Antibody levels in Ethiopian children five years after vaccination with two different doses of hepatitis B vaccine: Is there a need for booster vaccine?

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E Tsega, J Horton, E Nordenfelt, et al. Antibody levels in Ethiopian children five years after vaccination with two different doses of hepatitis B vaccine: Is there a need for booster vaccine? Can J Gastroenterol 1998;12(1):57-60. It was hypothesized that, following effective initial vaccination, a booster dose of hepatitis B vaccine will not be necessary in areas of hyperendemicity for hepatitis B virus (HBV) infection. A total of 314 Ethiopian children, ranging from two to 14 years old, were alternatively vaccinated with 10 and 20 µg hepatitis B vaccine doses, using the initial, one- and six-month schedule. Five years later, 210 of the vaccinees were retested for anti-HBV surface antibody titres. Both 10 and 20 µg doses of hepatitis B rDNA yeast vaccine were equally immunogenic and protective against HBV infection for at least five years despite marked reduction of mean antibody levels and geometric mean titres, with 11% of the vaccinees showing antibodies below the protective level. For firm further recommendations a longer follow-up period of vaccinees is suggested.

Key Words: *Booster vaccine, Doses, Ethiopian children, Hepatitis B vaccine*

Taux d'anticorps chez des enfants éthiopiens cinq ans après une vaccination au moyen de deux doses de vaccin contre l'hépatite B : le rappel est-il nécessaire?

RÉSUMÉ : Selon l'hypothèse, après une vaccination initiale efficace, une dose de rappel de vaccin contre l'hépatite B ne sera pas nécessaire dans les régions d'hyperendémie d'infections au virus de l'hépatite B. En tout, 314 enfants éthiopiens de 2 à 14 ans ont été vaccinés au moyen de doses de vaccin contre l'hépatite B de 10 et de 20 µg à six mois d'intervalle. Cinq ans plus tard, 210 des patients vaccinés ont été testés de nouveau pour un dosage des anticorps anti-HBV de surface. Les deux doses de 10 et de 20 µg de vaccin à levure contre l'hépatite (BrDNA) se sont révélées tout aussi immunogènes et protectrices contre l'infection au HBV pendant au moins cinq ans, malgré la réduction marquée des taux moyens d'anticorps et des moyennes géométriques, 11 % des sujets vaccinés ayant présenté des anticorps sous le taux de protection. Pour une recommandation plus ferme, il faudrait exercer un suivi plus long auprès des sujets vaccinés.

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Ethiopia is one of the hyperendemic areas for hepatitis B virus (HBV) infection. The hepatitis B virus surface antigen (HBsAg) carrier state is 8% to 12%, and the sequelae of HBV infection, chronic hepatitis, cirrhosis and hepatocellular carcinoma account for high morbidity and mortality (1-3).

Unlike in Southeast Asia, in Ethiopia vertical transmission is uncommon, but horizontal transmission occurs early in life within the family setting, and infection continues to rise gradually throughout adult life (4). Thus, although mass vaccination of newborns is an urgent need, the high cost of the available vaccines in third world countries prohibits implementation of such a program. To reduce the cost of the vaccine, the safety and immunogenicity of a rDNA HBV vaccine (Engerix B, SmithKline Beecham) were compared by administering 10 µg (group A) and 20 µg (group B) doses to two comparable (age and sex) groups of children between two and 14 years of age. Both doses, using the initial, one- and six-month schedule, were shown to be equally immunogenic, with seroconversion rates of 97% to 100% and anti-HBs geometric mean titres (GMTs) of 3421 to 6336 IU/L (5) a month after the third dose of vaccine. At the time of the vaccination trial, it was hypothesized that a booster injection of the vaccine after five to 10 years might not be needed because the repeated exposure to HBV in the endemic area could give rise to anamnestic response (ie, production, in response to an antigenic stimulus, of an antibody that has been produced in the host on some previous occasion) and, hence, an indefinite period of protection.

Therefore, determination of anti-HBs levels, five years after the initial vaccination, was planned in groups who received 10 µg (group A) and 20 µg (group B) of the vaccine, respectively.

SUBJECTS AND METHODS

Of 380 children (two to 14 years old) screened for HBsAg, antihepatitis B core (HBc) antigen and anti-HBs, 314 were found to be negative. These noninfected and nonimmune Ethiopian children (156 boys and 158 girls) were vaccinated with rDNA yeast-derived hepatitis B vaccine using the initial, one- and six-month schedule between October 1987 and March 1988. They did not have acute or chronic disease or a history of allergy to any vaccine preparation. Alternate subjects received either 10 or 20 µg of the vaccine intramuscularly into the deltoid muscle (5). The anti-HBs antibody titres and the GMT were determined a month after the first, second and third doses.

Parents of the vaccinees were advised to report to the hospital where they were vaccinated if their child developed jaundice during the ensuing five years. Five years later, during April and May 1993, blood specimens were collected to determine anti-HBs antibody levels. Results were obtained from 210 subjects (67% of the total 314 vaccinees), despite repeated attempts to contact all of the original vaccinees.

Anti-HBs antibody titres were determined by using the radioimmunoassay method (commercial kits from Abbott Laboratories), as in the authors' original study (5). The χ^2

TABLE 1
Levels of antihepatitis B virus surface (anti-HBs) antigen and geometric mean titre (GMT) after one month and after five years of vaccination

	Anti-HBs titre level (IU/L)	GMT (IU/L)
10 µg group (n=108)		
One month after vaccination	13,458.7	3651.5
Five years after vaccination	1193.6	192.6
20 µg group (n=102)		
One month after vaccination	16,834.7	4569.8
Five years after vaccination	843.6	261.2

TABLE 2
Distribution of antihepatitis B virus surface (anti-HBs) antigen titres in recipients of two different doses of hepatitis B vaccine one month and five years after vaccination

	Levels of titres (IU/L)				
	<10	10-100	101-1000	1001-10,000	>10,000
10 µg group (n=108)					
One month after vaccination	0	2	26	40	40
Five years after vaccination	16	25	37	27	3
20 µg group (n=102)					
One month after vaccination	3	2	14	34	49
Five years after vaccination	8	17	48	29	0

test was used for comparison where applicable, and the geometric mean and its 95% CI were used to describe the average of individual titres.

RESULTS

A total of 160 subjects (85 males and 75 females) in group A and 154 (71 males and 83 females) in group B initially completed the vaccination program. Of these, 108 (52 males and 56 females) from group A and 102 (43 males and 59 females) from group B were available for retesting after five years. For group A subjects, mean anti-HBs antibody titre and mean GMT of the 108 vaccinees (68% of the total of 160 initial vaccinees in group A) a month after the third dose were 13,458.7 IU/L and 3651.5 IU/L, respectively. Five years later, the anti-HBs titre and GMT of these vaccinees were only 9% (1193.6 IU/L) and 5% (192.6 IU/L), respectively, of the original values. Similarly, for group B subjects, the anti-HBs antibody titre level and the GMT of 102 (66% of the total 154 initial vaccinees in group B) decreased from 16,834.7 IU/L and 4569.8 IU/L, to 843.6 IU/L (5% of the original titre) and 261.2 IU/L (6% of the original GMT), respectively (Table 1). There was no difference in the mean anti-HBs titres and GMTs between males and females, and no difference in results between those younger and older than eight years of age.

The distribution of the anti-HBs titres in groups A and B a month after the complete vaccination and five years later are shown in Table 2. Thus, five years after the initial vaccination, there was a significant reduction in the anti-HBs titres in both groups, with 24 subjects below the accepted protective level (10 IU/L) and only three of the original 89 subjects with anti-HBs titre levels greater than 10,000 IU/L (all recipients of 10 µg dose).

Three subjects showed an increase in the anti-HBs levels five years after vaccination. All were females older than eight years of age; one was from group A (level increased from 121 to 294 IU/L) and two were from group B (4 to 83 IU/L, 9 to 1486 IU/L), and the latter two had an anti-HBs titre level of less than 10 IU/L a month after the initial complete vaccination.

Three vaccinees, two males and one female, all younger than eight years old and with high levels of antibodies initially and five years postvaccination, presented with acute viral hepatitis due to hepatitis A virus (HAV) infection (immunoglobulin [Ig] M anti-HAV-positive). All were icteric and clinically mild. No cases of clinical hepatitis B were identified.

DISCUSSION

Five years after vaccination, 89% of the vaccinees (186 of 210) still had protective levels of anti-HBs antibodies, but levels were markedly reduced to about 5% of the original mean titre and 6% of the original GMT. Twenty-four vaccinees (11%) had anti-HBs levels below the protective level of 10 IU/L; none of these reported icteric illness. Hadler and associates (6) have shown that, five years after vaccination, 10% to 15% of vaccinees had 'undetectable' levels of antibody, comparable with our observation above. As shown in Table 2, the distribution of anti-HBs titre levels soon after vaccination and five years later were similar in groups A and B. Thus, the 10 µg hepatitis B vaccine dose is as effective and immunogenic as the 20 µg dose for mass vaccination of children.

The use of 5 µg of hepatitis B rDNA yeast vaccine administered to children between three months and 11 years of age at initial dose and one month later has been shown by Lai et al (7) to be as effective as 10 or 20 µg of the same vaccine given in three doses, despite lower anti-HBs antibody titres, presumably due to anamnestic responses. If this observation is confirmed by similar studies, the cost of the vaccination could be further and significantly reduced, hence making it more readily available to third world countries. Also, reducing the number of doses from three to two, given at a short interval, could improve compliance.

Antibody levels higher than the initial levels five years after vaccination – as seen in three of our patients – may be due to anamnestic responses. Two of these patients were poor responders because their anti-HBs levels remained under 10 IU/L a month after three doses of the vaccine, and they were found to have antibody levels of 93 and 1486 IU/L, respectively, at five years. While the rise of anti-HBs level from 9 to 1486 IU/L is striking, the increase from 121 IU/L

and 41 IU/L, to 249 IU/L and 83 IU/L, respectively, is not impressive; the latter levels could be due to nonspecific variability or the declining phases of higher levels of anti-HBs following exposure to HBV infection. If this were truly an anamnestic response, it suggests that vaccinees are likely to be protected from HBV infection irrespective of the initial antibody level following vaccination. However, because antibody levels were not determined periodically, as in the study by Lai and associates (7) in whom 11 of 106 children (10%) were noted to have anamnestic response, it is difficult to exclude late responses to vaccination or subclinical HBV infection. Alanine aminotransferase, anti-HBc or HBsAg were not determined periodically or at the time of the last serum collection for anti-HBs. Thus, latent or asymptomatic HBV infection could not be identified. However, the three vaccinees who presented with jaundice had acute HAV infection as determined by positive sera for IgM anti-HAV, while their anti-HBs antibody levels were still high (342, 1070 and 1577 IU/L, respectively).

Although vaccine-induced antibody levels decline steadily over time, and up to 50% of adult and child vaccinees who respond adequately to vaccine may have low or undetectable antibody levels, immunological memory remains intact for at least seven to nine years (6,8,9). Based on this observation, recommendations from the United States Immunization Practices Advisory Committee state that there is no need for booster dose, and that serological testing to assess antibody level is not necessary in children and adults with normal immune status. Exceptions include hemodialysis and immunocompromised patients (10). Further recommendations will depend on a longer follow-up period of vaccinees.

CONCLUSIONS

This study confirms that 10 and 20 µg doses of hepatitis B rDNA yeast vaccine are equally immunogenic and protective against HBV infection for at least five years despite significant reduction of antibody level and GMT, with 11% of the vaccinees showing antibodies below the protective level. This is in keeping with our hypothesis that, in hyperendemic areas, anamnestic responses following vaccination would protect against HBV infection for a long time. While a longer period of follow-up is necessary, it is also advantageous for third world countries to conduct further studies using a 5 µg dose of the same vaccine administered twice instead of the currently recommended three doses, in order to improve compliance and reduce the cost of the vaccine.

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