

# Duration of Hepatitis B Immunity in Low Risk Children Receiving Hepatitis B Vaccinations From Birth

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**Background:** The duration of protection after hepatitis B vaccination of infants is unknown.

**Methods:** We determined antibody to hepatitis B surface antigen (anti-HBs) at 4–13 years of age in 363 low risk children who had been vaccinated starting at birth with hepatitis B vaccine. Those with nonprotective titers (<10 mIU/mL) received a booster dose. We similarly followed 16 children of hepatitis B surface antigen (HBsAg)-positive mothers.

**Results:** Of low risk infants receiving a plasma-derived vaccine, 41% (42 of 102) of those whose primary response was unknown and 24% (4 of 17) who had initially responded retained protective titers ( $\geq 10$  mIU/mL) of anti-HBs at 9 and 13 years, respectively. Of those who did not have protective antibody titers, 61% (33 of 54) and 67% (8 of 12), respectively, responded to a booster dose. In children of HBsAg-positive mothers, 31% retained protective anti-HBs at 12 years, and 90% (9 of 10) with nonprotective titers responded to a booster. In low risk children initially receiving a recombinant vaccine, 12.5% (26 of 208) and none (0 of 36) retained protective anti-HBs titers at 5 and 7 years of age, respectively. Of those who did not have protective titers, 90% (120 of 134) and 91% (32 of 35), respectively, responded to a booster.

**Conclusions:** Anti-HBs disappeared by 5 years of age in most children who were vaccinated with hepatitis B vaccine from birth. Although most children showed immunologic memory, one-third failed to demonstrate an anamnestic response to a booster dose. Additional long term studies of low risk infants are needed to determine duration of protection and the necessity for or timing of booster doses.

**Key Words:** hepatitis B vaccine, protection duration, booster dose, low risk population

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Hepatitis B virus (HBV) is a major global health concern with >350 million people chronically infected.<sup>1</sup> The strategy for the control of HBV infection, as outlined by the World Health Organization and endorsed by the Advisory Committee on Immunization Practices (ACIP), is the introduction of hepatitis B immunization at birth.<sup>2,3</sup> This strategy is designed to reduce the risk of early childhood acquisition of HBV and reduce the number of chronic carriers in endemic populations. In lower risk populations, such as the United States, where transmission of HBV primarily occurs in older individuals, newborn immunization is also used to prevent the small number of cases transmitted in early childhood. Also when the hepatitis B vaccination is initiated at birth, there is an increased likelihood that the child will complete the series.<sup>4,5</sup>

The duration of hepatitis B vaccine protection has not been firmly established. Long term protection of 10–12 years appears to occur for those infants at high risk whose mothers were positive for hepatitis B surface antigen (HBsAg) and hepatitis B e antigen.<sup>6–12</sup> However, the duration of protection in low risk infants whose mothers are negative for HBsAg and who receive hepatitis B vaccine from birth is unknown. In these populations, the risk of HBV increases during adolescence and early adulthood primarily because of the risk of sexual transmission.<sup>3</sup> Whether booster doses might eventually be necessary to extend protection through adulthood has not been established.

We examined the long term persistence of antibody to hepatitis B surface antigen (anti-HBs) in children ages 4–13 years whose mothers were HBsAg-negative and who originally received a course of hepatitis B vaccine starting at birth. We also assessed the status of immunologic memory for HBV by evaluating the response to a booster dose of a hepatitis B vaccine in those children whose serum anti-HBs had fallen below 10 mIU/mL, the accepted protective concentration.<sup>6</sup>

## MATERIALS AND METHODS

### Study Population

We conducted 2 studies in Alaska children. All the children but 1 were Alaska Natives. Since 1985, all Native children in Alaska have received hepatitis B vaccine as part

of a statewide vaccination program. Hepatitis B vaccination is initiated within the first 7 days of life, with the second dose given at 4–6 weeks and the third at 6 months of age. Until 1989, a plasma-derived hepatitis B vaccine (Heptavax-B, 10  $\mu$ g; Merck Sharp & Dohme, West Point, PA) was given. Since 1989, yeast recombinant hepatitis B vaccines [RecombivaxHB, 2.5  $\mu$ g (Merck Sharp & Dohme), or Engerix-B, 10  $\mu$ g (SmithKline Beecham, Rixensart, Belgium)] have been used. Study 1 consisted of children whose initial response to the hepatitis B vaccine series was unknown (groups 1a and 1b), and study 2 consisted of children with a documented anti-HBs titer  $\geq 10$  mIU/mL after the initial vaccine series (Groups 2a, 2b and 2c) (Table 1). All booster doses in both studies used RecombivaxHB.

The institutional review boards of the Alaska Area Native Health Service, the Indian Health Service and the Centers for Disease Control and Prevention approved the protocols for both studies. Approval was also obtained from the Anchorage Native Health Board and Southcentral Foundation. Written informed consent was obtained from the parents or guardians of the children plus verbal assents from all children older than 7 years.

## Study Design

**Study 1.** Two groups of children born to HBsAg-negative mothers and vaccinated in infancy were examined. The initial antibody responses after the primary vaccination for children in this study were unknown. The first group consisted of 102 children (Table 1) who had received plasma-derived vaccine in infancy (group 1a); the second consisted of 208 children who had received recombinant vaccine (group 1b). Potential participants were identified by a computer search of immunization records, and they were invited to participate.

At enrollment, sera were obtained from all children and tested for anti-HBs and antibody to hepatitis B core antigen (anti-HBc). Children who were anti-HBc-negative with anti-HBs  $< 10$  mIU/mL were randomized by a computer-generated schedule to receive either a 2.5- $\mu$ g booster dose at that time or deferred for 3 years. Serum specimens were obtained 10–14 days after the booster dose and were tested for anti-HBs.

Those returning in 3 years were retested for anti-HBs and anti-HBc. Children who were anti-HBc-negative and whose anti-HBs remained  $< 10$  mIU/mL then received a 2.5- $\mu$ g booster dose. After the study was under way, early results led to a desire to obtain more immediate data on the booster response of children who had originally received the plasma vaccine (group 1a). Rather than wait for 3 years, group 1a children whose booster dose had initially been deferred were recalled early, and the booster dose was given an average of 1.5 years after initial recruitment.

**Study 2.** These children were originally part of a long term follow-up study of children who had received hepatitis B vaccine from birth and had their sera tested for anti-HBs after completion of the initial vaccination series. Only children who responded with anti-HBs titers of  $\geq 10$  mIU/mL or  $\geq 10$  standard ratio units (used in or before 1986) were included. Group 2a consisted of 17 children of HBsAg-negative mothers who had received a plasma-derived vaccine (Table 1) and were boosted with 5  $\mu$ g of recombinant vaccine (Recombivax). Group 2b consisted of 36 children of HBsAg-negative mothers who had received a recombinant vaccine. Approximately one-half of the children in group 2b were randomly assigned to receive a 2.5- $\mu$ g dose of recombinant vaccine, whereas the remaining children received a 5- $\mu$ g dose. Group 2c included 16 children who were born of HBsAg-positive mothers and who had received a plasma-derived vaccine; they were boosted with 5  $\mu$ g of recombinant vaccine.

At enrollment, sera were obtained from all children and tested for anti-HBs and anti-HBc. The children were recalled at  $\sim 2$  months and 2 years after the booster dose and tested for anti-HBs. Those who did not respond initially (at the 2-month visit) to the booster dose with an anti-HBs  $\geq 10$  mIU/mL received additional doses of recombinant vaccine and were retested.

## Laboratory Testing

All serologic specimens were tested quantitatively by radioimmunoassay (RIA) for anti-HBc (CORAB; Abbott Laboratories, Abbott Park, IL) and qualitatively by RIA for

**TABLE 1.** Children Examined by Maternal HBsAg, Type of Hepatitis B Vaccine Given in Infancy, Age at Screening, and Results of Anti-HBs Screening

Group	No.	Maternal HBsAg	Primary Vaccine Series Beginning at Birth	Anti-HBs After Primary Series	Mean Age at Screening (yr)	Anti-HBs $\geq 10$ mIU/mL on Screen
Study 1						
1a	102	Negative	Plasma-derived*	Unknown	8.9	42 (41) <sup>†</sup>
1b	208	Negative	Recombinant <sup>‡</sup>	Unknown	5.1	26 (12)
Study 2						
2a	17	Negative	Plasma-derived*	$\geq 10$ mIU/mL	12.6	4 (24)
2b	36	Negative	Recombinant <sup>‡</sup>	$\geq 10$ mIU/mL	7.5	0 (0)
2c	16	Positive	Plasma-derived*	$\geq 10$ mIU/mL	12.1	5 (31)

\*10  $\mu$ g of Heptavax-B.

<sup>†</sup>Numbers in parentheses, percent.

<sup>‡</sup>2.5  $\mu$ g of RecombivaxHB.

anti-HBs (AUSAB-RIA; Abbott Laboratories). The anti-HBs titers were reported in milli-International Units (mIU) per mL using the WHO international reference standard.<sup>13</sup>

### Data Analysis

Anti-HBs  $\geq 10$  mIU/mL in a child was considered protected against hepatitis B infection.<sup>6</sup> An anamnestic response to a hepatitis B vaccine booster dose was defined as a rise of anti-HBs from  $< 10$  mIU/mL to  $\geq 10$  mIU/mL. Anti-HBs titers were log-transformed for calculating geometric mean titer (GMT), and comparisons of GMT over time were made with a paired *t* test with the log-transformed values. For analysis, persons with undetectable anti-HBs were assigned a value of 0.1 mIU/mL. Proportions were compared with the use of a  $\chi^2$  or Fisher exact test, as appropriate. All *P* values were two-sided.

## RESULTS

**Recipients of Plasma-Derived Hepatitis B Vaccine in Infancy.** Of the 102 children (group 1a) who had received 3 doses of a plasma-derived hepatitis B vaccine as infants, 42 (41%) had anti-HBs titers  $\geq 10$  mIU/mL at 8.9 years of age (Table 1). All were negative for anti-HBc. Fifty-four of the children, in whom the anti-HBs had fallen below 10 mIU/mL, received a booster dose of 2.5  $\mu$ g of a yeast recombinant hepatitis B vaccine, and 33 (61%) of these responded with anti-HBs  $\geq 10$  mIU/mL within a mean of 13.1 days (Table 2). There was no significant difference in the response of those children boosted immediately (52%) compared with those whose booster dose was delayed (69%) (*P* = 0.266). In group 2a, low risk children vaccinated on the same schedule but who were known to have responded to the initial vaccine series, 4 of 17 (24%) retained anti-HBs  $\geq 10$  mIU/mL at an average of 12.6 years of age. All were negative for anti-HBc. Twelve of those in whom anti-HBs had fallen to  $< 10$  mIU/mL were boosted with a recombinant vaccine, and 8 (67%) responded with anti-HBs  $\geq 10$  mIU/mL an average of 6 weeks later. Two years after the

booster dose, anti-HBs levels had fallen below 10 mIU/mL in 57% (4 of 7).

Among children whose mothers were HBsAg-positive (group 2c), 31% (5 of 16) had anti-HBs  $\geq 10$  mIU/mL at an average age of 12.1 years, all were negative for anti-HBc and 90% (9 of 10) of those with anti-HBs  $< 10$  mIU/mL responded to a booster dose (Table 2). Two years after the booster dose, anti-HBs levels had fallen below 10 mIU/mL in 57% (4 of 7).

The GMTs of anti-HBs (milli-International Units/mL) 2 months and 2 years postbooster were 11.0 and 3.0, respectively, for the low risk children (Group 2a) and 121.5 and 8.7 for the high risk children (Group 2c) (Table 3).

**Recipients of Recombinant Hepatitis B Vaccine in Infancy.** Of the 208 children (group 1b) who had received 3 doses of a recombinant hepatitis B vaccine as infants, only 26 of 208 (12.5%) maintained anti-HBs  $\geq 10$  mIU/mL at 5.1 year of age (Table 1). All were negative for anti-HBc. Of 134 children in whom the anti-HBs had fallen below 10 mIU/mL who received a booster dose of vaccine, 120 (90%) responded with anti-HBs  $\geq 10$  mIU/mL an average of 14 days after the booster dose (Table 2). There was a trend toward a decrease in the response of children who received an immediate booster dose (85%) versus children whose booster dose was delayed to 8.1 years of age (95%; *P* = 0.051). In group 2b, children who were known to have responded to the initial vaccine series, none of the 36 retained anti-HBs  $\geq 10$  mIU/mL at 7.4 years of age. All were negative for anti-HBc. Of those boosted with a 2.5- or 5- $\mu$ g dose of recombinant vaccine, 32 of 35 (91%) developed anti-HBs  $\geq 10$  mIU/mL an average of 2 months later (Table 2). All 3 of the nonresponders had received the 5- $\mu$ g booster dose, but this difference was not significant (*P* = 0.259). Anti-HBs in those who had responded dropped to  $< 10$  mIU/mL in 43% (9 of 21) 2 years after the booster dose. The GMTs of anti-HBs (mIU/mL) 2 months and 2 years postbooster for Group 2b were 95.6 and 5.8, respectively (Table 3).

**TABLE 2.** Response to One Dose of HBV Recombinant Vaccine as Booster in Children With Anti-HBs  $< 10$  mIU/mL

Group	Booster Vaccine* Dose Given ( $\mu$ g)	Immediate Boosting		Delayed Boosting		Total
		Av. age (yr)	Anti-HBs $\geq 10$ mIU/mL	Av. age (yr)	Anti-HBs $\geq 10$ mIU/mL	
Study 1						
1a	2.5	9.1	13/25 (52) <sup>†</sup>	10.4	20/29 (69)	33/54 (61)
1b	2.5	5.2	60/71 (85)	8.1	60/63 (95)	120/134 (90)
Study 2						
2a	5	12.6	8/12 (67)			8/12 (67)
2b	2.5/5	7.5	32/35 (91)			32/35 (91)
	2.5	7.5	14/14 (100)			14/14 (100)
2c	5	7.4	18/21 (86)			18/21 (86)
	5	12.1	9/10 (90)			9/10 (90)

\*RecombinaxHB.

<sup>†</sup>Numbers in parentheses, percent.

**TABLE 3.** GMTs of Anti-HBs After Boosting With 1 Dose of RecombivaxHB Vaccine Among Children with Anti-HBs <10 mIU/mL

Group	Vaccine Dose (µg)	Av. Age at Boosting (yr)	Immediately Following Booster Dose		2 yr Post Booster* GMT (mIU/mL)
			GMT (mIU/mL)	Av. days after booster dose	
Study 1					
1a	2.5	9.8	34 (16, 75) <sup>†</sup>	13.1	
1b	2.5	6.6	157 (102, 244)	13.6	
Study 2					
2a	5	12.6	11.0 (1.5, 81)	44	3.0 (0.3, 27)
2b	2.5/5	7.5	96 (53, 172)	58	5.8 (2.4, 13.7)
	2.5	7.5	63 (30, 134)	67	5.7 (2.3, 14.1)
	5	7.4	126 (53, 298)	52	5.9 (1.0, 34)
2c	5	12.1	122 (40, 399)	69	8.7 (0.8, 90)

\*Among children without extra doses of HB vaccine after the booster dose.

<sup>†</sup>Numbers in parentheses, 95% confidence intervals.

The results of anti-HBs screening and response to a booster dose of recombinant vaccine in the 5 groups are displayed in Figure 1. In both studies, significantly more of the low risk children who had received the plasma vaccine at birth (groups 1a and 2a) retained anti-HBs  $\geq 10$  mIU/mL at the time of screening than did low risk children who had received the recombinant vaccine at birth (groups 1b and 2b) (study 1,  $P < 0.001$ ; study 2,  $P = 0.008$ ). In the 2 groups of low risk infants (groups 1a and 2a) who originally received plasma vaccine but lost protective antibody and were boosted with recombinant vaccine, 39 and 33%, respectively, failed to respond with an anti-HBs level  $\geq 10$  mIU/mL. This is a higher rate of nonre-

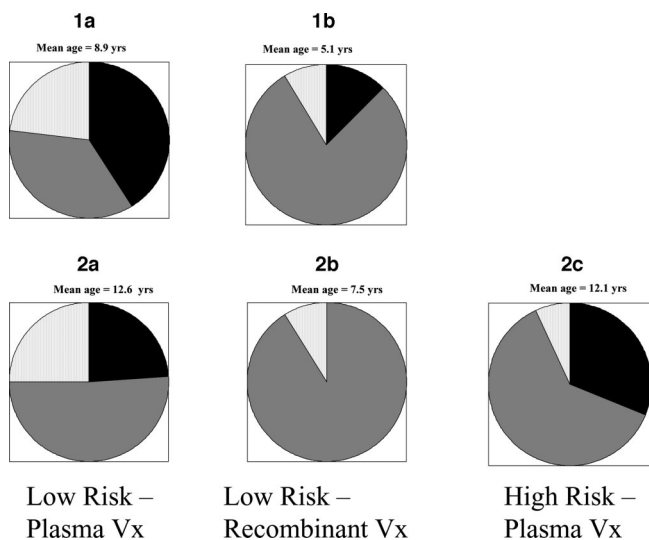
sponse to the booster dose than found in the 2 groups of low risk infants (groups 1b and 2b), 10 and 9%, respectively, who received recombinant vaccine beginning at birth, albeit the timing of the booster dose occurred at a later age in the plasma vaccine group than in the group initially receiving the recombinant vaccine.

**Antibody Titers.** The anti-HBs GMT after booster was similar to the original follow-up for the children who had received recombinant vaccine as infants (group 2b: original GMT, 75.2 mIU/mL; booster GMT, 96 mIU/mL;  $P = 0.390$ ) and those high risk infants receiving the plasma-derived vaccine (group 2c: original GMT, 113.5 mIU/mL; booster GMT, 121 mIU/mL;  $P = 0.935$ ); it was much lower for the low risk infants receiving the plasma-derived vaccine (group 2a: original GMT, 732 mIU/mL; booster GMT, 11.0 mIU/mL;  $P = 0.004$ ).

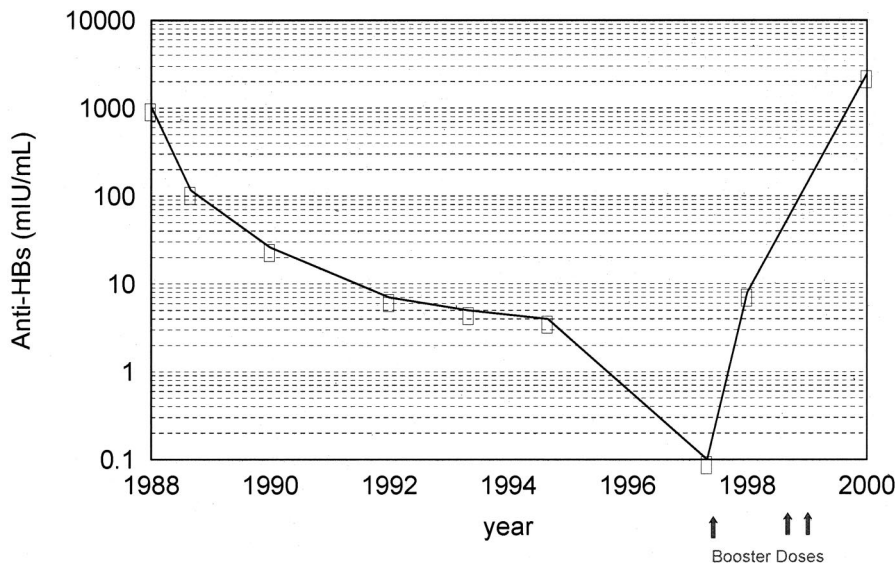
**Vaccine Nonresponders.** In the 5 groups, there were 43 children (35 from study 1, 8 from study 2) who did not respond to a booster dose. Of these children from study 2, 6 received additional doses of the recombinant vaccine and all responded with titers  $\geq 10$  mIU/mL. Two years postbooster, the individual anti-HBs titers were 37.5, 301.1 and 18.6 mIU/mL for the 3 low risk children who received only 1 additional dose and 3011 and 1875 mIU/mL for the 2 low risk children who received 2 additional doses. One high risk infant (group 2c) had an anti-HBs titer of 1045 mIU/mL at 9 months of age after his primary vaccination series. On 6 occasions during the ensuing 10 years his anti-HBs showed a gradual drop to  $< 1.0$  mIU/mL (Fig. 2). Seven weeks after a booster dose of recombinant vaccine, his anti-HBs titer was 7.7 mIU/mL. Two years after receiving 2 additional doses of vaccine, his anti-HBs titer was 2442 mIU/mL.

**DISCUSSION**

We have previously reported on long term protection in a population of Alaska Natives living in areas with a high prevalence of HBV infection.<sup>14</sup> In 1630 persons, anti-HBs titers



**FIGURE 1.** Proportions of Alaska children vaccinated (Vx) at birth who had anti-HBs titers  $\geq 10$  mIU/mL at screening and after boosting with recombinant HB vaccine. Anti-HBs: black section, screen  $\geq 10$  mIU/mL; dark gray section, screen  $\leq 10$  mIU/mL, booster response  $\geq 10$  mIU/mL; light gray section, screen  $< 10$  mIU/mL, booster response  $< 10$  mIU/mL.



**FIGURE 2.** Anti-HBs titers over time in a high risk child who received plasma-derived hepatitis B vaccine at birth and did not respond with  $\geq 10$  mIU/mL to a single booster dose of recombinant hepatitis B vaccine.

were  $\geq 10$  mIU/mL in 76% at 10 years after vaccination and 82% of those age 6 months–19 years at the time of vaccination.<sup>15</sup> In another study from this population in which individuals were tested before and after mass vaccination (newborn and catch-up programs), none younger than 10 years of age who had received hepatitis B vaccine at birth was HBsAg-positive 10 years after vaccination, compared with 16% of persons between 10 and 30 years of age.<sup>16</sup> In the current report, we studied primarily groups of children vaccinated with 3 doses of a hepatitis B vaccine in infancy who were at low risk for HBV exposure and thus more typical of industrialized countries.

In low risk children who received a plasma-derived vaccine in infancy (group 1a), 59% had anti-HBs  $< 10$  mIU/mL, and 39% of these were nonresponsive to a booster dose of hepatitis B vaccine. Although some may have been primary nonresponders, it is unlikely that all were so. It is important, however, that the primary nonresponse rate has a disproportionately large effect on the estimate of proportion of vaccinees retaining memory. Therefore we examined another group (group 2a) of recipients of the plasma-derived vaccine who had a response to the primary vaccination series starting at birth, and results were similar. This implies that although most low risk infants respond to plasma-derived vaccine, for one-fourth of them long term anamnestic memory to HBV may be lost.

In children vaccinated with a recombinant vaccine from birth, anti-HBs fell faster than in those who had received plasma-derived vaccine. However, immunologic memory at 5 years of age appeared to be good because 90% of children responded to a hepatitis B booster dose, and it is possible that 5–10% may have been primary nonresponders.<sup>3</sup> In a group of children who had a documented initial response to recombinant vaccine, the response to a booster dose was similar. These raise concerns about the durability of immunity in later

childhood when the recombinant vaccine is initiated at birth. Heijntink et al<sup>17</sup> have shown that there may be differences in the vaccines with regard to antigen presentation and resulting anti-HBs binding properties.

Our findings of the loss of anti-HBs over time in children vaccinated in infancy differ from those reported by some others. West et al<sup>18</sup> screened children at 12 years of age who had received a plasma-derived vaccine in infancy and were at low risk for hepatitis B exposure. None had anti-HBs  $< 10$  mIU/mL. Faustini et al<sup>19</sup> followed children at low risk who were vaccinated in infancy with a recombinant vaccine. By 5 years of age, only 7% had titers of anti-HBs  $< 10$  mIU/mL. A major difference between the children in those studies and ours is their age at initial vaccination. Those subjects were 2–3 months of age or older when they began their hepatitis B vaccine, whereas the infants in our studies began their series in the first week of life, a schedule recommended by ACIP. Indeed a study from Hawaii of low risk infants given recombinant vaccine starting at birth showed that only 19% had anti-HBs  $\geq 10$  mIU/mL at 6 years, yet all responded to a booster dose.<sup>20</sup> This suggests that starting the initial vaccination series later in infancy may result in better persistence of anti-HBs. However, starting at 2–3 months of age would not protect infants of HBsAg-positive mothers from perinatal transmission of HBV.

Vaccinated populations at high risk for continued exposure to hepatitis B might experience natural boosting because of exposure to HBsAg-positive household contacts, enhancing their duration of protection.<sup>21</sup> Several long term follow-up studies have been conducted in children of HBsAg-positive and hepatitis e antigen-positive mothers. In those studies, anti-HBs titers  $\geq 10$  mIU/mL ranged from 79 to 85% at 10–12 years of age.<sup>10,22</sup> Another study showed 42 in-

stances of vaccinated children living in HBsAg-positive households exhibiting natural boosts in anti-HBs titers during a 5-year follow-up period.<sup>23</sup> In our study, the proportion of high risk children who had anti-HBs <10 mIU/mL on follow-up was similar to that seen for the low risk children who received the same vaccine, although the response to booster dose was slightly higher. However, the small number of high risk children followed makes it difficult to draw conclusions.

Booster doses of hepatitis B vaccine are not currently recommended.<sup>24</sup> In populations at high risk for continuing exposure to hepatitis B virus, hepatitis B vaccine is protective for at least 10 years, the time during which the greatest risk of chronic infection after exposure occurs.<sup>16</sup> However, children at low risk for exposure to hepatitis B during childhood are at greater risk of exposure for hepatitis B infection as they approach adolescence and long term protection will be important during potentially sexually active years. Our data suggest that one-fourth of children who responded to a plasma-derived hepatitis B vaccine in infancy lost protective antibody by early adolescence and did not show evidence of anamnestic response to a booster dose, although the small number of participants makes it difficult to draw precise conclusions. In addition, the lack of an anamnestic response may not mean that children are not protected against HBV disease. The long incubation period of 4–8 weeks for HBV could allow time for immunologic memory to prevent acute illness or chronic carriage while not preventing active infection. Evidence of immunologic memory did not decrease despite delayed boosting of some children.

The importance of giving hepatitis B vaccine from birth is well-established; however, it will be very important to follow children into adolescence and early adulthood for evidence of clinically significant breakthrough infections indicating a possible need for routine booster doses. Also additional long term follow-up studies at school entry and adolescence, including ones evaluating the effects of a booster dose at these times, will be necessary for low risk children initially vaccinated for hepatitis B starting at birth.

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