Are Booster Doses of Hepatitis B Vaccine Necessary?

Current CDC Recommendations And Gaps in Knowledge

Division of Viral Hepatitis Centers for Disease Control and Prevention, USA
Current United States Recommendations for Hepatitis B Vaccination

- Selective vaccination of children, adolescents, and adults at increased risk of infection (1982)
- Prevention of perinatal transmission through routine screening of pregnant women (1984)
- Routine vaccination of infants beginning at birth (1991)
- Routine vaccination of adolescents (11-12 yrs) (1995)
- Catch-up vaccination of unvaccinated children and adolescents (through 18 yrs) (1999)

Recommendations endorsed by the U.S. Advisory Committee on Immunization Practices (ACIP), American Academy of Pediatrics (AAP), American Academy of Family Physicians (AAFP), and American Medical Association (AMA).
High-Risk Groups

- Injecting drug users
- Sexually active homosexual & bisexual men
- Heterosexual men and women with >1 sex partner
- Persons recently tx for another STD
- Sex contacts of persons with chronic hep B
- Household contacts of persons with chronic HBV infection
- Persons with occupational exposure (e.g., HCW’s)
- Recipients of certain blood products (clotting factors)
- Clients and staff of institutions for developmentally disabled
- Chronic hemodialysis patients
- International travelers
- Inmates of long-term correctional facilities
- Adoptees from high HBV endemic countries
Hepatitis B Vaccination in the United States: Coverage and Impact
Incidence of Acute Hepatitis B, United States, 1980-2001

Overall, 76% decline
Since 1990, 66% decline

Source: CDC National Notifiable Diseases Surveillance System
Hepatitis B Vaccination Coverage Among Children*, United States, 1990-2002

* 19-35 months old

Source: National Immunization Survey, CDC
Hepatitis B Vaccination Coverage Among Adolescents*, United States

*13-15 years old

Source: National Health Interview Survey, CDC
HBV Prevalence Among U.S. Born Children of Asian Immigrants, Atlanta, 1986 and 2002

1986 (pre-vaccination; n=251)
- HBsAg: 6.6%
- Anti-HBc: 0.6%

2002 (vaccination coverage ≥3 doses=98%; n=157)
- HBsAg: 0.6%
- Anti-HBc: 11.7%

Hepatitis B Incidence Among Health Care Workers & General Population
United States, 1982-1998

Source: Mahoney. Arch Intern Med. 1997; CDC
Current Booster Dose Recommendations
Current Recommendations for Booster Doses of Hepatitis B Vaccine

**Booster doses of hepatitis B vaccine are not currently recommended**

Recommendation based on:

- Long-term efficacy studies published to date
- Booster dose studies published to date
- U.S. surveillance data
  - of acute hepatitis B cases among children and adolescents, none report being vaccinated
  - suggests no breakthrough infections occurring among vaccinated infants and adolescents
## Long-Term Protection Studies Among Vaccinated Infants

<table>
<thead>
<tr>
<th>Country</th>
<th>Yrs</th>
<th>f/u</th>
<th>n</th>
<th>Anti-HBs &gt;10 mIU/mL</th>
<th>Anti-HBc positive</th>
<th>HBsAg positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>15</td>
<td>15</td>
<td>52</td>
<td>50%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Alaska</td>
<td>15</td>
<td>15</td>
<td>119</td>
<td>61%</td>
<td>1%</td>
<td>0</td>
</tr>
<tr>
<td>The Gambia</td>
<td>14</td>
<td>14</td>
<td>175</td>
<td>64%</td>
<td>31%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>12</td>
<td>12</td>
<td>148</td>
<td>74%</td>
<td>1%</td>
<td>0</td>
</tr>
<tr>
<td>Taiwan</td>
<td>12</td>
<td>12</td>
<td>951</td>
<td>37%</td>
<td>2.7%</td>
<td>--</td>
</tr>
<tr>
<td>Senegal</td>
<td>9-12</td>
<td>9-12</td>
<td>41</td>
<td>68%</td>
<td>27%</td>
<td>2%</td>
</tr>
<tr>
<td>Taiwan</td>
<td>10</td>
<td>10</td>
<td>805</td>
<td>85%</td>
<td>14%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Taiwan</td>
<td>10</td>
<td>10</td>
<td>118</td>
<td>67%</td>
<td>12%</td>
<td>0</td>
</tr>
<tr>
<td>Italy</td>
<td>10</td>
<td>10</td>
<td>53</td>
<td>68%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Italy</td>
<td>10</td>
<td>10</td>
<td>474</td>
<td>68%</td>
<td>1%</td>
<td>0</td>
</tr>
<tr>
<td>Thailand</td>
<td>8-10</td>
<td>8-10</td>
<td>76</td>
<td>62%</td>
<td>9%</td>
<td>0</td>
</tr>
</tbody>
</table>

## Long-Term Protection Studies Among Vaccinated Adults

<table>
<thead>
<tr>
<th>Country (Group)</th>
<th>Years of follow-up</th>
<th>n</th>
<th>Anti-HBs &gt;10 mIU/mL</th>
<th>Anti-HBc Positive</th>
<th>HBsAg Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alaska (20-49 yo)</td>
<td>15</td>
<td>182</td>
<td>59%</td>
<td>&lt;2%</td>
<td>&lt;0.2%</td>
</tr>
<tr>
<td>Italy (HCW)</td>
<td>10</td>
<td>310</td>
<td>85%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>U.S. (MSM)</td>
<td>10</td>
<td>127</td>
<td>91%</td>
<td>4%</td>
<td>0</td>
</tr>
<tr>
<td>Alaska²</td>
<td>9-10</td>
<td>1194</td>
<td>65-84%</td>
<td>0</td>
<td>1%</td>
</tr>
<tr>
<td>U.S. (MSM)</td>
<td>7-9</td>
<td>232</td>
<td>48%</td>
<td>7%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

1. Results for all 783 persons in study, not just those vaccinated at age 20-49 years.
2. Includes vaccinated children.

Summary of Long-Term Protection Data

10-15 years after vaccination of infants, children and adults:

• Decline in detectable levels anti-HBs
  – 48-91% ≥ 10 mIU/ml
• Serologic evidence of HBV infection in some vaccinated persons
  – <1% to 37% (highest in Gambia & Senegal)
• No symptomatic infections
• Development of chronic infection very rare
• **Suggests despite decline in anti-HBs, protection persists**
# Booster Doses Response Among Persons Vaccinated as Infants

<table>
<thead>
<tr>
<th>Country</th>
<th>Known Responder</th>
<th>Years follow-up</th>
<th>n</th>
<th>Pre-boost anti-HBs &gt;10 mIU/ml</th>
<th>Post-boost anti-HBs &gt;10 mIU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alaska</td>
<td>Yes</td>
<td>12.5</td>
<td>17</td>
<td>24%</td>
<td>76%</td>
</tr>
<tr>
<td>Alaska</td>
<td>Yes</td>
<td>12</td>
<td>16</td>
<td>31%</td>
<td>94%</td>
</tr>
<tr>
<td>Taiwan</td>
<td>Yes (?)</td>
<td>10</td>
<td>118</td>
<td>67%</td>
<td>100%</td>
</tr>
<tr>
<td>Italy</td>
<td>Yes</td>
<td>10</td>
<td>53</td>
<td>68%</td>
<td>100%</td>
</tr>
<tr>
<td>Samoa</td>
<td>No</td>
<td>9</td>
<td>41</td>
<td>39%</td>
<td>93%</td>
</tr>
<tr>
<td>Thailand</td>
<td>No</td>
<td>8</td>
<td>90</td>
<td>0¹</td>
<td>95%</td>
</tr>
</tbody>
</table>

¹Included only those with anti-HBs<10 mIU/ml

# Booster Doses Response Among Persons Vaccinated as Adults

<table>
<thead>
<tr>
<th>Country (group)</th>
<th>Follow-up</th>
<th>n</th>
<th>Pre-boost anti-HBs &gt;10 mIU/ml</th>
<th>Post-boost anti-HBs &gt;10 mIU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. (adults)</td>
<td>13</td>
<td>7</td>
<td>71%</td>
<td>100%</td>
</tr>
<tr>
<td>Alaska (HCW)</td>
<td>3-13</td>
<td>59</td>
<td>0(^1)</td>
<td>97-100%</td>
</tr>
<tr>
<td>Italy (HCW)</td>
<td>6</td>
<td>955</td>
<td>67% (3 dose)</td>
<td>97% (3 dose)</td>
</tr>
<tr>
<td>Spain (adults, kids)</td>
<td>6</td>
<td>182</td>
<td>94% (4 dose)</td>
<td>94% (4 dose)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>64%(^3)</td>
<td>96%(^3)</td>
</tr>
</tbody>
</table>

\(^1\) Included only those with anti-HBs <10 mIU/ml
\(^2\) Average age: 30 years
\(^3\) Used anti HBs >100 mIU/ml

Summary of Booster Dose Studies

- Among vaccinated infants and adults who lose detectable levels anti-HBs
  - majority respond to booster doses of vaccine
  - among documented responders, 97-100% boost

- Suggests presence of immune memory despite loss of anti-HBs
CDC Booster Dose Study: American Samoa

- 70 children born in 1991
- Received 3 doses recombinant hepatitis B vaccine at birth, 1, 6 months
- Tested for anti-HBs after primary series
- Received booster dose at 5 yrs old
- Anti-HBs testing at 2 wks, 4 wks, 1 yr post-boost
### Anti-HBs Response to Primary Series and Booster Dose: American Samoa

<table>
<thead>
<tr>
<th></th>
<th>Post-primary (13 months)</th>
<th>Pre-boost (60 months)</th>
<th>Post-Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>63 (90%)</td>
<td>26 (41%)</td>
<td>26 (100%)</td>
</tr>
<tr>
<td></td>
<td>7 (10%)</td>
<td>37 (59%)</td>
<td>0</td>
</tr>
<tr>
<td>70</td>
<td></td>
<td>0</td>
<td>4 (57%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 (100%)</td>
<td>3 (43%)</td>
</tr>
</tbody>
</table>

Anti-HBs >10 mIU/ml
Anti-HBs <10 mIU/ml
Distribution of Anti-HBs in Response to Booster Dose of Vaccine: Samoa

Anti-HBs (mIU/ml):  
- <10
- 10-99
- 100-999
- >1,000

Age in months

0 1 7 13 60 64 64 65 76

Percent

Primary series

Booster dose
Booster Doses Response Among Persons Vaccinated in Infancy: Samoa

Anti-HBs

GMT anti-HBs (mIU/ml)

Age in months

Primary Series

Booster Dose

>1,000 mIU/ml

100-999 mIU/ml

10-99 mIU/ml
Unanswered Questions and Gaps in Knowledge
Unanswered Questions

Of the various determinants of duration of protection, which are the most important?

- Age at vaccination
  - birth
  - later infancy
  - childhood
  - adulthood
- GMC post primary series
- Receipt of HBIG
- Vaccine type: plasma-derived vs. recombinant
- Infection pressure: endemicity, maternal HBV status, vaccination coverage
- Natural boosting
Natural Boosting and Infection Pressure

Is natural boosting important?
Is infection pressure important?
What is the relationship between the two?

- High vs. low endemic areas
- Areas with catch-up vaccination of older children, adolescents, adults (i.e., Alaska)
- Implications for movement to/from high endemic areas and potential for exposure
Protection from Infection: Infection Pressure vs. Natural Boosting

Continued infection pressure

Persistent natural boosting

Persistent protection

No infection: Protected

Example: China
– Infant vaccination
– No catch-up vaccination
– More HBsAg/HBeAg among adults

Example: Alaska
– Infant vaccination
– Catch-up of all susceptibles
– Less HBsAg/HBeAg among adults

Example: U.S. and W Europe
– low endemicity

No infection pressure

No natural boosting

Not protected

No infection: No infection pressure
Protection from Infection: Infection Pressure vs. Natural Boosting

- Continued infection pressure
  - Persistent natural boosting
  - Persistent protection
  - No infection: Protected

- No infection pressure
  - No natural boosting
  - Not protected
  - No infection: No infection pressure

Exposure: sexual, HCW, move to high endemic area

- No infection???
- Infection???
Ongoing CDC Long-Term Protection and Booster Dose Studies

**Palau (high endemic)**
- Adolescents (9-10 yrs) vaccinated at birth with recombinant vaccine

**Alaska (Anchorage, low endemic)**
- Children (5-7 yrs) and adolescents (10-13 yrs) vaccinated at birth with recombinant vaccine

**Alaska (villages, high endemic) (Vax Demo)**
- 22-23 year follow-up of infants (>6 months), children, and adults vaccinated with plasma-derived vaccine