Long-term hepatitis B immunogenicity studies in Alaska and the impact of vaccination on cirrhosis, chronic hepatitis B and liver cancer

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Long-term immunogenicity of HB vaccination in Alaska

- Hepatitis B vaccine first used in Alaska in 1981
- Studies of immunogenicity began at that time
Long-Term Immunogenicity & Efficacy: Children & Adults

- Alaska HBV Vaccine Demonstration Project: 1530 children and adults immunized in 1981
  - Followed yearly for 11 years and at year 15
  - No booster given at 1-11 and 15 years
  - % with anti-HBs levels > 10 mIU/ml
    - 5 years: 81% (JAMA 1989;261:2362-6)
    - 7 years: 74% (Arch Int Med 1991;151:1634-6)
  - 16 breakthrough infections, none symptomatic, transient HBV DNA at 4 log copies transiently present in 6 persons
Alaska HBV Vaccine Demonstration Project: 22 Year Follow-Up

- Residents of 7 villages, 9 villages not studied
- % with anti-HBs levels ≥ 10 mIU/ml
  - 5 years: 81%
  - 7 years: 74%
  - 15 years: 66%
  - 22 years: 60%
- 5 persons anti-HBc positive (all previously identified, all HBV DNA negative)

McMahon et al. J Infect Dis 2009
Vax Demo 22: Results in Persons Who Responded to Initial Series

- Booster dose Recombivax® 10 mcg given to those who with anti-HBs <10 mIU/mL
- 133/164 (81%) boosted to >10 mIU/mL

- Overall, 93% (95% CI: 91.0% – 95.6%) had evidence of immunity: either boosted at 10-14 days or had anti-HBs >10 mIU/mL at 22 years
Vax Demo 30: 2011-2012

- All communities visited three times
- Preliminary results to date:
  - Those previously studied at 22 years
    - 15% anti-HBs ≥ 10 mIU/ml among 61 persons who were boosted at 22 years
Anti-HBs levels in persons boosted at 22 years

- 60 days post
- 1 year post
- 8 years post

> 10 mIU/ml
Vax Demo 30: 2011-2012

- All communities visited three times
- Preliminary results to date:
  - Those previously studied at 22 years
    - 15% anti-HBs $\geq 10$ mIU/ml among 61 persons who were boosted at 22 years
    - 64% anti-HBs $\geq 10$ mIU/ml among 120 persons not boosted at 22 years
  - Of the 36% with $< 10$ mIU/ml, 94% (30/32) had anti-HBs $\geq 10$ mIU/ml at 4 weeks post booster

- Those who were not studied at 22 years
  - 48% anti-HBs ≥ 10 mIU/ml among 222 not studied at 22 years
  - Of the 52% < 10 mIU/ml, 88% (53/60) had anti-HBs > 10 mIU/ml at 4 weeks post booster
Studies of long-term immunogenicity following infant vaccination

• Studies of children vaccinated at birth, 1 month and 6 months of age
• Need for and timing of a booster dose?
• Maternal hepatitis status and vaccine type
Long Term Persistence of Anti-HBs In Alaska Native Children Immunized At Birth

Anti-HBs Persistence by Vaccine Type and Maternal Status

Age in years

Estimate of participants with anti-HBs >= 10mIU/mL

- Plasma vaccine, mothers HBsAg-negative
- Plasma vaccine, mothers HBsAg-positive
- Recombinant vaccine, mothers HBsAg-negative
- Recombinant vaccine, mothers HBsAg-positive
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 &gt;10</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 (61%)</td>
</tr>
<tr>
<td>Mom HBV-neg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 years</td>
<td>31%</td>
<td>10</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>Mom HBV+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 years</td>
<td>24%</td>
<td>12</td>
<td>8 (67%)</td>
</tr>
<tr>
<td>Mom HBV-neg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-15 years</td>
<td>21%</td>
<td>59</td>
<td>35 (59%)</td>
</tr>
<tr>
<td>Mom HBV-neg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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>
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</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>116</td>
<td>97%</td>
</tr>
<tr>
<td>7.5 years*</td>
<td>0%</td>
<td>35</td>
<td>91%</td>
</tr>
<tr>
<td>10-14 years**</td>
<td>14%</td>
<td>118</td>
<td>80%</td>
</tr>
<tr>
<td>15 years^</td>
<td>0%</td>
<td>35</td>
<td>62%</td>
</tr>
</tbody>
</table>

*Peds Infect Dis J 2004;23:650-5, **Pediatrics 2007;120:373-381
^Vaccine 2007;25:6958-64
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 2.5 mg doses recombinant vaccine at ages 10-12 years
  - Group 3 received 10 mcg plasma-derived vaccine at 13-15 years
Hepatitis B immunity, baseline, and after booster among those <10 mIU/ml at baseline

Among All                Among <10 mIU/ml at baseline

- Group 1
- Group 2
- Group 3
- Total

Pre-boost 2 wk post-boost 4 wk post-boost 6-9 yrs post-boost

% >= 10 mIU/ml

- Among All
- Among <10 mIU/ml at baseline
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; 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

• 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
Alaska Native Hepatitis B Control Program

- 1978: Establishment of a registry of HBsAg-positive persons
Alaska Native Hepatitis B Control Program

• 1978: Establishment of a registry of HBsAg-positive persons
• 1980: Screening of pregnant women for HBsAg
  – 1980-1981 HBlG administered to infants
  – 1982 addition of HB vaccine to infants
Alaska Native Hepatitis B Control Program

• 1978: Establishment of a registry of HBsAg-positive persons
• 1980: Screening of pregnant women for HBsAg
  – 1980-81 HBIG administered to infants
  – 1982 addition of HB vaccine to infants
• 1981-82: HB vaccine demonstration project
Alaska Native Hepatitis B Control Program

• 1978: Establishment of a registry of HBsAg-positive persons
• 1980: Screening of pregnant women for HBsAg
• 1981-82: HB vaccine demonstration project
• Alaska Native HB Mass screening and vaccination program
  – 1984-87 vaccination campaign: 52,000 Alaska Native persons screened; 40,000 susceptible persons vaccinated
  – 1984 to present: vaccination of all infants starting at birth
Alaska Native Hepatitis B Control Program

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- Alaska Native HB Mass screening and vaccination program
  - 1984-87 vaccination campaign: 52,000 Alaska Native persons screened; 40,000 susceptible persons vaccinated
  - 1984 to present: vaccination of all infants starting at birth
- 1982-present: Screening of HBsAg positive persons using AFP every 6 months, follow-up of elevations
  - 2001-present: ALT and AST testing added; HBV DNA testing of persons with elevations; persons with HBV DNA >2000 IU/ml evaluated for treatment
Incidence Symptomatic Hepatitis B in Alaska Native Peoples, 1981-2010

CDC/HIS Vaccine Demonstration Program begins in 16 villages of Yukon Kuskokwim Delta

- pregnant women screened/infants HBvax + HBIG
- begin universal newborns immunization

Statewide Program begins-all susceptibles immunized

Year

Rate per 100,000
Number of HBsAg-positive Alaska Native Children Under 20 Years of Age: 1988-2008

- **1988:** 450 HBsAg-positive
- **1993:** 300 HBsAg-positive
- **2003:** 20 HBsAg-positive
- **2008:** 10 HBsAg-positive

Percentage of HBsAg-positive:
- **1988:** 1.4%
- **1993:** 1.2%
- **1998:** 1.0%
- **2003:** 0.8%
- **2008:** 0.6%
HCC in Alaska Native Children <20 years of age

Annual Rate per 100,000

year of diagnosis

P value for trend = 0.002

Hepatology 2011;54:801-7
Conclusions

• Hepatitis B vaccination in Alaska has resulted in a generation of Alaska Native children who are free of hepatitis B and its sequelae.