

Long-Term Protection against Carriage of Hepatitis B Virus after Infant Vaccination

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Background. Carriage of hepatitis B virus (HBV) is a major risk factor for liver cirrhosis and hepatocellular carcinoma. Infant vaccination has been effective in preventing horizontal transmission during early childhood. It is unknown whether protection is maintained into early adulthood.

Methods. In 1984, early childhood vaccination was introduced in 2 rural Gambian villages. In 2003, serological assessment of 81.5% of 1350 eligible participants 1–24 years old was done, to determine vaccine efficacy against infection and carriage.

Results. Overall vaccine efficacy against infection and carriage was 83.4% (95% confidence interval [CI], 79.8%–86.6%) and 96.5% (85% CI, 93.9%–98.9%), respectively. Vaccine efficacy against infection was similar when restricted to primary responders (85.3%), but a significant effect of peak antibody concentration was found. Both vaccine efficacy and levels of hepatitis B surface antibody (anti-HBs) decreased with age, resulting in a vaccine efficacy against infection and carriage among 20–24-year-old participants of 70.9% (95% CI, 60.4%–80.5%) and 91.1% (95% CI, 75.8%–100%), respectively. Fifteen years after vaccination, fewer than half of the vaccinees had detectable anti-HBs. The prevalence of carriage in the unvaccinated population was similar to the prevalence 20 years earlier.

Conclusions. HBV vaccination early during life can provide long-lasting protection against carriage, despite decreasing antibody levels. The role played by subclinical boosting and the necessity of a booster need to be evaluated.

Recent World Health Organization (WHO) estimates indicate that more than one-third of the world's population (~2 billion people) have serological evidence of infection with hepatitis B virus (HBV) [1]. HBV carriage is associated with a 10–20-fold-increased risk of hepatocellular carcinoma; up to one-quarter of chronically infected persons may die as a result of the infec-

tion. It is estimated that >500,000 deaths are associated with HBV infection annually; in The Gambia, 10%–15% of deaths among adult males are a consequence of hepatocellular carcinoma and chronic liver disease [2]. Even in countries of low prevalence, the economic burden of this potentially life-threatening but preventable infection is considerable [3].

Transmission of HBV peaks during the first years of life in many countries in which HBV is endemic. In the absence of early childhood transmission, a peak can occur during adolescence or early adulthood with the onset of sexual activity, as found in industrialized countries. Before the introduction of infant vaccination, a study in Senegal (which neighbors The Gambia) showed that 80% of the population became infected during the first 7 years of life [4]. To prevent infection with HBV and its sequelae, routine infant vaccination against HBV has been recommended by the WHO since 1991 and has now been implemented in >150 countries worldwide, including The Gambia. The immune response to vaccination among young children is excellent [5]. Once vaccinated children reach adolescence, they enter a pe-

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riod of potential high risk of exposure as they become sexually active. For all countries that have introduced infant vaccination—as well as those that intend to—it is vital to know whether protection induced during infancy persists into adulthood or whether it needs to be boosted to achieve long-lasting protection.

Several studies conducted in countries with different pre-vaccination HBV epidemiologic characteristics have shown persistent protection for 10–15 years after infant vaccination despite waning antibodies, suggesting that there is no need for a booster before adolescence [6–13]. One study documented protection after 18 years of follow-up but included only 88 of 138 original subjects [14]. Longitudinal follow-up of infant vaccinees in The Gambia has shown that antibody levels decrease over time, with one-third of subjects having no detectable antibody after 10 years and most of the rest having very low levels [9]. The continued protection against carriage despite waning antibody levels may reflect effective immunologic memory [15] or a low risk of infection in that age group. At present, there are not enough data to assess whether immunologic memory and protection persist into adulthood [16, 17].

In unvaccinated populations, the risk of carriage is as high as 90% when infection occurs during infancy; during adolescence and adulthood, <10% of infected subjects are estimated to become carriers [18]. However, no data are available on the risk for those vaccinated during infancy of becoming a carrier on infection during adolescence or on exposure to sexual transmission in an area of high endemicity. Thus, it is not known how well vaccine efficacy is maintained with the onset of sexual activity in a population vaccinated as infants. Here, we present data from an open cohort of HBV vaccinees from 2 adjacent rural Gambian villages (Keneba and Manduar) 19 years after the initiation of infant vaccination.

METHODS

Subjects. The demographic and medical backgrounds of the villages have been described previously [19]. A clinic providing free medical care is open on a daily basis.

Baseline surveys of HBV infection showed a marked difference between the 2 villages in the prevalence of infection and carriage in each age category [20]. In 1984, all nonimmune children <5 years old were vaccinated against HBV. Since then, the vaccination program has included all children born in the villages. Follow-up surveys among the vaccinees were conducted in 1985, 1989, 1993, and 1998, to determine the magnitude and duration of the protective antibody responses induced by infant vaccination as well as vaccine efficacy against infection and carriage [19–23]. In 2003, we conducted another follow-up survey. For each survey, children vaccinated with ≥ 3 doses and ≥ 1 year old were eligible; 5 children vaccinated at <5 years old who had become infected during the initial primary vaccination course in 1984 were excluded.

Concurrent with the follow-up of vaccinees, we measured the prevalence of HBV carriage in the unvaccinated population, to assess the overall community prevalence of infection and carriage. In 2003, the total population of the villages was estimated to be nearly 2700 persons.

Vaccinations. After the 1984 survey, 232 children <5 years old who were still susceptible to HBV infection were randomly assigned to receive 1 of 3 different regimens of plasma-derived HB-Vax (Merck, Sharpe and Dohme); group 1 ($n = 82$) received three 20- μg doses intramuscularly (im), group 2 ($n = 71$) received one 20- μg dose im and two 2- μg doses intradermally (id), and group 3 ($n = 79$) received three 2- μg doses id [20]. Subsequent vaccination of newborns has continued with various regimens. Between 1984 and February 1992, the regimen was four 10- μg doses of HB-Vax (group 4 [$n = 429$]). The next 2 regimens were recombinant vaccine: the first was three 5- μg doses of Recombivax (Merck, Sharpe and Dohme) (group 5 [$n = 101$]), which was followed by three 10- μg doses of Engerix (Smith, Kline and French) (group 6 [$n = 10$]). Between 1993 and 2001, vaccination continued with first four and later three 2.5- μg doses of plasma-derived Hepacine (Cheil Foods and Chemicals) (group 7 [$n = 584$]). Since 2002, the regimen given has been three 10- μg doses of the recombinant Euvax vaccine (group 8 [$n = 25$]).

Serological assessment. After vaccination, concentrations of hepatitis B surface antibody (anti-HBs) were measured at ~ 11 months of age, to obtain an estimate of the peak anti-HBs response. At each survey, concentrations of hepatitis B core antibody (anti-HBc) and, if indicated, hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) were assessed. Originally, anti-HBc and anti-HBs were detected by radioimmunoassay (Sorin Biochemica); since 2003, a commercial EIA (ETI-AB-Corek Plus and ETI-AB-AUK; DiaSorin) has been used, in accordance with the manufacturer's instructions. Originally, samples that were positive for anti-HBc were tested for HBsAg by reverse passive hemagglutination assay (Wellcotest; Murex Diagnostics); since 2003, they have been tested by Determine HBsAg (Abbott Laboratories), a visually read, qualitative immunochromatographic assay. The sensitivity and specificity of these tests are similar. Blood samples were obtained from those newly determined to be positive for HBsAg after 6 months, to confirm carrier status. Samples that were positive for HBsAg were tested for HBeAg by EIA (Equipar Diagnostici).

Statistical analysis. Data were entered and validated using Access 2000 (Microsoft Office) and were linked to a general population database, also in Access 2000. Serological data and data from previous surveys were imported. Data were analyzed using Stata software (version 8; StataCorp).

Vaccine efficacy was calculated as $1 - (\text{prevalence among the vaccinees/prevalence among the nonvaccinees})$. The prevalence of infection and carriage in the 1984 population of Keneba and Manduar before the introduction of vaccination was used as

Table 1. Peak response for antibody to hepatitis B surface antigen (anti-HBs) after vaccination against hepatitis B virus, by vaccination group.

Peak anti-HBs response	Vaccination group							All (n = 1095)
	1 (n = 60)	2 (n = 41)	3 (n = 50)	4 (n = 355)	5 (n = 80)	7 (n = 484)	8 (n = 25)	
<10 mIU/mL	0 (0)	2 (4.9)	8 (16.0)	5 (1.4)	0 (0)	31 (6.4)	2 (8.0)	48 (4.4)
10–99 mIU/mL	2 (3.3)	4 (9.8)	11 (22.0)	9 (2.5)	4 (5.0)	62 (12.8)	4 (16.0)	96 (8.8)
100–999 mIU/mL	19 (31.7)	24 (58.5)	22 (44.0)	50 (14.1)	19 (23.8)	147 (30.4)	14 (56.0)	295 (26.9)
≥1000 mIU/mL	39 (65.0)	11 (26.8)	7 (14.0)	236 (66.5)	52 (65.0)	126 (26.0)	2 (8.0)	473 (43.2)

NOTE. Data are no. (%) of participants with the shown peak response. Sample sizes refer to those participating in the 2003 survey. For definitions of vaccination groups, see Methods; group 6 is not included because only 4 participants were included in the 2003 survey. For 183 (16.7%) of 1095 participants, no peak anti-HBs measurement was available.

baseline. Prevalence at that time remained stable from the age of 15 years onward, and, thus, the prevalence among the 15–19-year-old participants was extrapolated to reflect the prevalence among all adults. Logistic regression was used to predict prevalences in the vaccinated and unvaccinated groups, which were used to form predictions for vaccine efficacy.

As before, we assumed that the seroprevalence of anti-HBc and HBsAg reflected cumulative incidence, which enabled us to use age-specific seroprevalence in vaccinees (vs. those in the non-vaccinees). Cox regression was used to analyze the effect of time since infant vaccination on HBV infection status, allowing for potential confounding variables, and Kaplan-Meier curves were used to illustrate the effect. A parametric Weibull model was used to characterize the decrease in the probability of remaining uninfected against time since vaccination. Statistical significance was taken at the 5% level.

Definitions. Being vaccinated was defined as having received at least 3 doses of the vaccine at least 4 weeks apart. Infection was defined as the presence of anti-HBc with at least 30% inhibition, as stipulated by the manufacturer. If infection was found only during a single follow-up survey and was not confirmed subsequently, the person was considered to have had a transient infection [24]. Carriage was defined as the detection of HBsAg on 2 separate occasions at least 6 months apart. Prevalence was considered to reflect cumulative incidence.

A primary vaccine failure was defined as a peak anti-HBs response of <10 mIU/mL. A responder was defined as a vaccinee with a peak anti-HBs response of ≥10 mIU/mL or, in the absence of a peak anti-HBs measurement, an anti-HBs level of ≥10 mIU/mL in a subsequent survey in the absence of anti-HBc seroconversion. Secondary vaccine failure was defined as becoming positive for HBsAg, confirmed on a separate occasion at least 6 months later, despite responding to vaccination.

The present study was approved by the joint Gambia Government/Medical Research Council Ethics Committee. All subjects (and/or legal guardians if indicated) provided written, informed consent. Written feedback of individual results was provided to participants.

RESULTS

Subjects. At the time of the 2003 survey, 1350 inhabitants (1–24 years old) of both villages had been vaccinated with at least 3 doses, as described above. Of these, 1100 (81.5%) chose to participate, 136 (10.1%) refused, and 56 (4.1%) had died; the remaining 58 (4.3%) could not be traced. One sample was lost during transportation, leaving 1099 analyzable samples.

Surface antibody. Peak anti-HBs concentrations were available for 914 (83.2%) of 1099 subjects; 866 (78.8%) had a detectable peak anti-HBs response, and 48 (4.4%) were primary nonresponders. There were 143 (13.0%) subjects who had a missing peak anti-HBs measurement but who had an anti-HBs concentration of ≥10 mIU/mL in a subsequent survey while remaining negative for anti-HBc. These subjects were also classified as responders, giving a total of 1009 (91.8%) responders to vaccination.

The geometric mean titer (GMT) of peak anti-HBs concen-

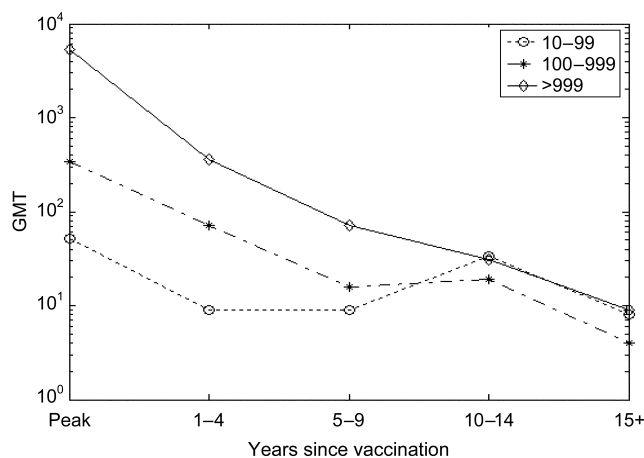


Figure 1. Decrease in levels of antibody to hepatitis B surface antigen (anti-HBs) with time since vaccination, by peak anti-HBs response (mIU/mL). Data are geometric mean titers (GMTs). The anti-HBs level was set at 1 mIU/mL for those with an anti-HBs level of <10 mIU/mL at follow-up.

Table 2. Cross-sectional prevaccination (1984) and current (for all participants and for vaccine responders only) prevalence of antibody to hepatitis B core antigen (anti-HBc) in 2003 among vaccinees, by age group.

Age group ^a (vaccination group)	1984		2003			
			All participants		Vaccine responders only ^b	
	Keneba	Manduar	Keneba	Manduar	Keneba	Manduar
All	318/621 (51.2)	246/309 (79.6)	71/788 (9.0)	40/311 (12.9)	59/726 (8.1)	31/283 (11.0)
1–4 years (7 and 8)	65/236 (27.5)	75/119 (63.0)	4/176 (2.3)	3/60 (5.0)	4/152 (2.6)	2/51 (3.9)
5–9 years (5–7)	112/205 (54.6)	88/104 (84.6)	16/203 (7.9)	6/88 (6.8)	11/180 (6.1)	4/77 (5.2)
10–14 years (4 and 5)	103/134 (76.9)	53/56 (94.6)	9/185 (4.9)	12/78 (15.4)	8/180 (4.4)	11/76 (14.5)
15–19 years (1–4)			23/148 (15.5)	13/65 (20.0)	23/145 (15.9)	9/60 (15.0)
20–24 years (1–3)	38/46 (82.6) ^c	30/30 (100) ^c	19/76 (25.0)	6/20 (30.0)	13/69 (18.8)	5/19 (26.3)

NOTE. Data are proportion (%) of subjects. For definitions of vaccination groups, see Methods.

^a Age at present survey.

^b Includes those with a peak response for antibody to hepatitis B surface antigen (anti-HBs) of ≥ 10 mIU/mL and those with an unknown peak anti-HBs response but with an anti-HBs level of ≥ 10 mIU/mL in a subsequent survey while remaining negative for anti-HBc.

^c In 1984, no further distinction in prevalence by age was made for those aged 15 and above, because it was assumed that prevalence would be more or less stable among adults.

trations varied according to vaccination group. Peak anti-HBs response by vaccination group is summarized in table 1.

Regardless of the vaccination group, the GMTs of anti-HBs concentrations initially decreased sharply over time and then leveled off, as described previously [23, 25]. This is illustrated in figure 1 for those who participated in each survey for which they were eligible and responded to the vaccine (764/1009). Among those followed for ≥ 15 years who responded to vaccination, 126 (49.6%) of 254 still had protective anti-HBs levels.

HBV infection. In total, 111 (10.1%) of the 1099 participants in the 2003 survey were positive for anti-HBc, among whom 17 (35.4%) of 48 had primary vaccine failure. Previous transient anti-HBc detection was observed among an additional 41 (3.7%) of the 1099 participants. Three additional subjects lost anti-HBc after having been persistently positive for anti-HBc in at least 2 consecutive surveys. Table 2 summarizes cross-sectional prevalence by age category for all participants and for only those participants who responded to vaccination. The prevalence of anti-HBc was higher in Manduar than in Keneba, but this difference did not reach statistical significance ($P = .06$). The prevalence was lowest among those 1–4 years old (3.0%, among all participants and among vaccine responders only) and increased to 26.0% (among all participants) and 20.5% (among vaccine responders only) in those 20–24 years old, with the pattern being similar in each village. No cases of jaundice have been recorded in any of the infected children.

For all eligible subjects in the 2003 survey, the time between the last vaccination date to complete the course and the date of their first HBV infection in any survey or the sample date in the 2003 survey (for subjects with no history of infection) was calculated. Cox regression analysis of time since vaccination showed a significant effect for peak anti-HBs response category ($P < .0001$; the proportional hazards assumption was satisfied), but there was no significant effect at the 5% level for the ex-

planatory variables sex, village, vaccination group, number of doses, and age at vaccination or for their interactions. Figure 2 shows the decrease in the probability of remaining uninfected against time since infection, stratified by peak anti-HBs response category. A proportional hazards Weibull model gave a shape parameter of 1.69, which was significantly different from 1 ($P < .0001$). Averaged over all categories, the probability of remaining uninfected against time since vaccination decreased from 99% (95% confidence interval [CI], 99%–100%) 2 years after vaccination to 81% (95% CI, 76%–85%) 18 years after vaccination.

HBV carriage. Eight (7.3%) of 110 subjects who tested positive for anti-HBc were carriers of HBsAg, giving an overall

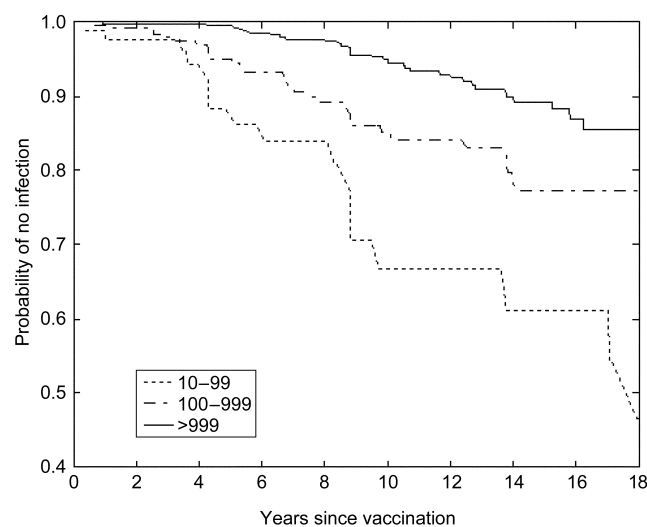


Figure 2. Probability of remaining uninfected (as determined by a lack of antibody to hepatitis B core antigen), by time since vaccination and peak response for antibody to hepatitis B surface antigen (mIU/mL).

Table 3. Prevaccination (1984) and 2003 prevalence of hepatitis B virus carriage, by age group.

Age group ^a (vaccination group)	1984		2003		
	Keneba	Manduar	Keneba	Manduar	Keneba and Manduar
All	83/623 (13.3) ^b	108/309 (35.0)	5/788 (0.6)	3/311 (1.0)	8/1099 (0.7)
1–4 years (7 and 8)	24/236 (10.2)	44/119 (37.0)	0/176 (0)	0/60 (0)	0/236 (0)
5–9 years (5–7)	32/205 (15.6)	34/104 (32.7)	2/203 (1.0)	1/88 (1.1)	3/291 (1.0)
10–14 years (4 and 5)	19/135 (14.1)	20/56 (35.7)	0/185 (0)	1/78 (1.3)	1/263 (0.4)
15–19 years (1–4)	8/47 (17.0) ^c	10/30 (33.3) ^c	1/148 (0.7)	1/65 (1.5)	2/213 (0.9)
20–24 years (1–3)			2/76 (2.6)	0/20 (0)	2/96 (2.1)

NOTE. Data are proportion (%) of subjects. For definitions of vaccination groups, see Methods.

^a Age at present survey.

^b For 2 subjects who tested negative for hepatitis B surface antigen in 1984, no result for antibody to hepatitis B core antigen was available; therefore, they are not included in table 2.

^c In 1984, no further distinction in prevalence by age was made for those aged 15 and above, because it was assumed that prevalence would be more or less stable among adults.

prevalence of carriage of 0.7% among the fully vaccinated participants (table 3). One new carrier was identified 7 years after infant vaccination (vaccination group 7), with an unknown peak anti-HBs response. During the 1998 survey, at 2 years of age, she was positive for anti-HBc (95% inhibition) but was negative for HBsAg. The newly identified carrier was the daughter of a previously identified carrier who had been vaccinated in 1984 (vaccination group 3) and a primary nonresponder. Four of the remaining 6 current carriers had primary vaccine failure (1 each in vaccination groups 2 and 4 and 2 in vaccination group 7). The other 2 carriers were primary responders (with peak anti-HBs responses of 10 mIU/mL [vaccination group 5] and 406 mIU/mL [vaccination group 4], respectively) and, thus, had secondary vaccine failure.

Five of the 8 current carriers tested positive for HBeAg, including the newly identified carrier. Three of the 4 carriers positive for HBeAg for whom a primary response was documented had primary vaccine failure. Two current carriers previously tested positive for HBeAg but were negative in the 2003 survey. HBV DNA levels were measured for 4 of the 8 carriers and ranged from 1.8×10^3 copies/mL in 1 subject who was negative for HBeAg to 2.1×10^9 , 2.2×10^9 , and 5.3×10^9 copies/mL in subjects who were positive for HBeAg.

Vaccine efficacy. The overall efficacy of the vaccination program to prevent infection and carriage in this population was calculated using the cross-sectional prevalence data from the 2003 survey, with the prevaccination population data as baseline. Vaccine efficacy in 2003 was 83.4% (95% CI, 79.8%–86.6%) against infection (as determined by detection of anti-HBc) and 96.5% (95% CI, 93.9%–98.9%) against carriage. Population vaccine efficacy against infection decreased with age, from 92.5% among those 1–4 years old to 70.9% (95% CI, 60.4%–80.5%) among those 20–24 years old, and efficacy against carriage decreased from 100% to 91.1% (95% CI, 75.8%–100%). Results were comparable among the populations of Keneba and Manduar, despite the different baseline pressures of infection.

The prevalence of infection in 2003 and in the baseline prevaccination survey of 1984 were modeled using logistic regression. For each model, a linear effect of age was highly significant, and, for 2003, peak anti-HBs response category was also highly significant. The predicted prevalence against age within each peak anti-HBs response category was calculated for all vaccinated subjects in 2003. Figure 3 shows the predicted vaccine efficacy (calculated from the 1984 and 2003 predicted prevalences) increasing with each higher peak anti-HBs response category and decreasing within each peak category after ~7 years.

Table 4 shows the actual vaccine efficacies stratified by age group and peak anti-HBs response category, which reflect the trends shown in figure 3 even though the CIs are wide because of small numbers in each group. There were too few carriers to assess any trends in vaccine efficacy by a formal analysis.

Vaccine failure. Primary vaccine failure occurred among 48

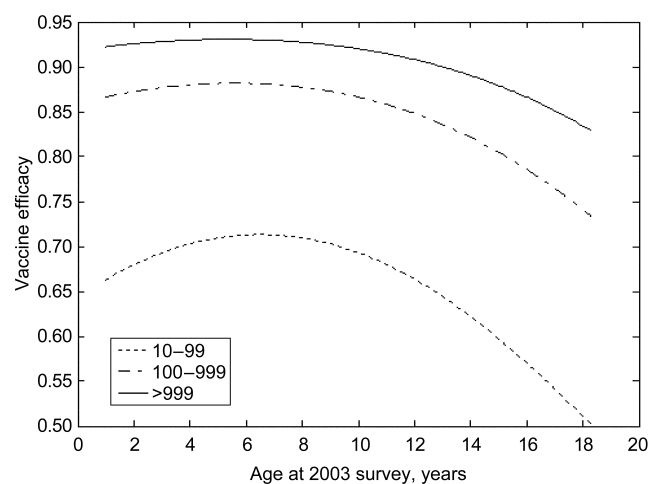


Figure 3. Vaccine efficacy against hepatitis B virus infection (as determined by detection of antibody to hepatitis B core antigen) among primary responders, by age and peak response for antibody to hepatitis B surface antigen (mIU/mL).

Table 4. Vaccine efficacy against infection with hepatitis B virus (HBV) as determined by detection of antibody to hepatitis B core antigen, by peak response for antibody to hepatitis B surface antigen (anti-HBs) and age group, among all responders and all vaccinees (program effectiveness) in 2003.

Age, years	Peak anti-HBs response				All responders	All vaccinees
	<10 mIU/mL	10–99 mIU/mL	100–999 mIU/mL	>999 mIU/mL		
All	41.6 (13.0–69.4)	69.1 (54.4–83.4)	81.1 (74.4–87.5)	87.1 (82.8–91.3)	85.3 (81.9–88.5)	83.4 (79.8–86.6)
1–4 years	100	87.3 (69.3–100)	89.0 (77.7–99.6)	100	91.3 (84.4–97.7)	92.5 (86.6–98.0)
5–9 years	38.2 (0–87.2)	82.2 (26.3–100)	89.4 (79.8–98.6)	90.3 (82.7–97.4)	90.9 (86.0–95.5)	88.3 (82.9–93.3)
10–14 years	100	69.6 (26.3–100)	85.8 (72.9–98.1)	91.8 (86.6–96.6)	91.4 (87.0–95.4)	90.3 (85.6–94.5)
15–19 years	36.1 (0–97.1)	49.2 (0–92.6)	70.3 (50.9–86.4)	88.1 (80.6–94.4)	82.6 (74.1–89.0)	81.1 (75.2–87.8)
20–24 years	2.2 (0–73.1)	39.0 (0–86.7)	79.9 (63.1–94.5)	84.5 (69.4–97.7)	77.1 (63.8–87.9)	70.9 (60.4–80.5)

NOTE. Data are percentage (95% confidence interval) of subjects.

(4.4%) of 1099 vaccinees. Primary failure across the vaccination groups ranged from 0 to 16% (table 1). Six (0.7%) of 866 subjects with a documented primary response subsequently became carriers and were classified as having secondary vaccine failure. Four of them (3 in vaccination group 2 and 1 in vaccination group 1) have since cleared HBsAg and are no longer carriers. The proportions with primary or secondary vaccine failure did not differ by village ($P = .6$ and $P = .4$, respectively).

Five of 48 participants with primary vaccine failure became carriers (1 each in vaccination groups 2, 3, and 4 and 2 in vaccination group 7) (10.4% vs. 0.7% carriage among primary responders; $P < .001$) and have to date all remained carriers. One previously identified carrier (in vaccination group 7) who declined to participate in the 2003 follow-up also had primary vaccine failure. For 1 current carrier (also in vaccination group 7), primary response status was unknown. In total, 13 vaccinees have ever been identified as carriers.

HBV carriage in the community. Before the initiation of the vaccination program in 1984, 83 (13.3%) of the 623 nonvaccinees in Keneba and 108 (35.0%) of the 309 nonvaccinees in Manduar were carriers; 43 (51.8%) and 77 (71.3%), respectively, of the carriers were also positive for HBeAg. Thus, among the total population, 6.9% in Keneba and 24.9% in Manduar ($P < .001$) were positive for HBeAg in 1984.

In 2003, serological results were available for 1004 (74.0%) of 1357 unvaccinated adults (≥ 15 years old). Of these, 187 (18.6%) were carriers—88 (13.9%) of 632 in Keneba and 99 (26.6%) of 372 in Manduar. The prevalence among the unvaccinated population decreased with age, from 73 (36.5%) of 200 among those 15–24 years old, to 50 (24.2%) of 207 among those 25–34 years old, to 22 (15.1%) of 146 among those 35–49 years old, to 33 (17.0%) of 194 among those 50–69 years old, and to 9 (7.8%) of 115 among those ≥ 70 years old. A similar pattern was seen in each village, but, as in 1984, a significantly higher prevalence was found in each age group in Manduar ($P < .001$). Fifteen (8.0%) of 187 unvaccinated carriers were also positive for HBeAg, the prevalence being similar in each village (6.8% and 9.1%; $P = .6$).

Among the total (vaccinated and unvaccinated) population from whom blood samples were obtained, the prevalence of carriage remained lower in Keneba (95/1585 [6.0%]) than in Manduar (104/742 [14.0%]) ($P < .001$). The overall prevalence of HBeAg positivity was low in Keneba (10/1584 [0.6%]) and Manduar (10/742 [1.3%]) ($P = .08$).

DISCUSSION

The main finding of our community-based study of an infant vaccination program with a 19-year follow-up was the persistent high vaccine efficacy against HBV infection (as determined by detection of anti-HBc) and carriage, despite continuously decreasing anti-HBs levels. The risk of becoming infected among those still susceptible remained stable during adolescence and early adulthood, but only a very few of the infected subjects became chronic carriers.

Five percent of the vaccinees failed to mount a primary response to the vaccine; of them, 8.6% became carriers, compared with 0.6% of responders. The transient presence of anti-HBc, as observed in 4% of the vaccinees during one of the follow-up surveys, may play a vital role in the maintenance of immunity. With time, however, the proportion of vaccinated children will increase and the infectivity of carriers will decrease; thus, the incidence of transient infection as determined by anti-HBc detection may decrease. In that case, natural boosting of vaccine-induced immunity would occur less frequently, which might reduce long-term vaccine efficacy. A similar situation has been described after measles vaccination [26]. Edmunds et al. [27] calculated that vaccination will have to be maintained for at least 80 years (the maximum life span of carriers) to ensure elimination of HBV, and recent theory has argued that endemic transmission may be possible even if the basic reproduction number is reduced via vaccination to < 1 [28].

The clinical long-term significance, if any, of transient infection and carriage is not yet known. One-third of the children who had become positive for anti-HBc in a previous survey subsequently tested negative, and one-third of the previously

identified carriers tested negative for HBsAg. This is consistent with findings in another Gambian cohort of children vaccinated as infants [9, 29] and implies that, even when vaccination fails to prevent infection or carriage, the duration might be shorter than that after natural infection. Furthermore, despite continuous passive surveillance in the area, we are not aware of cases of acute hepatitis among vaccinees. Longer follow-up is needed to assess the impact of transient infection and carriage on the risk of liver damage and hepatocellular carcinoma.

In the regression analyses, the vaccination schedule used did not have a significant effect on vaccine efficacy. The different vaccination regimens induced a wide variety of peak anti-HBs responses, which had a significant effect on the decrease in vaccine efficacy over time. Regardless of the magnitude of the peak response, the GMT had leveled off to around the threshold of detection (10 mIU/mL) after 10–14 years of follow-up in all groups, the percentage with detectable anti-HBs being <50% after that age. A recent study of a cohort of low-risk children vaccinated during infancy showed that even fewer children had protective antibodies 1 decade after vaccination [30]. Nevertheless, vaccine efficacy remained high, especially among those with a higher peak anti-HBs response, also after 20 years of follow-up. The significance of persistent anti-HBs levels after a primary response is unclear, but the consensus is that immunologic memory is sufficient to provide continuous protection even after vaccine-induced anti-HBs has become undetectable [31]. Our data show that the risk of infection (as determined by the presence of anti-HBc) among those still susceptible remains stable during adolescence and early adulthood. Previously, we showed that undetectable anti-HBs was the main risk factor for anti-HBc detection 1 year later [24]. The effect of (adolescent) boosting by repeat vaccination on the magnitude and timing of the immune response and on vaccine efficacy needs further study [17].

Before vaccination, the prevalence of infection and carriage was much higher in Manduar than in Keneba, despite these villages being adjacent and very similar in population and lifestyle; this suggests a much higher exposure, possibly related to a founder effect [14]. Among the older unvaccinated population, the prevalence of carriage has nearly halved over the past 20 years, although the difference between the villages has persisted. Among the younger vaccinees, there were no significant differences in the prevalence of infection or carriage between villages. Because there are very few young carriers (only a few of whom are positive for HBsAg), the pressure of infection on the population by the carrier population has decreased considerably.

In conclusion, infant HBV vaccination effectively prevented transmission for a period of up to 20 years, from early childhood to early adulthood. Continued follow-up is needed to assess the necessity of a booster during adolescence, to ensure that the primary goal of the vaccination program—the pre-

vention of hepatocellular carcinoma and liver cirrhosis—is achieved.

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