Duration of Protection After Infant Hepatitis B Vaccination Series

WHAT’S KNOWN ON THIS SUBJECT: Duration of protection among children and adolescents who have received the recombinant hepatitis B (HB) vaccination series is known to be long. Less is known about duration of protection of the vaccination series after being administered during infancy.

WHAT THIS STUDY ADDS: A robust response to a challenge dose of HB vaccine among adolescents indicates prolonged duration of protection against disease; the addition of a booster dose of HB vaccine to the routine immunization schedule for adolescents appears unnecessary.

abstract

BACKGROUND: Little is known about duration of protection after the infant primary series of hepatitis B (HB) vaccine in settings of low HB endemicity. This study sought to determine the proportion of adolescents immunized as infants who had protective titers of antibody to hepatitis B surface antigen (anti-HBs) before and after a challenge dose of vaccine.

METHODS: US-born 16- through 19-year-olds who received a recombinant HB vaccine 3-dose series initiated within 7 days of birth (group 1) or at ≥4 weeks of age (group 2) and completed by 12 months of age were enrolled. Participants had serologic testing before and 2 weeks after randomization to receive a challenge dose of 10 μg or 20 μg of Engerix-B. Baseline and postchallenge levels of anti-HBs were compared by group, challenge dosage, and demographic and behavioral characteristics.

RESULTS: At baseline, 24% had protective anti-HBs levels of ≥10 IU/mL; 92% achieved protective levels after challenge dose. Although group 1 had a lower proportion of seroprotection at baseline, group and challenge dosage were not associated with postchallenge proportion of seroprotection. Being in group 2, higher test dosage, higher baseline geometric mean titer, and nonwhite race were associated with significantly higher geometric mean titer after challenge dose.

CONCLUSIONS: More than 90% of study participants immunized against HB as infants exhibited a seroprotective response to a challenge dose of vaccine. Duration of protection from the primary infant HB vaccine series extended through the adolescent years in the setting of low HB endemicity. Pediatrics 2014;133:e1500–e1507

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KEY WORDS infant immunization, hepatitis B vaccine, hepatitis B, adolescent immunization

ABBREVIATIONS

anti-HBc—anti-HB core antigen
anti-HBs—hepatitis B surface antigens
CDC—Centers for Disease Control and Prevention
GMT—geometric mean titer
HB—hepatitis B
TCPA—Texas Children’s Pediatric Associates

Dr Middleman conceptualized and designed the study, implemented the methodology, was involved in all data analyses and interpretation, wrote the manuscript, and incorporated all manuscript revisions; Dr Baker helped design the study, provided all blood sample preparations and shipments, was involved in implementation of the methodology, and reviewed and revised the manuscript; Dr Kozinetz designed the statistical analyses, ran and interpreted the data analyses, and reviewed and revised the manuscript; Dr Kamili conducted quantitative and qualitative serologic tests on all samples, reviewed and helped interpret all laboratory data, and reviewed and revised the manuscript; Ms Nguyen conducted and interpreted data analyses, and reviewed and revised the manuscript; Dr Hu was involved in methodologic issues pertaining to the project, and was involved in data analyses and interpretation; Dr Spradling was involved in all methodologic issues pertaining to the project, was involved in all data analyses and interpretation, and provided substantial guidance to the development of the manuscript; and all authors provided final approval of the manuscript.

This trial has been registered at www.clinicaltrials.gov (identifier NCT01341275).

(Continued on last page)
In 1991, the Centers for Disease Control and Prevention (CDC) initiated a comprehensive program for the elimination of hepatitis B (HB) in the United States. A large part of that strategy included the recommendation for universal infant immunization with recombinant HB vaccine. Incidence rates of HB infection are now at an all-time low in the United States; from 1990 through 2007, rates of acute HB declined by 82%. There were 2890 reported cases of acute HB in 2011, representing an estimated 18 800 acute cases in 2011.1 A variety of studies worldwide have established that those immunized with HB vaccine as children, adolescents, and young adults maintain antibodies for many years. Antibody levels of HB surface antigen (anti-HBs) ≥10 IU/mL are accepted as evidence of seroprotection.2–4 Even when anti-HBs levels decline below this value among those who have received the HB vaccine 3-dose primary series, multiple studies reveal immune memory and a subsequent secondary immune response when exposed to the viral antigens.5 Anamnestic response to a challenge dose of HB vaccine is a standard method and perhaps the best proxy for assessing duration of immune protection against disease. The magnitude and duration of primary and boosted immune response is affected by multiple factors, including age at first dose, potential effect of natural boosting (increased titers in response to exposure to infection), primary series dose and response, and interval between challenge dose and primary series, each of which have differed with country of origin of the available research.5–13 Investigators have determined the duration of protection of HB vaccine among people in countries with varying degrees of HB endemicity. Results from Alaska examining duration of protection 22 years after plasma-derived HB vaccine was administered to infants have shown that higher anti-HBs titer after the primary series and higher anti-HBs before a challenge dose of vaccine predicted a more vigorous anamnestic response.6 Data from the United States and Taiwan reveal that titer decay is more rapid and anamnestic response to a challenge dose of HB vaccine more vigorous among those who received the recombinant vaccine versus the plasma-derived vaccine, although it is not clear whether these analyses controlled for time from primary series to challenge dose.7–9 Studies of children who received recombinant HB vaccine in infancy and were tested 5 to 10 years afterward indicate varying responses to a challenge dose of vaccine. Among Alaskan youth tested 5 to 7 years after receiving the recombinant HB vaccine series with the first dose at birth, 90% responded to a challenge dose of vaccine with seroprotective titers (≥10 IU/mL).9 Ninety-seven percent of seronegative Italian children immunized 10 years earlier at 3, 5, and 11 months of age responded with titers ≥10 IU/mL after a challenge dose of HB vaccine.10 In some areas of higher HB endemicity, rates of anamnestic responses to a challenge dose of vaccine seem somewhat less vigorous and were as low as 70% in Palau.11–13 In an area of high HB endemicity in Thailand, anamnestic responses to a challenge dose of vaccine were achieved in 95% of participants 20 years after a 4-dose infant series of recombinant HB vaccine.14 Other than among Alaska Natives, a study of long-term seroprotection of persons vaccinated as newborns and infants has not been conducted in a setting of low HB virus endemicity, such as the United States. As the cohort of Americans vaccinated as newborns and young children ages and experiences potential exposures to HB virus as adolescents and young adults, data are needed to assess whether this population should receive a booster dose of HB vaccine. This study determined the proportion of US-born, 16- to 19-year-olds now living in Texas immunized with HB vaccine at or shortly after birth who exhibit protective titers of anti-HBs both before (at baseline) and after a challenge dose of HB vaccine. Associations between response to a challenge dose of HB vaccine and factors including age at primary series initiation and the challenge dosage also were examined.

METHODS

This study was reviewed and approved by the institutional review boards of Baylor College of Medicine and the CDC. Informed consent was obtained from participants aged 18 and 19 years. Parental permission was obtained from parents and guardians for participation of minors aged 16 and 17. In addition, assent was obtained from participants aged 16 and 17 before their participation.

Recruitment

Adolescents 16 years to 19 years of age born in the United States who had received the primary HB vaccine series during infancy were eligible to participate in this study. Patient lists were obtained from a large pediatric medical practice in Houston, TX (Texas Children’s Pediatric Associates [TCPA]). TCPA includes 44 practices across the greater Houston area with patients of all races, ethnicities, and socioeconomic backgrounds. For the TCPA practices with space available for study personnel to conduct enrollment, an initial, automated phone call was made to the households of age-appropriate patients describing the study and asking interested families to call the research line. Fliers describing the study were posted in identified practice sites and sites close to those practices to alert interested patients in the area. To identify potential study participants, age-appropriate patient lists (including
several thousand patients) from identified practices that included HB vaccine immunization status were reviewed. A research coordinator called individual families to ascertain interest in and eligibility for the study. Those interested in participating were preliminarily screened for eligibility (using HB immunization dates) and were scheduled for an appointment at the practice site nearest their home. Immunization records regarding HB immunization status used to determine final eligibility were obtained using the medical record from the practice, immunization card from the patient, or the state immunization registry (ImmunTrac). To be eligible for study participation, adolescents had to have had exactly 3 doses of HB vaccine, with dates of administration in the record. The vaccination series had to have been initiated either within 7 days after birth (group 1) or at or after 4 weeks of age (group 2) (see Fig 1) and had to have been completed by age 12 months, with the third dose administered within 10 months of the first dose. Exclusion criteria included a history of HB; born to a mother with known HB infection; having received HB immune globulin as an infant; immunosuppression (such as HIV or chronic/current steroid use); pregnancy; current fever; or recent receipt of blood products, immune globulin, or any vaccine. Patients were recruited between April 2010 and December 2011.

Visit 1
All participants completed several data collection forms to provide demographic and behavioral information (completed confidentially) and to confirm eligibility. No participants were excluded from the study based on data provided after consent was obtained.

Weight was obtained to determine appropriate needle length for injection.15,16 Final group assignment was made using an eligibility checklist completed after review of the patient information. Five to 10-mL aliquots of blood were obtained for baseline quantitative anti-HBs and qualitative anti-HB core antigen (anti-HBc) determination before HB vaccine challenge dose administration. If anti-HBc was positive, HB surface antigen and HB virus DNA tests were performed. A sealed, computer-generated, random assignment card labeled with participant enrollment number (based on the order in which participants completed the informed consent) before the start of enrollment was opened by the study nurse coordinator to determine if the participant was to receive a 10-μg or a 20-μg challenge dose of HB vaccine (Engerix-B; GlaxoSmithKline, London, UK). The study nurse coordinator administered vaccines in an identical manner regardless of dose assignment.

Demographic/Behavioral Data
Demographic variables collected during the first visit included gender, date of birth, race/ethnicity, and insurance status at the first visit. Questions from the Youth Risk Behavior Surveillance System were used to collect data on behavioral risk factors for HB infection, including cigarette smoking, sexual activity, and substance and alcohol use. The CDC Youth Risk Behavior Surveillance System questions have established high rates of reliability.17

Visit 2
Thirteen to 15 days after enrollment, participants returned to the clinic and were questioned regarding interim illnesses or any adverse events. Blood was obtained to determine the postchallenge dose quantitative anti-HBs titer.

Laboratory Methods
Blood samples were centrifuged to separate sera, aliquoted, and stored at −80°C before shipment to the CDC Hepatitis Reference Laboratory in Atlanta, GA. Baseline serum samples were tested qualitatively to determine presence of anti-HBc and quantitatively to measure the levels of anti-HBs by using corresponding reagents on the VITROS ECI Immunodiagnostic System (Ortho-Clinical Diagnostics, Inc, Rochester, NY). Postchallenge dose sera from visit 2 were tested for levels of anti-HBs exclusively.

Statistical Analysis
Sample size was initially planned based on the calculation of required precision of the point estimate of positive anamnestic response (width of the 95% interval 0.1 for 1 proportion) in the target population, accounting for a 10% rate of attrition (ie, we expected 402 subjects to complete the research protocol). A total of 420 participants completed the study protocol.

Demographic and behavioral characteristics were compared between groups and between responders (those who achieved anti-HBs levels ≥10 IU/mL after the challenge dose) versus nonresponders by using 2-sample t test for the continuous variables and χ² test or Fisher’s exact tests for categorical variables. The prevalence of serologic markers was determined by dichotomizing the anti-HBs levels as <10 IU/mL or ≥10 IU/mL to define seroprotective status. The frequencies and proportions of documented seroprotection were compared between groups using χ² tests. The distributions of the pre- and postchallenge dose anti-HBs levels were examined and then log-transformed to achieve approximately normal distribution for parametric modeling and testing. For those anti-HBs values of 0, we used 0.05 for valid transformation. We compared the geometric mean titers (GMTs) and the 95% confidence intervals between groups by 2-sample t test.

To study the correlation between pre- and postchallenge dose anti-HBs titers, Spearman correlation coefficients were determined based on the original scale.
To identify the factors associated with the immune response to a challenge dose, univariate analyses were performed to determine associations with the outcome variable and group status. The associations with \( P \) values <.25, as well as the 3 biological factors affecting postchallenge dose anti-HBs levels (age at first dose in the primary series, dosage of the challenge vaccine, and prechallenge anti-HBs level) were considered in the models. Linear regression (backward model selection) controlling group, dosage, and prechallenge anti-HBs level was used to simultaneously identify predictors of postchallenge dose anti-HBs titers on the log scale. The predictive ability of the model was assessed by using the cross validation followed by the Copas test. A \( P \) < .05 was considered significant for all analyses. SAS software version 9.2 (SAS Institute, Inc, Cary, NC) was used for all analyses.

**RESULTS**

**Study Sample Characteristics**

A total of 423 participants were initially enrolled in the study; 420 completed the protocol (Fig 1). Demographic characteristics for the study participants (Table 1) reflect a racially, ethnically, and socio-economically diverse sample. Demographic characteristics, in general, are reflective of those in the city of Houston (23.1% Black/African American in 2010, US Census Bureau); the US Census Bureau does not separate race and ethnicity variables.18 There were some differences in demographic characteristics by group. Group 1 (first dose of the primary series administered within 7 days of age) participants were younger and were less likely to be white and to have private insurance. Although generally similar, participants in group 2 (first dose of the primary series administered \( \geq 4 \) weeks of age) engaged in slightly more frequent cigarette use (13% in group 2 vs 7% in group 1 reporting use in the past 30 days, \( P = .019 \)) and alcohol use (31% in group 2 vs 19% in group 1 reporting use within the past 30 days, \( P = .0069 \)). No statistically significant differences were observed in demographic characteristics when examining participants by those who received the 10-μg versus the 20-μg challenge dose of vaccine. None of the behavioral characteristics were associated with baseline titers. None of the participants was anti-HBc positive. No adverse events were reported at the second visit regarding the HB vaccine.

**Immune Response to a Challenge Dose**

At baseline, most (76%) participants had anti-HBs levels of <10 IU/mL (Table 2). Group 1 had a significantly higher proportion of participants with nonseroprotective levels. The proportion of participants achieving the level considered effective for seroprotection after receiving the challenge dose was 92%; there was no difference between groups 1 and 2 or among those receiving either challenge dose (10 μg or 20 μg) in the proportion of participants achieving seroprotection.

Differences in anti-HBs GMTs after challenge dose by group and test dosage (10 μg vs 20 μg) are shown in Table 3. GMTs in response to a challenge dose of HB vaccine were significantly higher among those in group 2 versus group 1 and among those who received the 20-μg versus 10-μg dosage. Various participant characteristics were associated with the achievement of seroprotection and with GMTs by bivariate analysis (Table 4).

**Factors Associated With Titer Response**

As noted, group and higher test dosage were both significantly associated with
TABLE 1 Participant Characteristics

<table>
<thead>
<tr>
<th>Gender</th>
<th>Group 1, n = 240</th>
<th>Group 2, n = 180</th>
<th>Total (n = 40)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47.5 (114)</td>
<td>50 (90)</td>
<td>49 (204)</td>
<td>.61</td>
</tr>
<tr>
<td>Female</td>
<td>52.5 (126)</td>
<td>50 (90)</td>
<td>51 (216)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>31 (74)</td>
<td>15 (27)</td>
<td>24 (101)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White</td>
<td>46 (110)</td>
<td>69 (124)</td>
<td>56 (234)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>23 (56)</td>
<td>16 (28)</td>
<td>20 (85)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>74 (178)</td>
<td>81 (146)</td>
<td>77 (324)</td>
<td>.09</td>
</tr>
<tr>
<td>No</td>
<td>26 (62)</td>
<td>18 (34)</td>
<td>23 (96)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insurance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private/HMO</td>
<td>66 (159)</td>
<td>80 (144)</td>
<td>72 (303)</td>
<td>.01</td>
</tr>
<tr>
<td>Medicaid</td>
<td>18 (43)</td>
<td>8 (14)</td>
<td>14 (57)</td>
<td></td>
</tr>
<tr>
<td>SCHIP</td>
<td>8 (19)</td>
<td>4 (7)</td>
<td>6 (26)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4 (9)</td>
<td>4 (8)</td>
<td>4 (17)</td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td>4 (10)</td>
<td>7 (7)</td>
<td>4 (17)</td>
<td></td>
</tr>
<tr>
<td>Age, mean</td>
<td>16.96 ± 0.65</td>
<td>17.37 ± 0.80</td>
<td>17.13 ± 0.75</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BMI, median</td>
<td>22.9 kg/m²</td>
<td>22.8 kg/m²</td>
<td>22.8 kg/m²</td>
<td>.41</td>
</tr>
</tbody>
</table>

HMO, health maintenance organization; SCHIP, state children’s health insurance program.

* P values were obtained from χ² tests for categorical variables and t test for continuous variables.

b Wilcoxon rank sum test used for nonparametric distribution of BMI among participants.

TABLE 2 Levels of Seroprotection (anti-HBs Titer ≥10 IU/mL) by Group

<table>
<thead>
<tr>
<th></th>
<th>Group 1, %</th>
<th>Group 2, %</th>
<th>Total, %</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline seroprotection</td>
<td>40.0</td>
<td>54.9</td>
<td>47.1</td>
<td>.20</td>
</tr>
<tr>
<td>Postchallenge dose seroprotection</td>
<td>90.4</td>
<td>93.9</td>
<td>91.9</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

* P value for χ² tests.

TABLE 3 GMT After Challenge Dose, by Group and Dose

<table>
<thead>
<tr>
<th>n</th>
<th>Post GMT</th>
<th>95% Confidence Interval of GMTs</th>
<th>Two-Sample t Test</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>240</td>
<td>487.84</td>
<td>319.65 to 744.54</td>
<td>.0001</td>
</tr>
<tr>
<td>Group 2</td>
<td>180</td>
<td>1745.77</td>
<td>1065.45 to 2680.49</td>
<td>.0001</td>
</tr>
<tr>
<td>Dose 10 μg</td>
<td>208</td>
<td>537.85</td>
<td>346.65 to 835.85</td>
<td>.007</td>
</tr>
<tr>
<td>Dose 20 μg</td>
<td>211</td>
<td>1314.87</td>
<td>816.43 to 2116.85</td>
<td>.007</td>
</tr>
</tbody>
</table>

Because log₁₀(0) is undefined, to determine GMTs, 0.05 was substituted for titers of 0.

postchallenge dose GMTs. The Spearman correlation coefficient between baseline and postchallenge dose anti-HBs was 0.69 (P < .0001). Participant characteristics associated with GMT response on bivariate analysis included marijuana use. Multiple regression analyses indicate that the variables independently associated with a higher GMT response to a challenge dose of vaccine include a higher baseline anti-HBs titer, older age at first dose of the primary series (group), higher test dosage, and nonwhite race, as well as an interaction of test dosage and marijuana use (at higher test dosage, those who smoke marijuana experienced a blunted response) (Table 5). BMI was not associated with the achievement of seroprotection or lower postchallenge-dose GMTs. Cross-validation indicated a good predictive ability of the model and there was no indication of over-fitting by the Copas test.

DISCUSSION

Our data suggest that 92% of US-born adolescents 16 through 19 years of age in the Houston metropolitan area immunized against HB with the recombinant vaccine as infants achieved seroprotective levels in response to a challenge dose of HB vaccine. Importantly, immune memory remained intact for most subjects, despite evidence elsewhere that the infant immune system has a diminished capacity to mount a robust response to the primary vaccination series. Although the timing of the initiation of the infant series was not associated with achieving seroprotection after a challenge dose, it was associated with the magnitude of anti-HBs response; initiation of the primary series within age 7 days versus age 4 weeks or older resulted in lower GMTs. However, it is not clear whether this difference in response has potential implications for duration of HB vaccine-associated protection into the third and fourth decades of life.

We also found that baseline anti-HBs titer was associated with the age at the first dose of HB vaccine; participants who had initiated their primary series in the first week of life had a significantly lower baseline anti-HBs than those who had initiated vaccination at age 1 month or later. Residual anti-HBs levels years after the primary series has been associated with the peak anti-HBs level achieved immediately after completion of the series. Although our participants did not receive postvaccination testing during infancy, we hypothesize that those vaccinated in the first week of life had lower peak anti-HBs levels relative to those starting vaccination at a slightly older age. Studies early in the use of recombinant HB vaccine indicated that infants <2 months of age experienced a less robust response to HB vaccine and were more sensitive to differences in primary series dose. It is important to note that the infant dose of HB vaccine in the United States through 1998 was 2.5 μg per dose; the current dose...
administered to infants in this country is either 5 mg (Recombivax, Merck, NJ) or 10 mg (Engerix). These higher doses have been associated with 100% seroprotection rates after the primary series among all infants born to non-infected mothers.20,21 It is possible that the higher doses ameliorate the effect of age on titer differences experienced after the primary series.

Other studies of anamnestic response to a challenge dose of HB vaccine years after receiving the recombinant product in infancy have shown variable results9–14; these studies vary by primary series schedule, dosage administered, number of doses for the primary series, and degree of endemicity of HB infection in the study areas. Our study data are unique for several reasons. The setting is one of low endemicity, suggesting the boosted response represents primary HB vaccine series protection without the aid of natural boosting. Our study contributes new data regarding duration of protection in a geographic area more reflective of the overall rates of HB in the United States. Despite the likely absence of natural boosting, the response to the challenge dose of HB vaccine was remarkably good. Study subjects were diverse, representing multiple races/ethnicities, which differed from other studies, and needle length was adjusted for varying weight among subjects. Finally, our study included the variable of challenge dosage, again noting a difference in immune response measured by quantitative GMTs, but likely not clinically relevant, as postchallenge seroprotection did not differ according to dosage.

Baseline anti-HBs titers were correlated with challenge dose response when examining rates of seroprotection as well as GMT. This has been reported previously. Duval et al2 found a correlation of between 0.73 and 0.88 (different values based on the vaccine manufacturer) for postprimary series, baseline, and postchallenge dose anti-HBs levels among those boosted 5 years after the primary series. For our study investigating response 16 to 19 years after the primary series, the correlation between baseline and postchallenge dose anti-HBs levels was 0.69, similar to what has been reported by others. However, the significance of higher GMTs is unclear given high rates of seroprotection among those with baseline GMTs, 10 IU/mL).

Race was also associated with differences in titer response to a challenge dose. White race was independently associated with less robust anamnestic response. This finding has not previously been reported. Recent advances in examining the association of immune response between “high” and “low” responders to vaccines with genotype differences have emphasized the role of genetic make-up in vaccine response.22–25 Race may serve as a proxy for these genetic differences.

<p>| TABLE 4 Participant Characteristics and Associations With Challenge Dose Response |
|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Factor</th>
<th>Responder, n = 386</th>
<th>Nonresponder, n = 34</th>
<th>P Value</th>
<th>GMT P Value</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>185</td>
<td>47.9</td>
<td>19</td>
<td>55.9</td>
</tr>
<tr>
<td>Female</td>
<td>201</td>
<td>52.1</td>
<td>15</td>
<td>44.1</td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>298</td>
<td>77.2</td>
<td>26</td>
<td>76.5</td>
</tr>
<tr>
<td>Yes</td>
<td>88</td>
<td>22.8</td>
<td>8</td>
<td>23.5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black/African American</td>
<td>96</td>
<td>24.9</td>
<td>5</td>
<td>14.7</td>
</tr>
<tr>
<td>Others</td>
<td>81</td>
<td>21.0</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>White</td>
<td>209</td>
<td>54.2</td>
<td>25</td>
<td>73.5</td>
</tr>
<tr>
<td>Insurance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicaid/SCHIP</td>
<td>82</td>
<td>22.0</td>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td>None</td>
<td>16</td>
<td>4.3</td>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td>Private/ HMO</td>
<td>274</td>
<td>73.7</td>
<td>29</td>
<td>83.6</td>
</tr>
</tbody>
</table>

During the past 30 d, how many days did you smoke cigarettes?
- 0 d: 349 | 90.9 | 29 | 85.3 | .35 | 831.02 | .98 |
- 1+ d: 35 | 9.1 | 5 | 14.7 | 820.88 |

During the past 30 d, how many days did you have at least one drink or alcohol?
- 0 d: 297 | 76.9 | 22 | 64.7 | .11 | 896.60 | .54 |
- 1+ d: 89 | 23.1 | 12 | 35.3 | 692.24 |

During the past 30 d, how may days did you have 5 or more drinks of alcohol in a row within a couple of hours?
- 0 d: 346 | 88.6 | 26 | 76.5 | .04 | 916.21 | .24 |
- 1+ d: 40 | 10.4 | 8 | 23.5 | 439.93 |

During the past 30 d, how many days did you use marijuana?
- 0 d: 337 | 87.3 | 26 | 76.5 | .11 | 980.58 | .02 |
- 1+ d: 48 | 12.7 | 8 | 23.5 | 320.55 |

During the past 30 d, how many times did you use illegal drugs?
- 0 times: 370 | 96.1 | 31 | 91.2 | .17 | 876.82 | .28 |
- 1+ times: 15 | 3.9 | 3 | 8.8 | 361.48 |

Have you ever had sexual intercourse?
- Yes: 253 | 66.1 | 22 | 64.7 | .87 | 931.25 | .33 |
- No: 130 | 33.9 | 12 | 35.3 | 861.88 |

HMO, health maintenance organization; SCHIP, state children’s health insurance program.
clinical significance of this finding is unclear, however, because race was not significantly associated with the more clinically relevant outcome of seroprotection. Further study is needed.

As has been reported, the dosage of vaccine, in this case the challenge dose, was associated with immune response. This finding may have clinical implications in the event a booster dose of vaccine is needed for adolescent or adult populations in the future. The higher dosage is more likely to result in a more vigorous immune response, which may have implications for duration of protection after the booster. The effect of marijuana on the effect of the challenge dose is also of interest. Although previous studies among adults have shown an association between immune response to the primary series and smoking cigarettes, no associations with marijuana and HB vaccine have previously been reported. This finding may have unique impact among adolescents who are engaging in risky behaviors.

This study had several limitations. First, it would have been ideal to know the anti-HBs levels of the participants after their primary series of HB vaccine to determine which participants were non-responders; postprimary series titers and manufacturer and lot number data for the primary series were not available. Second, although unlikely given the rigor with which vaccination status was assessed, it is possible that some participants received an undocumented additional dose of vaccine; however, the risk is likely distributed equally by group and risk factor. Third, despite its diversity, the study participants live in 1 metropolitan area and may not be representative of the entire continental United States. Finally, this study is directly applicable only to infants born in the United States between 1991 and 1998; infants born after 1998 received the higher dosage of vaccine. In the United States, the addition of a booster dose of hepatitis B vaccine to the routine immunization schedule for adolescents appears unnecessary. These data likely apply broadly to the continental US population at large. It will be important to follow up with a similar population 20 to 25 years after HB vaccine administration during infancy to determine duration of protection into the third decade of life.

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REFERENCES


TABLE 5 Multiple Linear Regression Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>SE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>2.54</td>
<td>0.11</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Log transformation of baseline titer</td>
<td>0.75</td>
<td>0.04</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Group (2 vs 1)</td>
<td>0.23</td>
<td>0.11</td>
<td>.04</td>
</tr>
<tr>
<td>Dose (20 vs 10 μg)</td>
<td>0.36</td>
<td>0.11</td>
<td>.002</td>
</tr>
<tr>
<td>Race (Black versus white)</td>
<td>0.42</td>
<td>0.13</td>
<td>.002</td>
</tr>
<tr>
<td>Race (Other versus white)</td>
<td>0.44</td>
<td>0.14</td>
<td>.002</td>
</tr>
<tr>
<td>Smoked marijuana (used versus not-used)</td>
<td>0.11</td>
<td>0.22</td>
<td>.61</td>
</tr>
<tr>
<td>Dose × smoked marijuana</td>
<td>−0.94</td>
<td>0.31</td>
<td>.003</td>
</tr>
</tbody>
</table>


(Continued from first page)

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