

# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

## **Differences in Response to a Hepatitis B Vaccine Booster Dose Among Alaskan Children and Adolescents Vaccinated During Infancy**

Taraz Samandari, Anthony E. Fiore, Susan Negus, James L. Williams, Wendi Kuhnert, Brian J. McMahon and Beth P. Bell

*Pediatrics* 2007;120:e373-e381; originally published online Jul 16, 2007;

DOI: 10.1542/peds.2007-0131

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/120/2/e373>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2007 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



# Differences in Response to a Hepatitis B Vaccine Booster Dose Among Alaskan Children and Adolescents Vaccinated During Infancy

Taraz Samandari, MD, PhD<sup>a,b</sup>, Anthony E. Fiore, MD, MPH<sup>a</sup>, Susan Negus, RN<sup>c</sup>, James L. Williams, CNP<sup>c</sup>, Wendi Kuhnert, PhD<sup>a</sup>, Brian J. McMahon, MD<sup>c</sup>, Beth P. Bell, MD, MPH<sup>a</sup>

<sup>a</sup>Division of Viral Hepatitis and <sup>b</sup>Epidemic Intelligence Service, Epidemiology Program Office, Centers for Disease Control and Prevention, Atlanta, Georgia; <sup>c</sup>Liver Disease and Hepatitis Program, Alaska Native Tribal Health Consortium, Anchorage, Alaska

The authors have indicated they have no financial relationships relevant to this article to disclose.

## ABSTRACT

**BACKGROUND.** The duration of protection provided by hepatitis B vaccination is unknown, but the presence of immune memory can be evaluated indirectly by measuring the immune response to a booster dose of vaccine.

**METHODS.** Participants included 74 adolescents (aged 11.7–14.9 years) who had received a plasma-derived 3-dose primary vaccine series and 138 adolescents (aged 10.0–14.7 years) and 166 children (aged 5.0–7.0 years) who received a recombinant 3-dose primary vaccine series. All were born to hepatitis B surface antigen–negative mothers and had received the first dose of hepatitis B vaccine within 7 days of birth. The proportion of participants with serologic evidence of protective immunity (antibody to hepatitis B surface antigen  $\geq 10$  mIU/mL) at baseline (prebooster), the proportion who developed an anamnestic response (increase to  $\geq 10$  mIU/mL or at or more than fourfold increase in antibody to hepatitis B surface antigen to  $> 10$  mIU/mL), and the geometric mean concentration by 1, 2, and 4 weeks after a 5- $\mu$ g recombinant vaccine booster dose were determined.

**RESULTS.** No participant had evidence of chronic hepatitis B virus infection. Overall, 99% of the group of children who received recombinant hepatitis B vaccine, 83% of the group of adolescents who received recombinant hepatitis B vaccine, and 69% of the group of adolescents who received the plasma-derived vaccine had an anamnestic response to a booster dose; among responders, the geometric mean concentration at 2 weeks postbooster was 3360 and 128 mIU/mL among adolescents who received plasma-derived vaccine with antibodies to hepatitis B surface antigen  $\geq 10$  and  $< 10$  mIU/mL at baseline, respectively, compared with 1283 and 369 mIU/mL among adolescents who received recombinant hepatitis B vaccine and 5091 and 696 mIU/mL for children who received recombinant hepatitis B vaccine. The anamnestic response rate at 2 weeks postbooster among participants with antibodies to hepatitis B surface antigen  $< 10$  mIU/mL at baseline was inversely associated with age; 97% of 5-year-olds responded compared with 60% of 14-year-olds.

**CONCLUSIONS.** Although most participants responded to a booster dose of hepatitis B vaccine, the significance of the increased proportion of nonresponses among older adolescents might indicate waning immune memory.

[www.pediatrics.org/cgi/doi/10.1542/peds.2007-0131](http://www.pediatrics.org/cgi/doi/10.1542/peds.2007-0131)

doi:10.1542/peds.2007-0131

### Key Words

hepatitis B, vaccination, adolescence, antibody, protective immunity

### Abbreviations

HBV— hepatitis B virus  
HBsAg— hepatitis B surface antigen  
anti-HBs— antibody to hepatitis B surface antigen  
ANMC— Alaska Native Medical Center  
CR— children who received recombinant hepatitis B vaccine  
AR— adolescents who received recombinant hepatitis B vaccine  
AS— adolescents who received plasma-derived vaccine  
GMC— geometric mean concentration

Accepted for publication Apr 3, 2007

Address correspondence to Anthony E. Fiore, MD, MPH, Influenza Division, Centers for Disease Control and Prevention, Mailstop A22, Atlanta, GA 30333. E-mail: [afiore@cdc.gov](mailto:afiore@cdc.gov)

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275); published in the public domain by the American Academy of Pediatrics

**H**EPATITIS B VIRUS (HBV) infection acquired during infancy and early childhood is a major cause of liver disease and liver cancer worldwide.<sup>1</sup> HBV infection can be safely and effectively prevented in infants and children by hepatitis B vaccination during infancy. The vaccine series is recommended for all infants in the United States beginning at birth, and the World Health Organization has recommended that all infants worldwide receive hepatitis B vaccination.<sup>2,3</sup> Substantial reductions in the prevalence of chronic infection and the incidence of acute hepatitis B have been demonstrated among children in populations where routine infant hepatitis B vaccination has been implemented.<sup>4-7</sup> However, the duration of protection after infants are vaccinated is unknown.<sup>8,9</sup> Loss of detectable concentrations of antibodies (anti-HBs) to hepatitis B surface antigen (HBsAg), the serologic marker of protection after a primary vaccine series, does not necessarily indicate loss of immunity. When tested in studies conducted 10 to 19 years after a primary vaccine series, 15% to 97% of vaccinated infants have low or undetectable concentrations of anti-HBs.<sup>10-17</sup> However, immunity may be preserved for most vaccinated persons, because a minority of study participants has any serologic evidence of HBV infection.<sup>10-17</sup>

Most studies that have demonstrated long-term vaccine effectiveness have been conducted among persons who likely have an ongoing risk of HBV exposure, such as infants born to women with chronic HBV infection or persons who live in communities with a high prevalence of HBV infection.<sup>10-16</sup> In populations that have a lower risk of infection, such as infants born to HBsAg-negative women, demonstrating long-term protection is more difficult, because ongoing risk of exposure might not be present, and continued low seroprevalence of markers of HBV infection might indicate lack of exposure rather than immunity. However, the presence of HBV-specific immune memory can be demonstrated by administering an additional (booster) dose of vaccine and measuring anti-HBs responses. A rapid increase in anti-HBs represents an anamnestic response and is considered to indicate the presence of HBV-specific immune memory.<sup>8,9,18</sup> However, the peak level of antibody response after a booster and the appropriate time to measure anti-HBs to determine anamnestic response has not been elucidated.

Routine hepatitis B vaccination beginning at birth has been provided to all Alaska Native infants since 1985,<sup>19</sup> well before routine immunization began in other parts of the United States and the rest of the world, with the exception of Taiwan.<sup>5</sup> Before routine hepatitis B vaccination programs were established, HBV infection was common among Alaska Native populations. In a large serosurvey of >52 000 Alaska Native people conducted during 1983-1987, 3.1% of the population had chronic HBV infection.<sup>20</sup> Compared with other regions of the United States, chronic HBV infection was largely responsible for high death rates from cirrhosis and hepatocel-

lular carcinoma in Alaska Native people.<sup>21,22</sup> Hepatitis B vaccination programs have resulted in significant declines in acute and chronic HBV infections among Alaska Native peoples, with few or no new chronic infections observed among vaccinated cohorts<sup>23</sup> or in regions of Alaska where vaccination coverage is high.<sup>4</sup>

Follow-up studies among Alaskan children born to HBsAg-negative women in Anchorage, where hepatitis B incidence has been similar to the rest of the United States during the past decade,<sup>24,25</sup> provide an early opportunity to assess long-term protection among adolescents who are at relatively low risk for exposure to HBV during early childhood. Ensuring that adolescents who were vaccinated as neonates remain immune to HBV infection is necessary to maintain progress toward elimination of HBV transmission. Nonimmune adolescents and young adults are at potential risk for exposures to HBV as a result of sexual activity or injection-drug use.<sup>26</sup> The objective of this study was to determine anti-HBs responses after a booster dose of hepatitis B vaccine among groups of early elementary school-aged children (5-7 years old) and older children/adolescents (10-14 years old) who were born to HBsAg-negative women in Anchorage. Our hypothesis was that, if immune memory was intact, >90% of persons who had received a primary series of hepatitis B vaccine should respond to a booster dose. A secondary purpose of this study was to compare responses to a booster dose at 1, 2, and 4 weeks.

## METHODS

### Study Population

This study received approval from institutional review boards at Centers for Disease Control and Prevention, the Alaska Native Tribal Health Consortium, and the Southcentral Foundation Native Health Board. The Alaska Native Medical Center (ANMC) was the site of recruitment. The ANMC serves as a primary care center for the 32 000 Alaska Native peoples living in Anchorage and surrounding communities within an ~1-hour drive from the city of Anchorage, as well as a tertiary care center for Alaska Native tribal hospitals and clinics throughout the state. Parents of children who were 5 to 7 or 10 to 14 years old and received care at the ANMC in Anchorage were contacted by mail to enroll their children in the study. Recruitment took place between October 3, 2001, and January 28, 2004. Only children who had been vaccinated at the ANMC with a 3-dose hepatitis B vaccine series, beginning with a dose in the first 7 days of life, and who had completed the series with appropriate dosages and intervals by 10 months of age were eligible for the study. The vaccine manufacturer and dosage of hepatitis B vaccine given were obtained if available. Children were excluded if they were born to a mother with chronic HBV infection; had ever received blood products; had received hepatitis B immune glob-

ulin as infants; had a sibling, father, or mother with chronic HBV infection; had a history of any allergic reaction to hepatitis B vaccines; had evidence of immunosuppression; or were taking immunosuppressive medications at the time of study recruitment. ANMC medical charts were used to verify vaccinations and other medical history. Participants were reimbursed \$25 for each visit to pay for travel and family child care expenses.

Three groups of participants were recruited and compared. We attempted to enroll  $\geq 175$  children and 175 adolescents, based on an expected frequency of children who would not respond to the booster dose of 10% and a desire to achieve a precision of within 5% for the estimate of nonresponse to vaccination each group. However, we began the study with the knowledge that our sample size might be constrained by the relatively small size ( $\sim 600$  children) of the eligible yearly birth cohort among Anchorage-area Alaska Natives.

The first group (children who received recombinant hepatitis B vaccine [CR]) included children who were 5 to 7 years old who received a 5- or 10- $\mu\text{g}$  (depending on the licensed vaccine formulation) 3-dose vaccine series of recombinant hepatitis B vaccine. The second group (adolescents who received recombinant hepatitis B vaccine [AR]) of children were  $\geq 10$  years old and had received a 3-dose recombinant vaccine series using any of the licensed dosages, which included at the time of vaccination 2.5-, 5.0-, and 10.0- $\mu\text{g}$  formulations. The third group (adolescents who received plasma-derived vaccine [AS]) consisted of children who were  $\geq 10$  years old who had received a 3-dose series with the plasma-derived vaccine (10  $\mu\text{g}$ ). When available, vaccine lot numbers were used to confirm the type of vaccine received. For some children in the AR or AS groups, the vaccine type was unknown for 1 or 2 doses in the 3-dose primary series. These doses were considered to be the same type as the known dose(s) in that series.

Participants were enrolled after obtaining a written consent from each child's parent/guardian. Verbal assent was also obtained from children  $\geq 7$  years of age. Each child's medical chart, including birth records, was reviewed to determine maternal HBsAg status, to ascertain primary immunization schedule, and to assure that no additional hepatitis B vaccine doses had been received. Participants had their blood drawn for serologic testing and were given a 5- $\mu\text{g}$  dose of pediatric recombinant hepatitis B vaccine (Recombivax; Merck & Co, West Point, PA) by intramuscular injection in a deltoid muscle. Participants or their parents or guardians were asked to keep a 3-day diary to record any adverse event. All of the participants were asked to return for phlebotomy 14 days and 28 days after the booster dose was administered. Participants were also offered the option to return for phlebotomy at  $\sim 7$  days after the booster, but this was not required for inclusion in the study. Participants were notified of test results by mail.

### Serologic Tests and Definitions

Blood specimens taken immediately before administration of the booster dose (day 0) were tested for quantitative anti-HBs (AUSAB; Abbott Laboratories, Abbott Park, IL) and antibody to hepatitis B core antigen (Ortho HBc ELISA Test System; Ortho, Raritan, NJ). If the antibody to hepatitis B core antigen test was positive, the sample was also tested for HBsAg (AUSZYME Monoclonal; Abbott Laboratories) and HBV DNA (Abbott HBV ASR, Abbott Molecular, Inc, Des Plaines, IL). Specimens drawn after day 0 were only tested for anti-HBs. Participants were considered immune if they had an anti-HBs concentration of  $\geq 10$  mIU/mL at the 2- or 4-week time point. Because the appropriate time to measure for anamnestic response is unknown, we included a 7-day draw in a subset of participants to see whether evidence of an anamnestic response could be demonstrated earlier than 14 to 28 days, which are the time points used in most published studies. Evidence of an anamnestic response at 1, 2, and 4 weeks was defined according to the baseline anti-HBs concentration. For those with baseline anti-HBs levels of  $\geq 10$  mIU/mL, an anamnestic response was defined as a fourfold or greater rise in anti-HBs concentration. For those with baseline anti-HBs levels of  $< 10$  mIU/mL, an anamnestic response was defined as an increase in anti-HBs concentration to  $\geq 10$  mIU/mL. Additional vaccine doses were offered to all of the participants who did not develop an anamnestic response to 1 dose, but testing after revaccination series doses was optional.

### Statistical Analysis

Comparisons of frequencies, proportions, and calculation of geometric mean concentrations (GMC) were performed in Epi Info 6.02 (Centers for Disease Control and Prevention, Atlanta, GA), Microsoft Excel (Microsoft, Redmond, WA), and SPSS 12.0 (SPSS Inc, Chicago, IL). The Kruskal-Wallis test was used to compare GMCs between groups.

### RESULTS

A total of 389 participants were enrolled. Three participants were excluded because vaccine type could not be determined for any dose. An additional 7 participants were excluded because they did not return for any visits after receiving the booster dose. One participant who received plasma-derived vaccine was excluded from subsequent analyses because of serologic evidence of resolved HBV infection (ie, tested positive for antibody to hepatitis B core antigen positive but negative for HBsAg negative and HBV DNA). Among the 378 remaining participants, 166 were in group CR, 138 in group AR, and 74 in group AS. The mean age for group CR was 5.9 years (range: 5.0–6.9 years), for group AR, 11.8 years (range: 10.0–14.7 years), and for group AS, 14.0 years (range: 11.7–14.9 years).

Of the children (CR) who received recombinant vaccine, 70 were classified as having received an Engerix B vaccine series (GlaxoSmithKline Biologicals, Rixensart, Belgium), and 96 received Recombivax. For 46, the vaccine used in 1 or 2 doses was not recorded. Of the adolescents who received recombinant vaccine, only 6 were classified as having received an Engerix B series. A Recombivax series was given to 132 children. The recombinant vaccine brand was not recorded for either 1 or 2 doses for 58 adolescents.

Among adolescents, the mean age of the group of AR participants was significantly less than that of AS participants. Group CR included significantly more boys compared with the other 2 groups. At least 95% of participants in all 3 of the groups were Alaska Native children. Overall, 19% of participants (16% of CR, 12% of AR, and 41% of AS groups, respectively) returned to provide the optional specimen at 1 week after the booster dose. More than 96% of participants in all 3 of the groups returned for week-2 and week-4 testing. The groups did not significantly differ according to mean age at completion of the primary series or days after booster when 1-, 2-, and 4-week postbooster blood draws occurred.

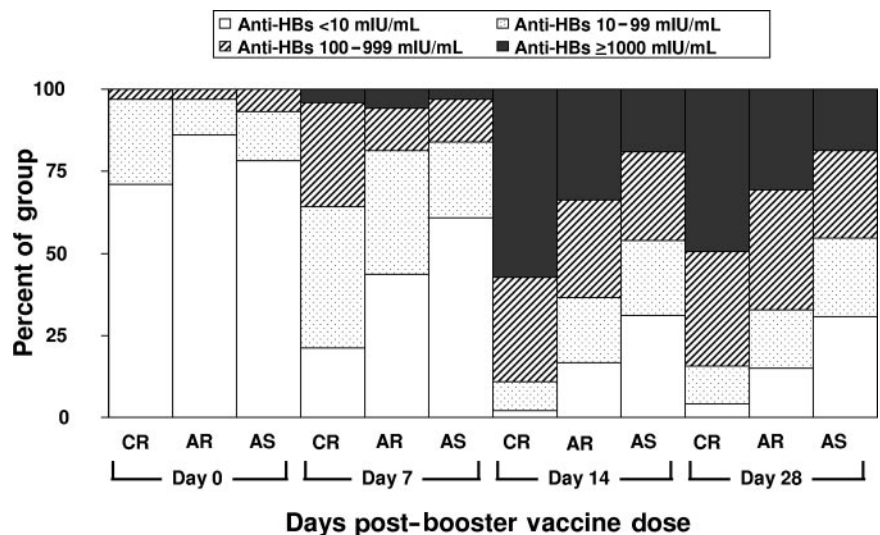
The distribution of anti-HBs responses at each time point is shown in Fig 1. The GMC at each time point by group is presented in Table 1. The highest proportion of persons meeting the criteria for an anamnestic response occurred at 2 weeks. At 1 week, only 40% to 79% met the criteria for an anamnestic response compared with 69% to 98% at 2 weeks. In addition, the GMC at 2 weeks was significantly higher than that at 1 week. At 4 weeks, there no appreciable difference in the proportion of those who met the definition of an anamnestic response, and the GMC for each group was lower. The GMC and proportion exhibiting an anamnestic response for the 2 adolescent groups was significantly less at 2 and 4 weeks after the booster dose compared with that of the

younger participants. Adolescents who received plasma-derived vaccine also had a significantly lower GMC and proportion who exhibited an anamnestic response at 2 and 4 weeks compared with adolescents who received recombinant vaccine.

The GMC at the 2- and 4-week time points for the 3 groups is shown in Fig 2. Participants who did not develop an anamnestic response are excluded so that differences in the magnitude of the response among participants who responded can be better represented. Within each group at both 2- and 4-week time points, the GMC of those with baseline anti-HBs levels of  $\geq 10$  mIU/mL was significantly higher compared with the corresponding time point among those with baseline anti-HBs levels of  $< 10$  mIU/mL. Among those with baseline concentrations of  $< 10$  mIU/mL, the CR group had a significantly higher GMC compared with both the AS and AR groups at 2 weeks and the AS group at 4 weeks. The GMC of the AR group was significantly higher than the AS group at 2 but not 4 weeks. Among those with baseline concentrations  $\geq 10$  mIU/mL at baseline, the GMC of the CR group was significantly higher at 2 and 4 weeks compared with the GMC of the AR group, and the GMC of the AS group was significantly higher than that of the AR group only at 4 weeks.

We also compared the response to a booster dose in children with low yet detectable baseline anti-HBs concentrations (between 0.0 mIU/mL and 9.9 mIU/mL) to those with baseline anti-HBs  $\geq 10$  mIU/mL and those with no detectable baseline anti-HBs (Table 2). All of the participants in the recombinant vaccine groups (CR and AR) who had anti-HBs levels of  $\geq 10$  mIU/mL at baseline had an anamnestic response to the booster dose at 2 weeks. Two AS participants with anti-HBs levels of  $\geq 10$  mIU/mL at baseline did not. Regardless of vaccine type used, adolescents from both groups who had no detectable anti-HBs at baseline were less likely to develop an

**FIGURE 1**  
Distribution of anti-HBs concentration before and after a booster dose of hepatitis B vaccine according to group. <sup>a</sup> Group CR indicates child recombinant, 5- to 7-year-olds who received recombinant vaccine series beginning at birth; AR, adolescent recombinant, 10- to 14-year-olds who received recombinant vaccine series beginning at birth; and AS, adolescent plasma-derived, 11- to 14-year-olds who received plasma-derived vaccine beginning at birth.



**TABLE 1 Anti-HBs Levels at Baseline and Response to Booster Dose According to Group and Time Point**

Group/Primary Series Vaccine <sup>a</sup>	Baseline			1 wk After Booster <sup>b</sup>			2 wk After Booster			4 wk After Booster		
	<i>n</i>	% Anti-HBs ≥10 mIU/mL	GMC, mIU/mL (95% CI)	<i>n</i>	% Anamnestic Response <sup>c</sup>	GMC, mIU/mL (95% CI)	<i>n</i>	% Anamnestic Response <sup>c</sup>	GMC, mIU/mL (95% CI)	<i>n</i>	% Anamnestic Response <sup>c</sup>	GMC, mIU/mL (95% CI)
CR ( <i>n</i> = 166)	166	29	22.0	27	79	22.0 (6.0–80.6)	162	98	1070 (779–1469)	158	99	653 (474–899)
AR ( <i>n</i> = 138)	138	14 <sup>d</sup>	4.6	16	56	4.6 (0.8–27.4)	133	83 <sup>d</sup>	148 (86.2–256) <sup>d</sup>	137	88 <sup>d</sup>	145 (89.1–237.0) <sup>d</sup>
AS ( <i>n</i> = 74)	74	21	3.2	30	40 <sup>d</sup>	3.2 (1.0–10.1) <sup>d</sup>	74	69 <sup>d,e</sup>	28.0 (11.0–71.0) <sup>d,e</sup>	74	71 <sup>d,e</sup>	29.8 (12.4–71.8) <sup>d,e</sup>

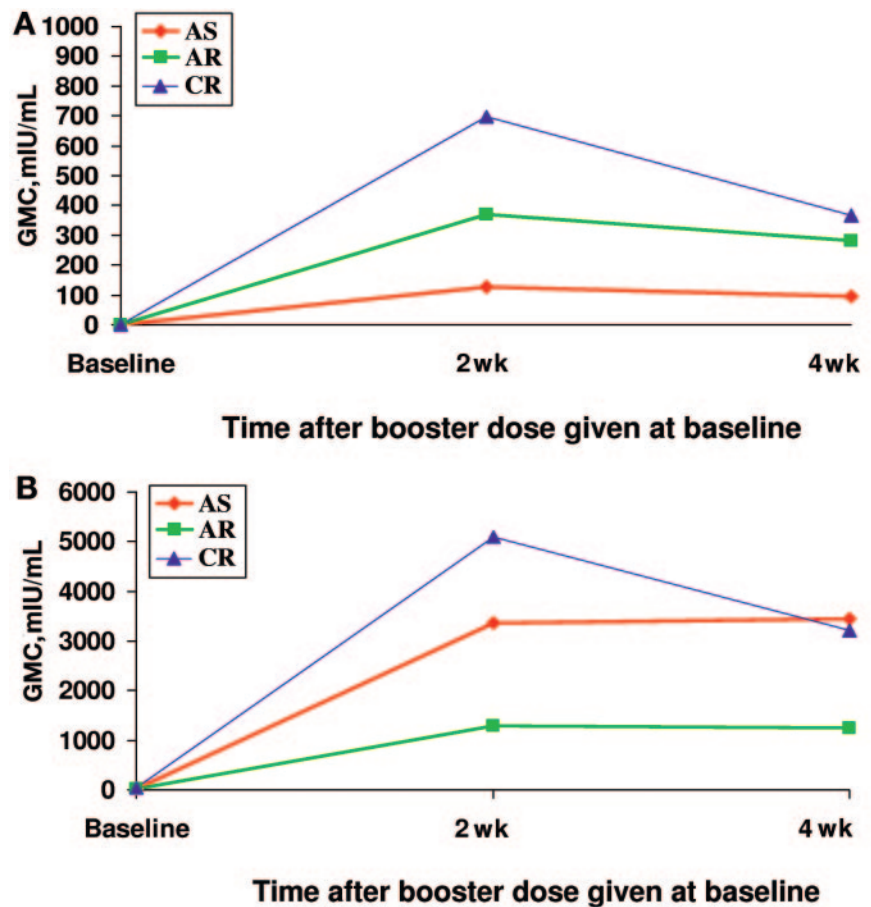
<sup>a</sup> Group CR indicates child recombinant and includes 5- to 7-year-olds who received recombinant vaccine series beginning at birth; AR, adolescent recombinant and includes 10- to 14-year-olds who received recombinant vaccine series beginning at birth; AS, adolescent plasma derived and includes 11- to 14-year-olds who received plasma-derived vaccine beginning at birth; CI, confidence interval.

<sup>b</sup> One-week specimen was optional for participants.

<sup>c</sup> For those with baseline anti-HBs levels of ≥10 mIU/mL, an anamnestic response was defined as a fourfold or greater rise in anti-HBs concentration. For those with baseline anti-HBs levels of <10 mIU/mL, an anamnestic response was defined as an increase in anti-HBs concentration to ≥10 mIU/mL.

<sup>d</sup> This was significantly less than group CR at this time point (*P* < .05).

<sup>e</sup> This was significantly less than group AR at this time point (*P* < .05).



**FIGURE 2**

A, Anti-HBs (GMC) at 2 and 4 weeks after a recombinant vaccine booster dose among participants with baseline anti-HBs levels of <10 mIU/mL and who had an anamnestic response according to group. B, Anti-HBs (GMC) at 2 and 4 weeks after a recombinant vaccine booster dose among participants with baseline anti-HBs levels of ≥10 mIU/mL and who had an anamnestic response according to group.

anamnestic response compared with those with baseline anti-HBs levels of ≥10 mIU/mL. Among adolescents who received plasma-derived vaccine, persons with low yet detectable anti-HBs were also significantly more likely to have an anamnestic response than children with no detectable anti-HBs. Among participants with no detectable or low yet detectable anti-HBs at baseline, children and adolescents who received recombinant vaccine were significantly more likely to have an anamnestic response compared with group AS. Among partici-

pants with no detectable anti-HBs at baseline, only 50% of group AS children had an anamnestic response compared with 95% and 81% of group CR and AR participants, respectively.

The percentage of children by age who developed an anamnestic response among those who had baseline anti-HBs levels of <10 mIU/mL is shown in Fig 3. Response rates did not differ significantly by group for any of these ages. In general, the proportion of children who had an anamnestic response decreased according to in-

**TABLE 2** Percentage of Participants With Anamnestic Response at 2 and/or 4 Weeks According to Baseline Anti-HBs Concentration, by Group

Group/Primary Series Vaccine <sup>a</sup>	Baseline Anti-HBs Level of <0.1 mIU/mL		Baseline Anti-HBs Levels Between 0.1 and 9.9 mIU/mL		Baseline Anti-HBs Levels of ≥10 mIU/mL	
	<i>n</i>	% Anamnestic Response	<i>n</i>	% Anamnestic Response	<i>n</i>	% Anamnestic Response
	CR ( <i>n</i> = 166)	66	95	50	100	50
AR ( <i>n</i> = 138)	87	81 <sup>b,c</sup>	31	77 <sup>b,c</sup>	20	100
AS ( <i>n</i> = 74)	38	50 <sup>b,c,d,e</sup>	21	76 <sup>b,c</sup>	16	88 <sup>b</sup>

<sup>a</sup> Child recombinant includes 5- to 7-year-olds who received recombinant vaccine series beginning at birth; adolescent recombinant includes 10- to 14-year olds who received recombinant vaccine series beginning at birth; adolescent/plasma derived includes 11- to 14-year-olds who received plasma-derived vaccine beginning at birth.

<sup>b</sup> This is significantly less than group CR with same baseline anti-HBs category.

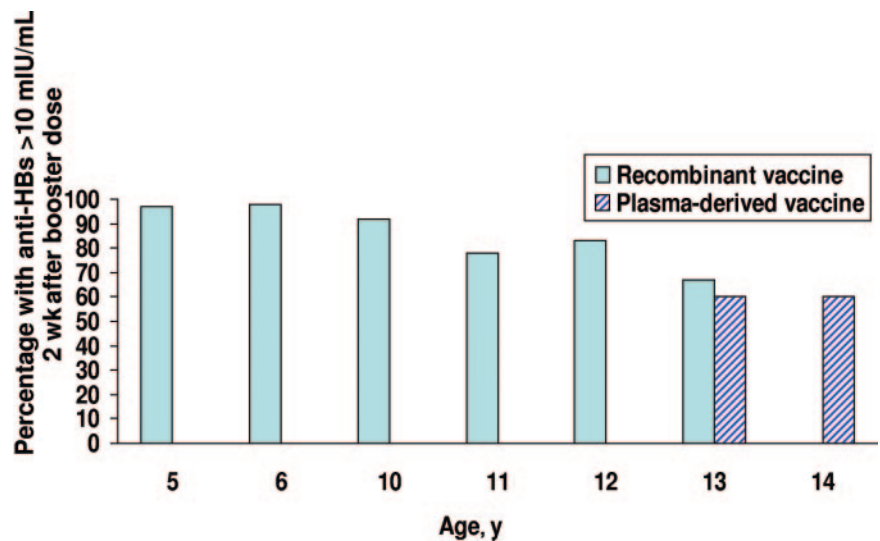
<sup>c</sup> This is significantly less than participants with baseline anti-HBs levels of ≥10 mIU/mL in same group.

<sup>d</sup> This is significantly less than group AR with same baseline anti-HBs category.

<sup>e</sup> This is significantly less than participants with baseline anti-HBs levels between 0.1 and 9.9 mIU/mL in same group.

**FIGURE 3**

Children with an anamnestic anti-HBs response at 2 weeks after a booster dose of hepatitis B vaccine by age among persons with baseline anti-HBs levels of <10 mIU/mL. Solid bars indicate the percentage who developed an anamnestic response to a recombinant vaccine booster dose among those who received a recombinant vaccine primary series. Hatched bars indicate the percentage who developed an anamnestic response to a booster dose among those who received a plasma-derived vaccine primary series.



creasing age ( $\chi^2$  for trend,  $P < .001$ ). Each age group >10 years old was significantly less likely to have an anamnestic response compared with children 5, 6, or 10 years of age. In addition, 13- or 14-year-olds were less likely to have an anamnestic response compared with 11- or 12-year-olds.

Among 23 children tested who did not have an anamnestic response and subsequently received a second dose of vaccine, 19 (83%) responded with an anti-HBs concentration  $\geq 10$  mIU/mL, including 7 whose anti-HBs levels rose to  $\geq 1000$  mIU/mL. Of the remaining 4 participants, 2 responded to a third dose with anti-HBs concentrations that increased to  $\geq 10$  mIU/mL, and 2 never responded even after a third dose.

## DISCUSSION

In Alaska, as well as in many other settings, previous studies have demonstrated excellent long-term protection from HBV infection among children vaccinated as neonates and born to HBV-infected women or among

children who were vaccinated beginning at  $\geq 3$  months of age.<sup>10-17</sup> In this study, we sought evidence of continued long-term protection during early adolescence among children and adolescents whose primary vaccination series began within 7 days of birth but who were also born to women who did not have HBV infection. For participants who had lost seroprotective concentrations of anti-HBs, the presence of specific immune memory was inferred by demonstrating anamnestic responses to a booster dose of vaccine. In this study, testing for an anamnestic response at 2 weeks seemed to offer the best opportunity to capture a response that was most convincingly because of an anamnestic response rather than a primary response.

Our study found that 71% to 86% of children immunized starting at birth had concentrations of anti-HBs levels of <10 mIU/mL, the level generally measurable by commercial assays. Previous studies have shown that peak anti-HBs concentrations among young infants are significantly lower after a primary series compared with

persons who start the series as older children or adults,<sup>2,23</sup> and lower postvaccination concentrations might result in shortening the time to loss of detectable anti-HBs after a primary series. This could explain why such a high proportion of children have levels <10 mIU/mL in this population as compared with Alaska Native older children and adults followed for the same period of time.<sup>23</sup> Nevertheless, the findings of our study indicate that despite the loss of seroprotective concentrations of anti-HBs in most participants, nearly all child and most adolescent participants had evidence of immunity.

Older participants were less likely to have an anamnestic response, and those who responded had a less robust response, compared with younger participants. Furthermore, some of the observed anti-HBs responses to the booster dose, particularly in the older age groups, were similar in magnitude to those observed among previously unvaccinated adolescents or adults after receipt of the first dose of the vaccine series.<sup>27-30</sup> However, 2 observations suggests that most participants were exhibiting an anamnestic response rather than a primary response. First, only 10% to 30% of persons who receive hepatitis B vaccine will achieve an anti-HBs response  $\geq 10$  mIU/mL 1 month after the first dose. In contrast, most of the adolescents in this study reached an anti-HBs concentration  $\geq 10$  mIU/mL by 4 weeks after vaccination. Second, most adolescents in our study showed a rapid anti-HBs response in which protective concentrations of anti-HBs were observed within 2 weeks of the booster dose, making it unlikely that these responses represent primary immunization responses that might be seen in a persons who had never been vaccinated or had lost immunity.<sup>18</sup>

The lack of postprimary series testing results in this study makes it difficult to determine why adolescents who had received the serum-derived vaccine were less likely to have an anamnestic response to a booster dose compared with younger adolescents and children who received recombinant vaccine during the primary series. Adolescents enrolled in this study who received 10- $\mu$ g doses of plasma-derived vaccine during their primary series would have been expected to have primary responses similar to those who received a 5- or 10- $\mu$ g dose of recombinant vaccine and, therefore, would be expected to have similar rates of anti-HBs decline.<sup>31</sup> The most likely explanation for the relatively high proportion of AS participants (40% of 14-year-olds) who did not respond is that this group is older than the adolescent group that received recombinant vaccine, and the time that had elapsed since the primary series is longer. Immune system function is less developed among infants compared with that of older children and adults, and protection wanes with time among infants vaccinated against some other antigens, such as mumps, pertussis, or measles.<sup>32,33</sup> Another possibility for increased

loss of anamnestic responses among the older children is the slight differences in antigen between the plasma-derived versus the recombinant vaccines. Perhaps children who were originally vaccinated with plasma-derived vaccine respond less well to a recombinant vaccine booster dose.

We did not find evidence that loss of a demonstrable anamnestic response among older participants, which was most notable among those who received plasma-derived vaccine during their primary series, indicates susceptibility to HBV infection. In studies conducted in endemic areas, long-term protection after vaccination with plasma-derived vaccine has been shown to last  $\geq 18$  to 19 years,<sup>15,16</sup> and a large majority of children vaccinated at birth have an anamnestic response to a booster dose as much as 15 years later.<sup>13</sup> However, in endemic areas, studies indicating that a high proportion of vaccinated infants and children retain protective concentrations of anti-HBs in adolescence and exhibit a booster response if revaccinated might be because of "natural boosting" from exposure to HBV-infected persons in the household and community. Evidence of natural boosting has been demonstrated in areas of Alaska that are endemic for HBV.<sup>34</sup>

Additional studies are needed to determine whether larger proportions of adolescents who received the recombinant vaccine during infancy will become unable to demonstrate an anamnestic response as they grow older. One possible explanation for why a lower proportion of adolescents who had received recombinant vaccine at birth boosted compared with children who also received the same recombinant vaccine is that many of the adolescents received a primary series consisting of three 2.5- $\mu$ g doses (a licensed Recombivax dose at the time of vaccination), whereas all of the younger participants received 5- $\mu$ g (Recombivax) or 10- $\mu$ g (Engerix-B) doses of vaccine during the primary series. This may have resulted in lower final anti-HBs concentrations after the primary series in those who received the 2.5- $\mu$ g dose. Previous studies have shown that vaccinated persons who receive an additional dose some years after the primary series develop anti-HBs levels that are similar in magnitude to the concentration that was achieved after the primary series,<sup>10,11,35,36</sup> and higher levels of anti-HBs postprimary series usually correspond with the amount of HBsAg antigen in the dose of the vaccine given.<sup>12,31</sup> Manufacture of the 2.5- $\mu$ g vaccine dose of Recombivax for use in the United States ceased in 1999.<sup>37</sup>

There are several other possible explanations for the finding that the older adolescents in this study had a lower proportion in whom an anamnestic response could be demonstrated compared with those in other published long-term protection studies. First, participants were vaccinated beginning at birth as part of routine immunization by their usual health care providers but not tested until study enrollment later in childhood

or adolescence. Therefore, participants in this study differed from those in most other published long-term protection studies conducted among children or adults at higher risk of infection in that they did not receive postvaccination testing after their primary series during infancy, and a larger-than-expected proportion might have been primary nonresponders. Older study participants, among whom anamnestic responses were less common, might have had unusually low seroprotection rates after the primary series. However, because >95% of the CR group developed an anamnestic response, it is likely that the proportion of nonresponders to the primary series in this group was ~5%, which is similar to other studies conducted in infants who receive their first dose shortly after birth and have anti-HBs levels tested. In addition, the dose and brand or type of vaccine used for the primary series was not determined for some participants; therefore, differences in anamnestic responses could not be assessed by using these parameters. However, standard, licensed dosages and brands were used for all of the children, and mixed-brand regimens are considered acceptable in clinical practice.

The same characteristics that distinguish participants in this study from other published studies make them similar to most children who receive hepatitis B vaccination as part of their routine infant vaccination schedule. For the large majority of immunized children, postvaccination testing is not recommended, and schedules that include >1 dosage or brand are accepted. Exposures to HBV before adolescence and, therefore, opportunities for stimulation of immune memory by "natural boosting"<sup>16</sup> were likely uncommon. No participants in this study were known to have household contact with any persons with chronic HBV infection. Thus, findings from this study might be pertinent to vaccination programs in developed countries, including the United States, where hepatitis B vaccine is incorporated into the routine infant vaccination schedule, and the prevalence of HBV infection is low. Participants in this study might exhibit similar immunologic responses after vaccination to other populations where the risk of infection before adolescence is low.

The clinical importance of an anamnestic response after a booster dose is unknown and might not accurately reflect memory. Among vaccinated persons who have lost the capacity to mount a detectable anamnestic response, protection from chronic infection or symptomatic infection might persist even if protection from acute, asymptomatic infection is no longer present. The relative magnitude of anti-HBs responses might not be important if sufficient neutralizing antibody can still be generated to prevent chronic or symptomatic HBV infection within the 4- to 12-week incubation period that precedes clinical evidence of infection. Alternative laboratory tests that are capable of demonstrating continued immunity

are not available for persons with low or undetectable anti-HBs who were vaccinated >10 years previously.

## CONCLUSIONS

We found that almost all of the children given a booster dose of vaccine and >80% of adolescents overall responded to a booster dose of hepatitis B vaccine years after the primary immunization series starting at birth. However, the finding that older children are less likely to demonstrate an anamnestic response underscores the need to conduct additional studies to monitor long-term protection after vaccination during infancy. In addition, continued public health surveillance is required to identify and investigate any breakthrough infections among vaccinated cohorts. Some persons vaccinated as infants against respiratory diseases that are more easily transmissible, such as measles, mumps, or pertussis, have been shown to lose protection from infection during adolescence, leading to recommendations for booster doses of these vaccines during adolescence.<sup>32,33,38</sup> If immunity engendered by hepatitis B vaccine wanes in older adolescents and young adults who began their vaccine series as neonates, then HBV infections could occur in older adolescence and adulthood. Administering a booster dose of hepatitis B vaccine during childhood or early adolescence, perhaps as a component of a combination vaccine containing other recommended vaccine antigens, is feasible and might offer longer-term protection through adulthood. However, additional studies are needed before booster dose(s) of hepatitis B vaccine intended to maintain long-term immunity can be recommended.

## REFERENCES

1. World Health Organization. Hepatitis B, fact sheet number 204. Available at: [www.who.int/mediacentre/factsheets/fs204/en/index.html](http://www.who.int/mediacentre/factsheets/fs204/en/index.html). Accessed October 11, 2006
2. Mast EE, Margolis HS, Fiore AE et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1—immunization of infants, children, and adolescents [published correction appears in *MMWR Morb Mortal Wkly Rep*. 2006;55:158–159]. *MMWR Recomm Rep*. 2005;54(RR-16):1–31
3. World Health Organization. Hepatitis B vaccines: WHO position paper. *Wkly Epidemiol Rec*. 2004;79:255–262
4. Harpaz R, McMahon BJ, Margolis HS, et al. Elimination of new chronic hepatitis B virus infections: results of the Alaska immunization program. *J Infect Dis*. 2000;181:413–8 Feb
5. Ni YH, Chang MH, Huang LM, et al. Hepatitis B virus infection in children and adolescents in a hyperendemic area: 15 years after mass hepatitis B vaccination. *Ann Intern Med*. 2001:796–800
6. Centers for Disease Control and Prevention. Acute hepatitis B among children and adolescents: United States, 1990–2002. *MMWR Morb Mortal Wkly Rep*. 2004;53:1015–1018
7. Bonanni P, Pesavento G, Bechini A, et al. Impact of universal vaccination programmes on the epidemiology of hepatitis B: 10 years of experience in Italy. *Vaccine*. 2003;21:685–691
8. European Consensus Group on Hepatitis B Immunity. Are

- booster immunisations needed for lifelong hepatitis B immunity? *Lancet*. 2000;355:561–565
9. FitzSimons D, François G, Hall A, et al. Long-term efficacy of hepatitis B vaccine, booster policy, and impact of hepatitis B mutants. *Vaccine*. 2005;23:4158–4166
  10. Petersen KM, Bulkow LR, McMahon BJ, et al. Duration of hepatitis B immunity in low risk children receiving hepatitis B vaccinations from birth. *Pediatr Infect Dis J*. 2004;23:650–655
  11. Dentinger CM, McMahon BJ, Fiore AE, et al. Anti-HBs persistence and response to a hepatitis B vaccine (HB) boost among Yup'ik Eskimos 22 years after HB vaccination [abstract 1028]. In: *Abstracts of the Infectious Diseases Society of America 43rd Annual Meeting*. Alexandria, VA: Infectious Diseases Society of America; 2005
  12. Dentinger CM, McMahon BJ, Butler JC, et al. Persistence of antibody to hepatitis B and protection from disease among Alaska Natives immunized at birth. *Pediatr Infect Dis J*. 2005;24:786–792
  13. Lu CY, Chiang BL, Chi WK, et al. Waning immunity to plasma-derived hepatitis B vaccine and the need for boosters 15 years after neonatal vaccination. *Hepatology*. 2004;40:1415–1420
  14. Liao SS, Li RC, Li H et al. Long-term efficacy of plasma-derived hepatitis B vaccine: a 15-year follow-up study among Chinese children. *Vaccine*. 1999;17:2661–2666
  15. Yuen MF, Lim WL, Chan AOO, et al. 18-year follow-up study of a prospective randomized trial of hepatitis B vaccinations without booster doses in children. *Clin Gastroenterol Hepatol*. 2004;2:941–945
  16. Van der Sande MAB, Waight P, Mendy M, et al. Long-term protection against carriage of hepatitis B virus after infant vaccination. *J Infect Dis*. 2006;193:1528–1535
  17. Zanetti AR, Mariano A, Romano L, et al. Long term immunogenicity of hepatitis B vaccination and policy for booster: an Italian multicentre study. *Lancet*. 2005;366:1379–1384
  18. Banatvala JE, Van Damme P, Oehen S. Lifelong protection against hepatitis B: the role of vaccine immunogenicity in immune memory. *Vaccine*. 2001;19:877–885
  19. McMahon BJ, Rhoades ER, Heyward WL, et al. A comprehensive programme to reduce the incidence of hepatitis B and its sequelae in Alaskan natives. *Lancet*. 1987;2(8568):1134–1136
  20. McMahon BJ, Schoenberg S, Bulkow L, et al. Seroprevalence of hepatitis B viral markers in 52,000 Alaska Natives. *Am J Epidemiol*. 1993;138:544–549
  21. McMahon BJ, Alberts SR, Wainwright RB, Bulkow L, Lanier AP. Hepatitis B-related sequelae: prospective study in 1400 hepatitis B surface antigen-positive Alaska native carriers. *Arch Intern Med*. 1990;150:1051–1054
  22. Lanier AP, McMahon BJ, Alberts SR, Popper H, Heyward WL. Primary liver cancer in Alaska natives. 1980–1985. *Cancer*. 1987;60:1915–1920
  23. McMahon BJ, Bruden DL, Petersen KM, et al. Antibody levels and protection after hepatitis B vaccination: results of a 15-year follow-up. *Ann Intern Med*. 2005;142:333–341
  24. Centers for Disease Control and Prevention. Summary of notifiable diseases, United States 1994. *MMWR Morb Mortal Wkly Rep*. 1994;43(53):1–80
  25. Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 2004. *MMWR Morb Mortal Wkly Rep*. 2004;53(53):1–79
  26. Goldstein ST, Alter MJ, Williams IT, et al. Incidence and risk factors for acute hepatitis B in the United States 1982–1998: implications for vaccination programs. *J Infect Dis*. 2002;185:713–719
  27. Wiedermann G, Scheiermann N, Goubau P, et al. Multicentre dose range study of a yeast-derived hepatitis B vaccine. *Vaccine*. 1987;5:179–183
  28. Schiff GM, Sherwood JR, Zeldis JB, Krause DS. Comparative study of the immunogenicity and safety of two doses of recombinant hepatitis B vaccine in healthy adolescents. *J Adolesc Health*. 1995;16:12–17
  29. Cassidy WM, Watson B, Ioli VA, Williams K, Bird S, West DJ. A randomized trial of alternative two- and three-dose hepatitis B vaccination regimens in adolescents: antibody responses, safety, and immunologic memory. *Pediatrics*. 2001;107:626–631
  30. Zanetti AR, Tanzi E, Pozzi A, Romano L, Bergamini F. Yeast-derived hepatitis B vaccine in dental students: a three year follow-up study. *Vaccine*. 1990;8:205–208
  31. Greenberg DP. Pediatric experience with recombinant hepatitis B vaccines and relevant safety and immunogenicity studies. *Pediatr Infect Dis J*. 1993;12:438–445
  32. Broder KR, Cortese MM, Iskander JK, et al. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2006;55(RR-3):1–34
  33. Watson JC, Hadler SC, Dykewicz CA, Reef S, Phillips L. Measles mumps and rubella: vaccine use and strategies for elimination of measles, rubella and congenital rubella syndromes and control of mumps—recommendations of the Advisory on Immunization Practices. *MMWR Recomm Rep*. 1998;47(RR-8):1–57
  34. Bulkow LR, Wainwright RB, McMahon BJ, Parkinson AJ. Increases in levels of antibody to hepatitis B surface antigen in an immunized population. *Clin Infect Dis*. 1998;26:933–937
  35. Seto D, West DJ, Ioli VA. Persistence of antibody and immunologic memory in children immunized with hepatitis B vaccine at birth. *Pediatr Infect Dis J*. 2002;21:793–795
  36. Williams JL, Christensen CJ, McMahon BJ, et al. Evaluation of the response to a booster dose of hepatitis B vaccine in previously immunized healthcare workers. *Vaccine* 2001;19:4081–4085
  37. Centers for Disease Control and Prevention. Notice to readers: FDA approval of change in pediatric formulation for Recombivax HB. *MMWR Morb Mortal Wkly Rep*. 1999;48:34–35
  38. Centers for Disease Control and Prevention. ACIP provisional recommendations for prevention of varicella. Available at: [www.cdc.gov/nip/vaccine/varicella/varicella\\_acip\\_recs\\_prov\\_june\\_2006.pdf](http://www.cdc.gov/nip/vaccine/varicella/varicella_acip_recs_prov_june_2006.pdf). Accessed October 10, 2006

## Differences in Response to a Hepatitis B Vaccine Booster Dose Among Alaskan Children and Adolescents Vaccinated During Infancy

Taraz Samandari, Anthony E. Fiore, Susan Negus, James L. Williams, Wendi Kuhnert, Brian J. McMahon and Beth P. Bell

*Pediatrics* 2007;120:e373-e381; originally published online Jul 16, 2007;  
DOI: 10.1542/peds.2007-0131

### Updated Information & Services

including high-resolution figures, can be found at:  
<http://www.pediatrics.org/cgi/content/full/120/2/e373>

### References

This article cites 34 articles, 4 of which you can access for free at:  
<http://www.pediatrics.org/cgi/content/full/120/2/e373#BIBL>

### Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):  
**Infectious Disease & Immunity**  
[http://www.pediatrics.org/cgi/collection/infectious\\_disease](http://www.pediatrics.org/cgi/collection/infectious_disease)

### Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
<http://www.pediatrics.org/misc/Permissions.shtml>

### Reprints

Information about ordering reprints can be found online:  
<http://www.pediatrics.org/misc/reprints.shtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

