Hepatitis B vaccination and HBIG administration policies implemented for premature babies; Vaccines concurrently administered with the hepatitis B vaccine birth dose

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Immunization of preterm and low birth weight infants

- Preterm (PT, <37wks) and low birth weight (LBW, <2,500gm) infants are at greater risk of morbidity from vaccine preventable diseases.

- Gestational age (GA) and birth weight (BW) should not be limiting factors in delaying vaccination in clinically stable infants.

- Reduced or divided doses are not recommended and vaccines are generally well tolerated.
Hepatitis B vaccine

- The only vaccine recommended for administration at birth in developed countries:
- Although HBsAg screening of pregnant women is recommended, women without prenatal care have higher HBsAg seropositivity rates.
- Provides early protection in infants at risk for postnatal HBV transmission.
- HBV vaccine given closer to birth increases the likelihood of vaccination completion on time.
Completion of Hepatitis B Vaccine Series by Time of First Dose

Seroconversion rates in PT and LBW infants after HBV vaccine at birth (I)

- In 1994 AAP recommended that in PT<2,000g first dose is deferred if born to HBsAg(-) mothers based on:
- Lau et al: 99 PT with BW<1,750g. vaccinated at birth

<table>
<thead>
<tr>
<th></th>
<th>&lt;2,000g (N=57)</th>
<th>&gt;2,000g (N=42)</th>
<th>Full Term (N=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seroconversion rate (%) (95%CI)</td>
<td>78.9 (66.1-78.9)</td>
<td>90.5 (77.4-97.3)</td>
<td>100 (91.7-100)</td>
</tr>
<tr>
<td>HBsAb titer (miu/ml) (95%CI)</td>
<td>61 (27,138)</td>
<td>262 (101,680)</td>
<td>679 (265,1742)</td>
</tr>
</tbody>
</table>
Peak HBs-antibody titers after 3 doses of hepB vaccine in PT infants

All infants vaccinated within first 7 days of life and tested 1 month post 3rd dose.

Deferring birth dose in low risk PT infants with BW<2,000g

- Group A: BW<2,000g vaccinated at 1,2,7 months
- Group B: BW>2,000g vaccinated at 0,1,6 months
Hepatitis B vaccine:
Follow up of PT infants at 3-3.5 yrs

<table>
<thead>
<tr>
<th>Group</th>
<th>Group 1 Premature</th>
<th>P-value (1 vs 2)</th>
<th>Group 2 Premature</th>
<th>P-value (2 vs 3)</th>
<th>Group 3 Full term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial vaccination</td>
<td>At birth (n = 57)</td>
<td></td>
<td>At 2,000g (n = 40)</td>
<td></td>
<td>At birth (n = 39)</td>
</tr>
<tr>
<td>Positive AntiHBs (%)²</td>
<td>54.4</td>
<td>&lt; 0.001</td>
<td>92.5</td>
<td>&lt; 0.05</td>
<td>71.8</td>
</tr>
<tr>
<td>GMC (IU/l) mean (SD)</td>
<td>14.2 (11.1)</td>
<td>&lt; 0.001</td>
<td>119 (4.8)</td>
<td>&lt; 0.005</td>
<td>32.7 (9.2)</td>
</tr>
</tbody>
</table>

² positive AntiHBs defined as ≥ 10 IU/l; AntiHBs: hepatitis B surface antibody; GMC: geometric mean concentration
Seroconversion rates in PT and LBW infants after HBV vaccine at birth (II)

- Many other studies (1997-1999) supported AAP recommendation for postponing birth dose of HBV vaccine in PT/LBW infants (<2,000g) born to HBsAg (-) mothers.
- Additional risk factors identified for inadequate immunogenic response:
  - Poor weight gain
  - Steroid use
- All studies showed good immunologic response when first dose administered at 1 month regardless of GA or BW.
- Need to protect infants exposed to multiple blood products and surgical interventions.
## Recommendations for hepatitis prophylaxis in PT and LBW infants born to HBsAg (-) mothers

<table>
<thead>
<tr>
<th>Infants with BW &lt; 2,000g</th>
<th>Infants with BW &gt; 2,000g</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Dose 1 at 30 days of age or before discharge if earlier.</td>
<td>- Dose 1 at birth or when medically stable.</td>
</tr>
<tr>
<td>- Total of 3 doses at 1-2, 2-4, and 6-18 mos.</td>
<td>- Total of 3 doses at 1-2, 2-4, and 6-18 mos.</td>
</tr>
<tr>
<td>- May use combination vaccines</td>
<td>- May use combination vaccines</td>
</tr>
<tr>
<td>- No need for post – vaccination testing.</td>
<td>- No need for post – vaccination testing.</td>
</tr>
</tbody>
</table>

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### Recommendations for hepatitis prophylaxis in PT and LBW infants born to HBsAg (+) mothers

**Infants with BW < 2,000g**
- HBIG+HepB vaccine within 12h of birth.
- Immunize with 4 doses: 0, 1, 2-3, 6-7mos
- Check HBsAg and anti-HBs at 9-15mos
- If negative re-immunize with 3 doses at 2 mos intervals and retest.

**Infants with BW > 2,000g**
- HBIG+HepB vaccine within 12h of birth.
- Immunize with 3 doses: 0, 1, 6 mos
- Check HBsAg and anti-HBs at 9-15mos.
- If negative re-immunize with 3 doses at 2 mos intervals and retest.
Recommendations for hepatitis prophylaxis in PT and LBW infants born to a mother with unknown HBsAg status

<table>
<thead>
<tr>
<th>Infants with BW &lt; 2,000g</th>
<th>Infants with BW &gt; 2,000g</th>
</tr>
</thead>
<tbody>
<tr>
<td>- HepB vaccine (by 12h)</td>
<td>- HepB vaccine (by 12h)</td>
</tr>
<tr>
<td>- If mother’s HBsAg not available by 12h give also HBIG.</td>
<td>- Can wait for mother’s HBsAg status up to 7 days.</td>
</tr>
<tr>
<td>- Vaccinate with 4 doses total.</td>
<td>- Vaccinate with 3 doses total.</td>
</tr>
</tbody>
</table>

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CONCLUSIONS (I)

- Evaluating medical condition of newborn.
- Screening HBsAg status of the mother*. If testing not available administer birth dose.
- May defer birth dose to 30 days of age if low risk infant with BW<2,000g.
- Newborns born to mother with HBsAg (+) or unknown status, should be vaccinated at birth and receive total 4 doses* (0,1,2-3,6-7mos) if BW<2,000g. If limited resources available 3 vaccine doses should be given?

* If resources available

Hepatitis B prophylaxis in PT and LBW infants

CONCLUSIONS (II)

- HBIG (0.5ml) IM should be administered to all newborns needing post-exposure prophylaxis irrespectively of GA or BW*.
- Use of needles of 5/8 inch length.
- Alternative 4 dose schedules have been tested in PT (0,1,5,9 or 0,1,2,12)

* If resources available

Hepatitis B prophylaxis in PT infants: Suggested recommendations for areas with limited resources

- Hepatitis B vaccine can be safely administered in PT infants at birth.
- If maternal HBsAg screening not available, hepatitis B vaccine birth dose should be administered to all PT newborns.
- If HBIG available, administer 0.5ml, irrespectively to GA and BW, to all PT needing post-exposure prophylaxis.
- In PT infants with BW<2,000g, 4 doses of hepatitis B vaccine should be administered.
Vaccines concurrently administered with hepatitis B birth dose

- Data on
  - BCG
  - IPV
Co-administration of hepB and BCG in newborns

Table 1  Immune response to BCG: vaccinal lesions and tuberculin reactions in infants immunized at birth with BCG simultaneously or not with hepatitis B vaccine

<table>
<thead>
<tr>
<th>Months post BCG vaccination</th>
<th>BCG + HB (n = 38)</th>
<th>BCG (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Vaccinal lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>32 (84)</td>
<td>36 (90)</td>
</tr>
<tr>
<td>3</td>
<td>35 (92)</td>
<td>35 (88)</td>
</tr>
<tr>
<td>4</td>
<td>25 (66)</td>
<td>31 (78)</td>
</tr>
<tr>
<td>Tuberculin reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size &gt; 6 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>26 (68)</td>
<td>31 (77.5)</td>
</tr>
<tr>
<td>Mean size (mm)</td>
<td>8.5</td>
<td>9.6</td>
</tr>
<tr>
<td>95% confidence limits (mm)</td>
<td>6.9 - 10.1</td>
<td>7.7 - 11.6</td>
</tr>
</tbody>
</table>
**Co-administration of hepB and BCG in newborns**

**Table 3** Anti-HBs response after primary immunization starting at birth

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of children</th>
<th>Vaccine</th>
<th>&gt;10 mlU ml⁻¹ No. (%)</th>
<th>Geometric mean (mlU ml⁻¹)</th>
<th>95% confidence limits (mlU ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>33</td>
<td>BCG + HB</td>
<td>29 (87.9)</td>
<td>90</td>
<td>46–177</td>
</tr>
<tr>
<td>B</td>
<td>31</td>
<td>HB</td>
<td>25 (80.6)</td>
<td>93</td>
<td>40–218</td>
</tr>
</tbody>
</table>

Coursaget P et al. Vaccine 1992
Influence of BCG on antibody and cytokine responses to neonatal vaccination

- BCG induces potent Th1 response to mycobacterial antigens in newborns.
- When BCG was administered at birth together with OPV and HepB vaccine in 35 newborns it increased cellular and Ab responses to HBV and Ab response to oral polio vaccine.
- Promoted Th1 and Th2 response to unrelated vaccines through maturation of dendritic cells.
BCG vaccination in PT infants

62 PT <35wks vaccinated with BCG at postconceptional age of:
- Group A: 34-35wks
- Group B: 38-40wks

Saliou P et al: BCG should not be given at birth in PT <33 wks GA
Co-administration of hepB and IPV in PT infants

- In Israel outbreak of polio type 1 in 1998 had as victim an unvaccinated 2mos.
- ~50% of PT <1:8 Ab titer to polio.
- 50 PT (30-35wksGA, >1,000g) received IPV+HepB vaccine at birth and compared with PT and FT infants receiving only HepB vaccine at birth and IPV at 2 mos.
- Safe and effective way providing protection from both diseases.
Vaccines concurrently administered with hepatitis B birth dose

- Both BCG and IPV can be co-administered at birth with hepatitis B vaccine with similar immune responses to those observed after separate administration of each vaccine.

- No study of co-administration of BCG and HepB in PT infants.