Hepatitis B Vaccine Studies in Alaska

Brian J McMahon
Viral Hepatitis Program
Alaska Native Medical Center
Long-term HB Vaccine and Booster Studies Conducted in Alaska

- Vax Demo
  - Vax Demo Booster
- Long-term Infant
  - LTI Child Booster
- Child Booster
- Employee Booster
- Yo Hep
- Long-term Protection of Vaccine on Incidence and Prevalence of HBV
Hepatitis B Vaccine Demonstration Program (Vax Demo): Conducted in 1981 in Western Alaska

- 1630 Seronegative Yupik persons ages 6 months and older from 17 villages vaccinated with plasma-derived vaccine at 0, 1 and 6 months
- Follow-up serology testing yearly for first 11 years then at year 15
- HBV DNA tested on all persons who acquired anti-HBc during study period
- Report of interim analysis published at 5, 7 and 10 years; 15 year results submitted
Vax Demo: Initial Results

• 94% developed protective antibody levels
• Persons < 20 years old had:
  – The highest response rate (99%)
  – The highest antibody levels
• Persons > 50 years had lower response rate: (70%)
Hepatitis B Vaccine Demonstration Program: Long-term Follow-up

• 10 year follow-up
  – 76% still had protective anti-HBs levels
  – 0.09% got HBV infection (anti-HBc+)
  – None developed clinical hepatitis or became a carrier

• 15 year follow-up
  – 66% still had protective anti-HBs levels
  – None developed clinical hepatitis or became a carrier
# Hepatitis B Vaccine Demonstration Program: Long-term Follow-up

<table>
<thead>
<tr>
<th>Follow-up Period</th>
<th>% protected (anti-HBs)</th>
<th>No. Infected Incidence</th>
<th>No. HBV-DNA +</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Year</td>
<td>81%</td>
<td>4</td>
<td>Not Done</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.45/1000)</td>
<td></td>
</tr>
<tr>
<td>7-year</td>
<td>74%</td>
<td>8</td>
<td>Not Done</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.85/1000)</td>
<td></td>
</tr>
<tr>
<td>10-year</td>
<td>* 76%</td>
<td>13</td>
<td>Not Done</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.94/1000)</td>
<td></td>
</tr>
</tbody>
</table>
Vax Dem: 22-Year Follow-up

- 22 year follow-up study in 2003-2004
  - Contact 1030 of the original participants from 7 villages
  - Test for hepatitis B markers
  - If anti-HBs < 10 mIU, give booster dose of hepatitis B vaccine and retest at
    - 10-14 days
    - One month
    - One year
Conclusion: Vax Demo Study

• Long-term protection in children and adults lasts at least 15 years after hepatitis B vaccination
• Booster doses in these groups are not needed for at least 15 years.
Long-term Protection of Infant Hepatitis B Vaccination: LTI Study

• Objectives
  – To determine the persistence of protective anti-HBs among a cohort of AN successfully immunized with HB vaccine beginning at birth
  – To determine the frequency and characteristics of breakthrough infections among this cohort

Manuscript in preparation
LTI Study: Methods

• Study population
  – Convenience sample of AN infants who completed the recommended series of HB vaccine during 1984-1995
  – Responded to vaccine (anti-HBs ≥ 10miu/ml)
LTI Hepatitis B Study: Methods

• Laboratory
  – Serologic testing for anti-HBs and anti-HBc done every other year until age 16 years old
  – Specimens positive for anti-HBc
    • Tested for HBsAg
    • Tested for HBV DNA using PCR
LTI Results

- Total number of children: 334
- Median specimens per child: 5
  - Range 2-11 specimens
- Median years of follow-up: 10
- Percent males: 55%
LTI: Results

• Vaccine type
  – Plasma-derived 99 (30)
  – Recombinant 235 (70)

• Maternal HBsAg status
  – Positive 136 (41)
  – Only 8 (6%) HBeAg-positive
  – Negative 198 (59)
Hepatitis B Vaccine: Long-term Protection when Administered to Newborns: Conclusions

• No evidence of serious breakthrough infections at 16 years of follow-up, but asymptomatic anti-HBc+ infections occur.

• Loss of protective anti-HBs when vaccinated in infancy more rapid than persons vaccinated >6 months of age.

• Protection from hepatitis B lasts for at least 16 years.
Other Studies involving Long-Term Follow-up on Infant Hepatitis B Vaccination

• Most studies have been performed in Infants of HBsAg/HBeAg+ mothers

• Marked variability in vaccine schedule and number of immunizations:
  – starting at birth vs. at 2-3 months of age
  – Administering last dose at 6 vs. 12 months
  – Administering 3 vs. 4 doses
Other Studies involving Long-Term Follow-up on Infant Hepatitis B Vaccination

• 51%-85% of children of HBsAg/HBeAg+ mothers vaccinated in infancy had anti-HBs levels $\geq$ 10 mIU/ml at 10 years

• Study from Hawaii in low risk infants given 2.5 mcg recombinant vaccine at birth: Only 19% had anti-HBs levels $> 10$ mIU/ml at 6-years but all responded to a booster dose

• Our study suggests anti-HBs decline more rapid in children of HBsAg+/HBeAg- or HBsAg- moms
Hepatitis B Child Booster Studies

• Purpose: To determine the response to a booster dose in children who received hepatitis B vaccine during infancy.
  – Child Boost: 310 children whose initial response to hepatitis B vaccine is unknown
  – LTI Boost: 47 children who had documented anti-HBs level of $\geq 10$ mIU after vaccination
Long-Term Immunogenicity & Efficacy: Vaccination in Infancy

• 310 children immunized on schedule starting at birth but response to vaccination unknown
  - 208 tested at age 5: children with anti-HBs < 10 mIU were given a booster dose
  - 102 children deferred testing until age 9, then those with < 10 mIU were given a booster dose
Long-Term Immunogenicity and Response to a Booster Dose in Low Risk Children Immunized in Infancy: Vaccine Response Unknown

<table>
<thead>
<tr>
<th>No.</th>
<th>Vaccine Type</th>
<th>Maternal HBsAg</th>
<th>Mean Age</th>
<th>%Anti-HBs ≥ 10 mIU</th>
<th>Booster Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>102</td>
<td>Plasma</td>
<td>negative</td>
<td>8.9 years</td>
<td>41%</td>
<td>33/54 (61%)</td>
</tr>
<tr>
<td>208</td>
<td>Recomb</td>
<td>negative</td>
<td>5.1 years</td>
<td>12%</td>
<td>120/134 (90%)</td>
</tr>
</tbody>
</table>

Petersen. Ped Infect Dis 2004: accepted
Long-Term Immunogenicity and Response to a Booster Dose in Children Immunized in Infancy: Responded Initial Vaccination

<table>
<thead>
<tr>
<th>No.</th>
<th>Vaccine Type</th>
<th>Maternal HBsAg</th>
<th>Mean Age/years</th>
<th>%Anti-HBs ≥ 10 mIU</th>
<th>Booster Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Plasma</td>
<td>negative</td>
<td>12.6</td>
<td>4/17 (24%)</td>
<td>8/12 (67%)</td>
</tr>
<tr>
<td>36</td>
<td>Recomb</td>
<td>negative</td>
<td>7.5</td>
<td>0/36 (0%)</td>
<td>32/35 (91%)</td>
</tr>
<tr>
<td>16</td>
<td>Plasma</td>
<td>Positive</td>
<td>12.1</td>
<td>5/16 (31%)</td>
<td>9/10 (90%)</td>
</tr>
</tbody>
</table>
LTI Conclusions

• Anti-HBs levels over time in children vaccinated in infancy decline at a rapid rate with those receiving recombinant vaccine falling the fastest.
• Response to a booster dose of vaccine at 5 to 7 years of age is good (90%).
• Some children at 9 to 12 years fail to respond to a booster dose including 10% to 30% of those who were known to respond to the initial series.
Long-Term Immunogenicity & Efficacy: Health Care Workers

- 59 HCR who responded to vaccination 5 to 15 years previously with low or absent anti-HBs levels were randomized into a 10mcg or 2.5 mcg booster dose
  - 98% anamnestic response at 10-14 days
  - 100 % anamnestic response at 1 month

Vaccine 2001;19:4081-85
Anti-HBs levels following a booster dose of hepatitis B vaccine

![Graph showing Anti-HBs levels following a booster dose of hepatitis B vaccine. The graph compares levels at different time points (Booster, Day 14, Day 28, 1 year) for two different doses (2.5 mcg, 10 mcg) and two different concentration ranges (<10 mIU, 10-50 mIU).]
Yo-Hep (Youth Hepatitis) Booster Study in Alaska Natives

- Effectiveness of hepatitis B booster dose in children who were vaccinated with recombinant vaccine starting at birth
- Groups studied:
  - 200 children ages 4-5 years
  - 200 children ages 10-13 years
- Follow-up anti-HBs testing at 10 – 14 days and one month
- Results: Fall 04
Hepatitis B Vaccination in Alaska

- 1980: Screening Pregnant women in 2 hospitals; HBIG to infants HBsAg+ mothers
- 1981-82: Hepatitis B vaccine demonstration project in Southwest Alaska
- 1983-87: 53,000 Alaska Natives (75%) screened and 40,000 susceptible were vaccinated
- 1984-present: Universal Hepatitis B vaccination of all infants
- 1987: Estimated 90% susceptible persons in endemic areas immunized
Impact of Hepatitis B Immunization Program on the HBV in Alaska Native Population

- Declining incidence of acute hepatitis B
- Generation of children free of chronic HBV
- Impact of immunization on the portion of HBeAg-positive (infectious) Carriers in population
- Trend toward decreasing incidence of HCC in persons < 30 years of age
Incidence Symptomatic Hepatitis B in AK Natives 1981-2001

- 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
  - newborn immunization
Bristol Bay Hepatitis Survey

- Serosurvey in 1984 of 603 persons ≤ 30 years of age 10 years after initiation of universal hepatitis B Immunization
  - Prevalence of HBsAg in 1984 was 13%
  - Prevalence of HBsAg in 1994:
    - Ages 0-10 0
    - Ages 11-15 8%
    - Ages 16-20 18%
    - Ages 21-30 21%

Harpaz J Infect Dis 2000;181:413-8
Age-specific Prevalence of HBV Infection
Bristol Bay Eskimos, 1994

- Anti-HBc (+)
- HBsAg (+)

Routine Infant Immunization

Positive (%) vs. Age (years)

0  5  10  15  20  25  30  35

0  5  10  15  20  25  30  35

CDC DVRD
Impact of Hepatitis B Vaccination: HBeAg and Anti-HBe Over Time


% HBeAg % anti-HBe

0 10 20 30 40 50 60 70 80 90 100
Chronic Hepatitis B in Alaska Natives Outcome Study

- All Alaska Natives are offered testing every 6 months for liver enzymes and AFP
- Consented participants also at baseline have:
  - HBV Genotype
  - HBV DNA levels
  - A sample is tested for viral mutations that may be associated with liver disease:
    - Pre-core mutant: Development of cirrhosis
    - Core-promoter mutation: Development of liver cancer
HBV Immunization: Questions

How do we determine when, if ever, to boost.

– Wait for symptomatic hepatitis to occur in vaccinated individuals (i.e. measles)
– Vaccinate at time when we can no longer demonstrate anamnestic response