breast feeding is not a contraindication.
- Beware of immunocompromised patients.
- Excretion in stools: especially within the first 7 days (8-45%), cave handhygiëne!
- AAP en ACIP guidelines:
  - Immunizing premature infants once they reach 6 weeks of age, are clinically stable, and are being or have been discharged from the hospital.
Rotavirus vaccination - Belgian Health Council recommendation for premature infants.

- Both (monovalent $[Rotateq®]$ and pentavalent $[Rotarix®]$) vaccines are save and efficacious
- 1st dose
  - 6 weeks but before 16 weeks!
- All doses before 32 weeks
Do not forget! – Cocoon vaccination!

- Contact persons should best be vaccinated against pertussis, influenza, (Mc).
  - Familial contacts:
    - (parents, siblings, grandparents)
  - Health personel:
    - Doctors, Nurses and Students!
    - Role for occupational doctor.
## Belgian Health Council – Vaccination schedule for premature infants

<table>
<thead>
<tr>
<th></th>
<th>0 weken</th>
<th>4 weken</th>
<th>8 weken</th>
<th>12 weken</th>
<th>16 weken</th>
<th>6-9 maanden</th>
<th>12 maanden</th>
<th>13 maanden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difterie</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>x5</td>
</tr>
<tr>
<td>Tetanus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
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<td>x5</td>
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<tr>
<td>Pertussis</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td>x5</td>
</tr>
<tr>
<td>Haemophilus influenza type b</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td>x5</td>
</tr>
<tr>
<td>Polio</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>x5</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>(x1)</td>
<td>(x1)</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>x5</td>
</tr>
<tr>
<td>Pneumokokken PCV</td>
<td>x</td>
<td></td>
<td>x^2</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x5</td>
</tr>
<tr>
<td>Meningokokken C</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>x5</td>
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<td>Mazelen</td>
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<td>x5</td>
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<tr>
<td>Bof</td>
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<td></td>
<td></td>
<td>x5</td>
</tr>
<tr>
<td>Rubella</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>x5</td>
</tr>
<tr>
<td>Rota</td>
<td>x^4</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>x5</td>
</tr>
</tbody>
</table>

1. When mother is Hep B carrier: Hyperimmune immunoglobulines at birth. If neonate < 2000 g two extra pediatric Hep B doses or ½ of adult hep B vaccine dose. If > 2000g at birth 1 extra HepB vaccine dose is enough. Check immunity 4 weeks after primary vaccination (5 month)
2. Pneumococcal vaccine (PCV-13) additional dose at 3 month (3+ 1 dose schedule)
3. Primary MMR vaccination at 6 + 12 month and booster at 10-12y if risk of exposure to measles
4. Rota vaccine not earlier then 6 weeks but not later then 16weeks. Beware for vaccine virus transmission in NICU. No interference with breastfeeding and IV Immunoglobulines
5. Earlier booster doses of Hexavalent and Mc vaccine at 13 month instead of 15 month.
Thanks Superior Health Council co-workers

- Geert Top,
- Pierre Van Damme,
- Corinne Vandermeulen,
- Heidi Theeten,
- Anne Malfroot,
Vaccination of preterms ...

Be in time, before it is too late!

Is within our hands