Increases in Levels of Antibody to Hepatitis B Surface Antigen in an Immunized Population

Lisa R. Bulkow, Robert B. Wainwright,* Brian J. McMahon, and Alan J. Parkinson

Hepatitis B vaccine is effective in preventing infection with hepatitis B virus (HBV), but its duration of protection is unknown. To examine the effect of exposure to HBV on an immunized population, data were analyzed from a cohort of Alaska Natives who were immunized and then followed up annually for 10 years. A boost in antibody to hepatitis B surface antigen (anti-HBs) was defined as a fourfold rise in levels to \( \geq 20 \text{ mIU/mL} \) that was not accompanied by the presence of antibody to hepatitis B core antigen or attributable to interim vaccination. During 10 years of follow-up, 8.2% of 1,595 vaccinees had boosts in anti-HBs. Persons with boosts did not differ significantly from those without boosts in terms of age, gender, village, initial level of anti-HBs, or level of anti-HBs before the boost. These results underscore the continued exposure to HBV among vaccinees and the continued protection against disease that the vaccine provides.

Methods

The recruitment, vaccination, and follow-up of this cohort have been described in detail elsewhere [6, 9]. In brief, beginning in 1981, a group of 1,630 persons from 15 villages in southwest Alaska received three doses each of plasma-derived hepatitis B vaccine (Heptavax, Merck, West Point, PA). Children younger than 11 years of age received a 10-\( \mu \text{g} \) dose; all other participants received a 20-\( \mu \text{g} \) dose.

Serum specimens were collected annually and tested for anti-HBs (AUSAB, Abbott Laboratories, North Chicago, IL) and antibody to hepatitis B core antigen (anti-HBc) (CORAB, Abbott Laboratories) by RIA. Serum specimens positive for anti-HBc were retested and if again positive were then tested for hepatitis B surface antigen (HBsAg) (AUSRISA II, Abbott Laboratories). Serum specimens were redrawn from all study participants whose retests were positive for anti-HBc, and the second specimen was tested to confirm positivity for anti-HBc. Levels of anti-HBs were measured in milli–international units; measurements were calculated by using a World Health Organization reference standard diluted to contain 125 mIU/mL. Testing was performed at the Arctic Investigations Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Anchorage, Alaska.

We defined a boost in anti-HBs as a fourfold or greater rise in levels to at least 20 mIU/mL in two consecutive specimens \( \geq 2 \) years apart that was not accompanied by the presence of anti-HBc or HBsAg or attributable to interim vaccination. The requirement to achieve a level of at least 20 mIU/mL was made to exclude small changes in persons with marginally detectable levels of anti-HBs.

Hepatitis B vaccine has been widely distributed to individuals in this region who were not project participants, and a limited number of participants were likely to have received additional doses. We reviewed the medical records of all parti-
Participants who had a fourfold or greater rise in levels of anti-HBs in consecutive specimens \( \leq 2 \) years apart for documentation of additional vaccinations.

Proportions were statistically analyzed by using the \( \chi^2 \) test or Fisher’s exact test as appropriate, or the test for linear trend in proportions. Correlations were calculated by using Spearman’s rank correlation. All \( P \) values were two-sided. Results were considered to be statistically significant when \( P < .05 \).

**Results**

**Vaccination and Serological Responses During 10 Years**

Of the 1,630 participants who received the vaccine on schedule, 1,595 remained negative for anti-HBc during administration of the three doses of vaccine. At the time of administration of the first dose, the participants ranged in age from younger than 1 year to 83 years. The mean age of the participants was 19.4 years, and the median age was 13 years. Seventy-five percent of the participants were younger than 26 years of age at that time. Males accounted for 49% of the cohort. Of those participants from whom serum specimens were obtained 1 year after the first dose of vaccine, 94.1% (1,349 of 1,434) had an antibody response (level of anti-HBs, \( \geq 10 \) mIU/mL).

Participation throughout the follow-up period was good: specimens were drawn from 1,194 (75%) of 1,595 persons at HBV, but this difference did not achieve statistical significance.

The level of initial response to hepatitis B vaccine was also not a predictor of boosts in anti-HBs: 8.4% of persons who did not respond, 5.4% of those with an initial response between \( \geq 10 \) mIU/mL and \( < 50 \) mIU/mL, and 8.9% of others had boosts \((P = .923)\). The level of anti-HBs in the specimen obtained immediately before the boost varied from undetectable (12% of individuals) to \( \geq 1,000 \) mIU/mL (7%). The median level before the boost was 69.4 mIU/mL. The median level after the boost was 944 mIU/mL: 81% of persons had a level of \( \geq 100 \) mIU/mL, and 48% had a level of \( \geq 1,000 \) mIU/mL.

Boosts in anti-HBs occurred throughout the study period from the first year to the ninth year of follow-up. When paired serum specimens were examined, the smallest proportion of boosts was seen in the first year after vaccination (0.7%), and the largest proportion was seen in the fifth year (2.4%). There tended to be more boosts later in the study \((P = .036; \text{test for trend})\); a boost was shown in 1.8% of specimen pairs in the subsequent 3 years.

**Boosts in the Population**

Two hundred thirty-three individuals were identified who had a fourfold or greater increase in levels of anti-HBs between 1 and 10 years after administration of the first dose of vaccine. We found evidence that 52 persons who had had a fourfold rise had received additional hepatitis B vaccine during the follow-up period. In 46 of these persons, the rise in the level of anti-HBs was temporally associated with this vaccination. In 10 of the persons who had a fourfold rise, the rise was concurrent with the appearance of anti-HBc. Of the 177 participants with a fourfold rise not attributable to antibody to hepatitis B core antigen (anti-HBc) seroconversion or vaccination, 130 had a rise to a level of \( \geq 20 \) mIU/mL after the boost.

Omitting the participants who underwent seroconversion, the proportion of persons who had boosts in anti-HBs alone did not vary significantly by age, with boosts in 8.0% of those younger than 20 years of age at the first dose, 9.7% of those 20 to 49 years of age, and 6.0% of those 50 years of age or older \((P = .915)\). Likewise, the proportion did not vary by gender, with 8.3% of males and 8.2% of females having a boost \((P = .956)\). Residents of households that contained a chronically HBsAg-infected person (10.4% of participants) tended to have more boosts in anti-HBs (11.0%) than did others (7.9%), but this difference was not significant \((RR = 1.39; P = .226)\).

Proportions of boosts in anti-HBs by community of residence varied from a low of 5.0% to a high of 16.1%, but this difference was not significant \((P = .722)\) (table 1). The proportion of boosts in each village was positively associated with the proportion of villagers who were chronically infected with HBV, but this difference did not achieve statistical significance \((r_s = .423; P = .116)\).

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Logistic regression analysis was used to examine the roles of age, gender, initial response, village, presence of an individual chronically infected with HBV in the household, and anti-HBc seroconversion following boosts in anti-HBs. The only factor that was significantly associated with a boost in anti-HBs was anti-HBc seroconversion \((P < .001)\) (table 2). After adjustment for anti-HBc seroconversion, no other factors were significant, although the presence of a person chronically infected with HBV in the household showed a trend. If both boosts in anti-
Table 1. Study participants, proportions of persons chronically infected with HBV, and proportions of boosts in anti-HBs by community of residence in a study of Alaska Natives.

<table>
<thead>
<tr>
<th>Community</th>
<th>No. of participants</th>
<th>Specimen pairs evaluated</th>
<th>Proportion (%) chronically infected with HBV</th>
<th>No. (%) * with boosts in anti-HBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>59</td>
<td>386</td>
<td>10.8</td>
<td>4 (8.3)</td>
</tr>
<tr>
<td>B</td>
<td>18</td>
<td>85</td>
<td>9.8</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>C</td>
<td>33</td>
<td>249</td>
<td>9.7</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td>D</td>
<td>24</td>
<td>155</td>
<td>8.1</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>E</td>
<td>127</td>
<td>858</td>
<td>6.0</td>
<td>10 (8.1)</td>
</tr>
<tr>
<td>F</td>
<td>62</td>
<td>392</td>
<td>5.3</td>
<td>4 (6.9)</td>
</tr>
<tr>
<td>G</td>
<td>192</td>
<td>1,213</td>
<td>4.0</td>
<td>21 (11.5)</td>
</tr>
<tr>
<td>H</td>
<td>131</td>
<td>749</td>
<td>4.0</td>
<td>12 (9.7)</td>
</tr>
<tr>
<td>I</td>
<td>203</td>
<td>1,175</td>
<td>4.0</td>
<td>15 (7.6)</td>
</tr>
<tr>
<td>J</td>
<td>59</td>
<td>403</td>
<td>3.2</td>
<td>8 (15.1)</td>
</tr>
<tr>
<td>K</td>
<td>20</td>
<td>107</td>
<td>2.6</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>L</td>
<td>122</td>
<td>820</td>
<td>2.5</td>
<td>6 (5.0)</td>
</tr>
<tr>
<td>M</td>
<td>54</td>
<td>279</td>
<td>2.2</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>N</td>
<td>235</td>
<td>1,300</td>
<td>1.3</td>
<td>16 (7.0)</td>
</tr>
<tr>
<td>O</td>
<td>256</td>
<td>1,444</td>
<td>0.9</td>
<td>21 (8.4)</td>
</tr>
<tr>
<td>Total</td>
<td>1,595</td>
<td>9,615</td>
<td>4.8</td>
<td>130</td>
</tr>
</tbody>
</table>

NOTE. anti-HBs = antibody to hepatitis B surface antigen; HBV = hepatitis B virus.
* Percentage among persons negative for antibody to hepatitis B core antigen who did not have a boost as a result of interim vaccination.

HBs and anti-HBc seroconversions were classified as HBV events and treated as cases in the dependent variable, no significant associations were seen.

Discussion

This project was undertaken to examine the pattern of boosts in anti-HBs in a cohort of persons immunized against HBV infection who live in an area in which HBV is hyperendemic. Excluding rises in levels of anti-HBs that were attributable to subsequent revaccination or anti-HBc seroconversion, a total of 130 persons (or 8.2% of 1,595 persons) had boosts in anti-HBs during the 10 years of follow-up.

Comparisons with other studies are difficult because of differences in the length of follow-up and in the definition of a boost in anti-HBs. Lai et al. [11] observed 42 significant increases in levels of anti-HBs in 318 children over 5 years of follow-up; their definition required a level of anti-HBs of $>100$ mIU/mL in children with levels of $<10$ mIU/mL before the boost and levels of anti-HBs of $>200$ mIU/mL with a twofold

Table 2. Results of logistic regression analysis of boosts in anti-HBs in 1,395 Alaska Natives.

<table>
<thead>
<tr>
<th>Result</th>
<th>Dependent variable—boosts in anti-HBs vs. all others</th>
<th>Dependent variable—boosts in anti-HBs plus positive for anti-HBc vs. all others</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted model including only that factor</td>
<td>Adjusted for persons positive for anti-HBc</td>
</tr>
<tr>
<td></td>
<td>RR $P$ value</td>
<td>RR $P$ value</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Result</th>
<th>RR</th>
<th>$P$ value</th>
<th>RR</th>
<th>$P$ value</th>
<th>RR</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive for anti-HBc</td>
<td>3.23</td>
<td>&lt;.001</td>
<td>1.48</td>
<td>.109</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-49</td>
<td>1.3</td>
<td>.273</td>
<td>1.19</td>
<td>.407</td>
<td>1.48</td>
<td>.109</td>
</tr>
<tr>
<td>&gt;50</td>
<td>0.75</td>
<td></td>
<td>0.72</td>
<td></td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.04</td>
<td>.752</td>
<td>1.01</td>
<td>1.00</td>
<td>1.08</td>
<td>.647</td>
</tr>
<tr>
<td>Initial level of anti-HBs of &lt;50 mIU/mL</td>
<td>0.83</td>
<td>.527</td>
<td>1.03</td>
<td>.920</td>
<td>0.68</td>
<td>.144</td>
</tr>
<tr>
<td>From a household with a person chronically infected with HBV</td>
<td>1.66</td>
<td>.069</td>
<td>1.73</td>
<td>.053</td>
<td>1.53</td>
<td>.124</td>
</tr>
<tr>
<td>Village (14 terms)</td>
<td>1.66</td>
<td>.543</td>
<td>1.63</td>
<td>.688</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Persons with boosts attributable to interim vaccination and those for whom levels of anti-HBs were not measured at the initial follow-up were omitted from this analysis. anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to hepatitis B surface antigen; HBV = hepatitis B virus.
increase in other children. Coursaget et al. [12] saw four sharp rises in antibody levels in 141 children 5 or 6 years after vaccination during infancy; these researchers’ definition of a sharp rise was not clear. Lee et al. [13] found increases in 58 (11%) of 548 serum specimen pairs from 171 infants born to mothers positive for hepatitis B e antigen over 5 years; they defined an increase as a fourfold rise. Hadler et al. [14] found that 3.5% of vaccinated homosexual men had a fourfold rise over 5 years of study. Our rate appears similar to or slightly less than the rates in these studies, although our follow-up period was the longest and our cohort was the largest studied and included a variety of age groups and both genders. In addition, the exposure to natural infection in persons in our study was probably quite variable as village-specific rates of HBsAg positivity ranged from 0.9% to 10.8%.

We were not able to correlate boosts in anti-HBs with any available factors such as age, gender, initial level of anti-HBs, village of residence, or presence of a person chronically infected with HBV in the household. Since only about 10% of the participants lived in households with an individual chronically infected HBV, our ability to examine this factor was limited. There was a trend for more boosts to occur in villages with more chronically infected persons, but this trend was not statistically significant. Documented carriers of HBsAg provide a likely reservoir for HBV as vaccination of susceptible persons has been extensive (>90%) in this region [15]. The possibility of mutant HBVs that could cause boosts in anti-HBs also exists in this population.

Boosts in anti-HBs occurred in individuals with a wide range of levels of anti-HBs before the boost. Although levels in 12% of individuals were undetectable, the median level before the boost was 69.4 mIU/mL, and 7% had a level of anti-HBs of ≥1,000 mIU/mL. Since serum samples were drawn and tested at approximately yearly intervals, the levels of anti-HBs may not represent the actual levels just before exposure. After boosts occurred, 48% of persons had levels of ≥1,000 mIU/mL, again not necessarily at the peak of response. Similarly, since serum samples were drawn annually, the development of transient levels of anti-HBc or HBsAg may have also gone undetected. We [9] previously documented that persons who seroconvert to anti-HBc tend to have lower levels of anti-HBs than do other vaccinees during the year before anti-HBc seroconversion.

The incomplete follow-up of participants is a limitation of our study. Of 1,595 persons, about 75% were followed up for the entire period, and another 8.4% were followed up after the 10-year study period. The HBV status of the remaining 16.6% of persons is unknown, although HBV infection is known not to have been diagnosed for any of them.

Thus, it appears that in this population of Alaska Natives, HBV continues to circulate. In addition to the 13 persons who had anti-HBc and the nine persons who possibly seroconverted to anti-HBc during the 10 years of follow-up [9], 130 persons had strong evidence of exposure to HBV. No vaccine recipients enrolled in the study became chronically infected with HBV during this period, nor were any cases of acute clinical hepatitis B detected in vaccinees. These results continue to support the view held by many researchers and public health experts [2, 16] that in populations with good coverage of hepatitis B vaccine and a good response to hepatitis B vaccination, protection persists for extended periods after the initial vaccine series. In populations for whom HBV is endemic, such as Alaska Natives, the duration of this protection may be enhanced by repeated exposure to HBV, resulting in periodic boosts in levels of anti-HBs.

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References


