Response to Booster Dose in Children Immunized with Hepatitis B Vaccination at Birth in Alaska

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Declarations and Off Label Use of Medications

• Declarations: None
Persistence of Anti-HBs and Booster Response in Children Immunized in Infancy

• Studies on the prevalence of anti-HBs levels in children at a given age after infant HB immunization differ widely

• Proportion of children with anti-HBs level > 10mIU/ml (protective level) at a given age is influenced by multiple factors including:
  – Peak Level of anti-HBs after last dose
  – Exposure to HBV
Peak Level of Anti-HBs after Age of First and Last Dose of Vaccine

• Date when 1\textsuperscript{st} dose administered:
  – Higher if 1\textsuperscript{st} dose given after 2 months of age than at birth

• Total number of Doses administered:
  – 4 doses > 3 doses > 2 doses

• Strength of each dose and type of vaccine
  – 10 mcg > 5 mcg > 2.5 mcg

• Spacing of dosages:
  – Higher if last dose given at 12 vs. 6 months of age
Environment Infant is Born Into: Natural Boosting

- Mother HBeAg-positive vs. HBeAg-negative
- Presence of HBsAg-positive persons in household
  - HBeAg positive vs. HBeAg-negative contacts
- Prevalence of HBsAg-positive persons in community:
  - Proportion children vs. adults
  - Proportion HBeAg-positive vs. negative
  - HBV predominant genotype.
Median Age of HBeAg Seroconversion by Genotype: Median 21 Years Follow-up*

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No. HBeAg+</th>
<th>Age 50% lost HBeAg</th>
<th>Age 75% lost HBeAg</th>
</tr>
</thead>
<tbody>
<tr>
<td>A_2</td>
<td>34</td>
<td>19.8</td>
<td>32.1</td>
</tr>
<tr>
<td>B_6</td>
<td>6</td>
<td>19.5</td>
<td>27.5</td>
</tr>
<tr>
<td>C_2</td>
<td>36</td>
<td>47.8</td>
<td>58.1</td>
</tr>
<tr>
<td>D</td>
<td>305</td>
<td>18.0</td>
<td>27.3</td>
</tr>
<tr>
<td>F_1</td>
<td>126</td>
<td>16.1</td>
<td>24.5</td>
</tr>
</tbody>
</table>

Gastroenterology 2007;133:1452-57 *P<.001 genotype C vs. other genotypes
Changing Pattern of HBV in Alaska

• Western Alaska went from a high endemic area prior to 1984 to an intermediate endemic area after 2000 due to:
  
  – Introduction of universal newborn HB immunization in 1984
  
  – Massive catch-up vaccination program in children and adults 1984-1988
    
    • 53,000 persons (90% of population in endemic areas) screened and 40,000 vaccinated
  
  • Marked change in infectivity of chronic HBV carriers between then and now
Rapid Drop in Transmission of HBV

• Elimination of acute hepatitis B in children
  – Elimination of HCC in children

• No HBsAg carriers < 20 years of age in 2011

• Prevalence of HBeAg in HBsAg-positive adults and children has fallen from 40% to ~1%
Incidence Symptomatic Hepatitis B in Alaska Native Peoples 1981-2008

- CDC/HIS Vaccine Demonstration Program begins in 16 villages of Yukon Kuskokwim Delta
- Statewide Program begins—all susceptibles immunized
  - pregnant women screened/infants HBvax + HBIG
  - begin universal newborns immunization
Number of HBsAg-positive Alaska Native Children Under 20 Years of Age: 1988-2008

Figure 2.

Number of HBsAg-positive Alaska Native Children Under 20 Years of Age: 1988-2008
HCC in Alaska Natives <20 years of age

P value for trend = 0.002

Hepatology 2011;54:801-7
Natural Boosting in Alaska

- Defined as a 4 fold rise in anti-HBs without anti-HBc in Vax Demo study presented earlier
- Only measured during the first 10 years after immunization.
- Evidence of natural boosting found in 8.2% of 1530 persons followed during this period
  - Prevalence of natural boosting likely to have decreased since number of anti-HBc breakthrough infections fell from 25 between first 15 years to 0 between 15 and 22 years

Hepatitis B Long-Term Immunogenicity in Newborns Vaccinated in Alaska

• Multiple studies from Alaska have shown that anti-HBs levels fall faster in those immunized at birth than those immunized as children or adults

• <5% given recombinant and <15% plasma vaccine have anti-HBs ≥ 10 mIU/ml at 10 years of age

• Only about 50% have a booster response at older adolescence
Long Term Persistence of Anti-HBs In Alaska Native Children Immunized At Birth

Anti-HBs Persistence by Vaccine Type and Maternal Status

- Plasma vaccine, mothers HBsAg-negative
- Plasma vaccine, mothers HBsAg-positive
- Recombinant vaccine, mothers HBsAg-negative
- Recombinant vaccine, mothers HBsAg-positive
Long-term Efficacy of HBV Vaccine Administered in Infancy: Alaska Study

- 6 children had an HBV breakthrough infection
- None of these children were symptomatic or became HBsAg positive
- 2 of these had HBV DNA transiently

Ped Infect Dis J 2005;24:786-92
**Alaska Booster Dose Studies in Children Given Recombinant Hepatitis B Vaccine Starting at Birth**

<table>
<thead>
<tr>
<th>Age at Boost</th>
<th>% anti-HBs &gt;10</th>
<th>No. Boosted</th>
<th>No. (%) response</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years*</td>
<td>12.5%</td>
<td>134</td>
<td>90%</td>
</tr>
<tr>
<td>5-7 years**</td>
<td>29%</td>
<td>158</td>
<td>99%</td>
</tr>
<tr>
<td>7.5 years*</td>
<td>0%</td>
<td>35</td>
<td>91%</td>
</tr>
<tr>
<td>10-15 years**</td>
<td>5%</td>
<td>138</td>
<td>88%</td>
</tr>
<tr>
<td>15 years^</td>
<td>0%</td>
<td>35</td>
<td>51%</td>
</tr>
</tbody>
</table>

*Peds Infect Dis J 2004;23:650-5, **Pediatrics 2007;120:373-381
^Vaccine 2007;25:6958-64
# Alaska Booster Dose Studies in Children Given Plasma Hepatitis B Vaccine Starting at Birth

<table>
<thead>
<tr>
<th>Age at Boost</th>
<th>% anti-HBs</th>
<th>No. Boosted</th>
<th>No. (%) response</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 years</td>
<td>41%</td>
<td>54</td>
<td>33 (67%)</td>
</tr>
<tr>
<td>Mom HBV-neg</td>
<td>31%</td>
<td>10</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>12 years</td>
<td>24%</td>
<td>12</td>
<td>8 (67%)</td>
</tr>
<tr>
<td>Mom HBV-neg</td>
<td>21%</td>
<td>74</td>
<td>71%</td>
</tr>
<tr>
<td>12-15 years</td>
<td>21%</td>
<td>74</td>
<td>71%</td>
</tr>
<tr>
<td>Mom HBV-neg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Yo-Hep Booster Dose Study

- 378 Children who received 3 doses of hepatitis B vaccine:
  - Dose #1 birth to 7 days, dose #2 6 weeks to 12 weeks, dose # 3 6- 9 months.
- Three Groups:
  - CR: 166 Children who received recombinant vaccine as primary series 5-7 years ago
  - AR: 138 Adolescents who received recombinant vaccine as primary series 10-14 years ago
  - AS: 74 Adolescents who received serum-derived vaccine as primary series 10-14 years ago
Proportion with an anamnestic anti-HBs response by age, at 2 weeks after a booster dose of hepatitis B vaccine, among persons with baseline anti-HBs<10 mIU/mL
Figure 2b. Anti-HBs (GMC) at 2 and 4 weeks after a booster dose among participants with an anamnestic response (non-responders excluded), baseline anti-HBs <10 mIU/mL, by group

Differences between groups within each figure:
*Significantly less than CR group GMC at this timepoint
†Significantly less than AR group GMC at this timepoint
‡Significantly less than AS group GMC at this timepoint
Yo-Hep follow-up Study in Children Who Received Booster Dose 6-9 Years Previously

• 107 Children divided into 3 groups were tested: All had responded to a booster dose
  – Group 1 received 2.5 mg doses recombinant boosted at 5-6 years of age
  – Group 2 received 2.5mg doses recombinant vaccine at ages 10-12 years
  – Group 3 received 10 mcg plasma-derived vaccine at 13-15 years

• 60% anti-HBs was < 10 mIU/ml at 6-9 years
Yo-Hep Booster Dose Study Results

• Factors significant for the anti-HBs > 10 mIU 6-9 years post boost:
  – Pre-boost anti-HBs level
  – Response to booster dose at 2 and 4 weeks

• GMT Pre and Post booster dose
  – GMT pre-booster dose was 6.6
  – GMT was 353.9 4-6 weeks post boost
  – GMT 6-9 years post booster dose was 6.9
Hepatitis B Antibody Levels Pre- and Post-Vaccine Booster, by Initial Vaccine Series

GMC, mIU/mL (logarithmic scale)

- AP (n=18)
- AR (n=38)
- CR (n=51)
- All (N=107)
Hepatitis B Immunity Pre- and Post-Vaccine Booster, by Initial Vaccine Series

- **AP (n=18)**
- **AR (n=38)**
- **CR (n=51)**
- **All (N=107)**
Anti-HBs Falls Rapidly After Booster Dose

• Two other Alaska studies:
  – Vax Demo 22
    • Only 41% had anti-HBs > 10mIU 1 year post boost
    • GMC fell from 87 at 2 weeks to 8 at 1 year
  – Health Care Worker (HCW) Booster Dose Study
    • Rapid fall of GMC 1 year post booster dose
Anti-HBs levels following a booster dose of hepatitis B vaccine in HCW

Williams Vaccine 2001;19:4081-85
Conclusions Regarding Long-term Efficacy of Hepatitis B Vaccine

- Hepatitis B protects completely against acute symptomatic HBV and chronic HBV
  - Up to 22 years in those immunized as children and adults including HCW; 30 year study pending
  - Up to 15 years in those immunized as infants
Conclusions Continued

• Protection may wane over time as seen by failure to respond to a booster dose
  – 7% immunized as children or adults by 22 years
  – Up to 40% immunized as infants by 15 years
  – However T Helper and memory cells likely remain longer and could protect against acute or chronic HBV disease.

• Response to booster dose falls rapidly even by 1 year
  – Following response to booster dose may not be an adequate method to determine long-term immunity