

Long-term effectiveness of infancy low-dose hepatitis B vaccine immunization in Zhuang minority area in China *

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Subject headings hepatitis B vaccine; immunization; HBsAg; risk factor

Abstract

AIM To observe the long-term effectiveness of low-dose immunization strategy and risk factors of HBsAg carriers in immunized children of Zhuang minorities of Longan County in the 9th year after infancy immunization.

METHODS Two epidemiologic methods, a cross sectional follow up study and a case-control study, were used for the evaluation of the serological effect and the determination of the risk factors. Hepatitis B virus markers were detected with radioimmunoassay.

RESULTS The protective anti-HBs-positive rate was 43.8% in 1183 children aged 1-9 years, who were immunized with three doses of 10 µg hepatitis B vaccine in infancy according to 0, 1 and 6 months schedule. It declined from 87.9% in the first year to 37.1% in the 9th year after vaccination. The HBsAg-positive rate was 1.6%, not increasing with age during 9 years after the infant immunization program. Compared with 14.0% of HBsAg-positive rate of the baseline survey in 1985, the effectiveness of hepatitis B vaccine immunization was 88.6%. Of 36 immunized children with positive HBsAg, 89.1% were likely attributable to HBsAg positivity of their mothers.

CONCLUSION The long-term effectiveness of infancy low-dose hepatitis B vaccine immunization

is high, and the booster is not needed 9 years after the vaccination in the Zhuang minority area where hepatitis B is highly endemic. A high-dose immunization strategy should be recommended in order to further decrease the current HBsAg-positive rate.

INTRODUCTION

Hepatitis B (HB) infection is a major public health problem in developing countries, and hepatitis B vaccine immunization has become a principal strategy to control this disease^[1-3]. Longan County, inhabited mostly with Zhuang minorities, is a high endemic area of hepatitis B and hepatocellular carcinoma in China. The infant low-dose immunization program integrated with EPI has been implemented in this county for 9 years. In order to provide the evidences for developing the strategy to further improve the effectiveness of immune protection, a study on long-term effectiveness of the low-dose strategy and the risk factors of immunized children with positive HBsAg was conducted in Longan.

MATERIALS AND METHODS

Sample size and subjects

A total of 1183 children aged 1-9 years were sampled as a vaccination group for the observation of long-term effectiveness in terms of cluster sampling. Those children were born in the period between 1987 and 1996 in Longan County, who had the vaccination record of three doses of 10 µg-plasma-derived hepatitis B vaccine, according to 0, 1 and 6 months schedule of the regimen in which the infancy vaccination was integrated with EPI and without predelivery HBsAg and HBeAg screening for their mothers, and without the booster. In this county, the infant HB vaccination covered 90%, ranging from 75% to 97% between 1987 and 1996.

A total of 3645 children aged 1-9 years were selected as a control group from the subjects of a cross-sectional survey on hepatitis B virus infection of children aged 1-10 years of Longan in 1985. None of the controls had received HB vaccines. The prevalences of their hepatitis B infection markers were representative of the infection level of the -

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young population before HB immunization.

Mothers of vaccinated children were selected from both groups of the families of the immunized children, who were HBsAg-positive confirmed serologically after 1987 and who were HBsAg negative in 1996, respectively.

Study methods

A cross-sectional follow-up study and a case-control study were adopted for the evaluation of the serological effect and the determination of risk factors of HBsAg carriers after infancy vaccination.

Hepatitis B vaccine

Plasma-derived hepatitis B vaccines used from 1987 to 1996 were produced by the National Institute of Biological Products, Beijing (10 µg/per ampoule).

Lab test

Radioimmunoassay (RIA) was used for the detection of anti-HBs, anti-HBc and HBsAg. The protective anti-HBs-positive was defined as S/N-ratio ≥ 10.0, and anti-HBc inhibition ratio ≥ 75% and HBsAg S/N-ratio ≥ 2.1 (need confirmation in lab testing) were defined as the sera positive. When comparing with the result of the baseline survey, the anti-HBs-positive was defined as S/N-ratio ≥ 5.0 (retesting for specimens with anti-HBs level of 2.1 to 5 S/N-ratio). RIA reagent kits were provided by the National Institute of Biological Products, Beijing.

Data analysis

Both softwares, dBase-III and EPI-info 6.01, were used for the data base and the statistics analysis.

RESULTS

Comparison of positive rates of anti-HBs before and after immunization

The protective anti-HBs-positive rate was 48.8% on average in 1183 immunized children aged 1-9 years after infancy vaccination, which decreased from 87.9% in the first year to 37.1% in the 9th year. Comparison with the results of the baseline survey in 1985 and the anti-HBs-positive rates for both groups of children before and after the immunization program are shown in Table 1.

Table 1 Comparison of anti-HBs-positive rates between the immunized children and the unimmunized children

Age group (year)	Immunized children			Unimmunized children		
	n	Positive ^a	%	n	Positive ^a	%
1	219	165	75.3	759	117	15.4
3	317	198	62.5	539	121	22.4
5	310	148	44.7	590	204	34.6
7	248	131	52.8	655	238	36.3
9	89	49	55.1	364	125	34.1
Total	1 183	691	58.4	2 907	805	27.7

^aAnti-HBs-positive was defined as S/N ratio ≥ 5.

Table 1 shows that the anti-HBs-positive rate for each age group of vaccinees after the immunization was significantly higher than that of controls ($P < 0.01$), suggesting that the infant low-dose immunization in Longan was effective; however, the anti-HBs-positive rate significantly decreased with age 9 years after the infancy immunization.

Comparison of positive rates of anti-HBc before and after immunization

The anti-HBc-positive rates for both groups of children are shown in Table 2.

Table 2 Anti-HBc-positive rates between the immunized and the unimmunized children

Age group (year)	Immunized children			Unimmunized children		
	n	Positive ^a	%	n	Positive ^a	%
1	219	7	3.2	759	85	11.2
3	317	8	2.5	539	92	17.1
5	310	16	5.2	590	142	24.1
7	248	9	3.6	655	181	27.6
9	89	8	9.0	364	111	30.5
Total	1 183	48	4.1	2 907	611	21.0

^aAnti-HBc-positive was defined as inhibitory ratio ≥ 75%.

Table 2 shows that the anti-HBc-positive rate of the vaccinees after the immunization was significantly lower than that of the controls ($P < 0.01$), indicating that the HBV infection frequency in the immunized children 9 years after the vaccination was lower than before; and among the immunized children the anti-HBc-positive rate had a trend of increasing with age, but there was no significant difference between the age groups ($P > 0.05$).

Comparison of positive rates of HBsAg before and after immunization

Of 1183 immunized children, 19 (1.6%) HBsAg-positive children was found. The results of pre and post-vaccination are shown in Table 3.

Table 3 HBsAg-positive rates between the immunized and the unimmunized children

Age group (year)	Immunized children			Unimmunized children		
	n	Positive ^a	%	n	Positive ^a	%
1	219	2	1.6	1 115	56	5.0
3	317	3	1.0	638	98	15.4
5	310	7	2.3	691	131	18.9
7	248	4	1.6	772	147	19.0
9	89	2	2.3	429	77	18.0
Total	1 183	19	1.6	3 645	509	14.0

^aHBsAg-positive was defined as S/N ratio ≥ 5.

Table 3 shows that the HBsAg-positive rate was 1.6% in the immunized children, being significantly lower than 14.0% in the unimmunized children ($P < 0.01$), and the effectiveness of the hepatitis B vaccine immunization was 88.6% 9 years after in-

fancy vaccination; in addition, the HBsAg-positive rate was not increasing with age ($P>0.05$).

Study on the risk factors of HBsAg-positivity of immunized children

A case-control study on the risk factor of HBsAg-positivity of immunized children was conducted. A number of 36 individuals were sampled from the HBsAg-positive children (sampling proportion of 85.7%) as a case group, and 516 individuals from the HBsAg-negative children as control group (sampling proportion of 44.6%), in the vaccination population. The results of sera HBsAg detection for their mothers are shown in Table 4.

Table 4 Comparison of HBsAg-positive mothers between case and control groups

Positive HBsAg of mother	Case group	Control group	Total	OR	P
Yes	23	84	107	9.16	<0.01
No	13	435	448		
Total	36	519	555		

Table 4 shows that among the immunized children, the HBsAg-positive rate of the mothers of 36 HBsAg-positive children after infancy vaccination was 9.16 times that of the mothers of the control (OR = 9.16, $P<0.01$), and the attributable risk (AR) was estimated as 89.1%. It is indicated that after the immunization, the possibility of HBsAg seroconversion of offsprings for the HBsAg-positive mothers was significantly higher than that for the negative mothers, and the HBsAg positivity of immunized children was mainly due to the HBsAg carrying mothers.

DISCUSSION

Longan County is a remote minority area, and an area of high HBV endemicity in China. To evaluate the effectiveness of the immunization strategy with low-dose of HB vaccine for infants and without predelivery HBV markers screening for their mothers is of important significance for the control of HBV infection of this kind of areas. The HBsAg-positive rate decreased from 14.0% of the unimmunized children aged 1-9 years in 1985 to 1.6% of the immunized children 9 years after the infancy vaccination, and the effectiveness of the vaccine protection was 88.6% for the immunized population. Based on this data, the HBsAg-positive rate of children aged 1-9 years in the whole county was estimated as 2.84% ($0.9 \times 0.016 + 0.1 \times 0.14$), and the effectiveness of the HB vaccination was 79.7% for the

whole population with same age. The HBV infection will be effectively controlled in the Zhuang minorities of Longan as the HBsAg carriers decreased obviously in children below age of 9 years. The results indicate that the low-dose immunization strategy used in Longan is successful for the hepatitis B control, and beneficial in health economics for the remote minority areas in China.

To further improve the protective effectiveness of HB vaccine immunization in population is still a problem which calls for studies. In recent years, the average coverage of HB immunization of infants was around 90%, ranging from 75% to 97%, in this area. If the coverage can be expanded, a higher effectiveness will be obtained. In addition, it is also important to determine the risk factors of HBsAg-positive children after vaccination. Our results from a case-control study revealed that the yielded HBV infection among the immunized infants was mainly due to the HBsAg positivity of their mothers (AR = 89.1%), therefore, perinatal HBV infection, i.e., failure of HB vaccine immunization, was probably the most important reason for this. It is imperative and of great benefit to recommend a high-dose immunization strategy for neonates of mothers carrying HBeAg based on the predelivery screening with the improvement of economic condition of this area.

The results of our study showed that the vaccine-induced antibody level was decreasing year by year, but the HBsAg-positive rate always fluctuated around 2% among the immunized population. Our findings are similar to the results of Edward^[4], Whittle^[5] and Xu^[6]. This phenomenon can be explained with the vaccine-induced immunologic memory for hepatitis B surface antigen. This study indicates that the time table for booster of HB vaccine has not been determined due to lack of relative evidences 9 years after this immunization strategy, and the follow-up studies should be continued in Longan.

REFERENCES

- 1 Coursaget P, Chotard J, Vincelot P, Diopmar I, Yvonnet B, Sarr M. Seven-year study of hepatitis B vaccine efficacy in infants from an endemic area (Senegal). *Lancet*, 1986;ii:1143-1145
- 2 Sung JL and Asian Regional Study Group. Hepatitis B virus eradication strategy for Asia. *Vaccine*, 1990;8(Suppl):95-99
- 3 Chao HL. Study on immune persistence and protective effect of hepatitis B vaccine. *Chin J Experiment Clin Virol*, 1995;9:1-4
- 4 Edward T, James C, Robert JG, Anne CB. Nine-year follow-up study of a plasma-derived hepatitis B vaccine in a rural African setting. *J Med Virol*, 1993;40:204-209
- 5 Whittle HC, Maine N, Pikington J, Menely M, Fortuin M, Bunn L. Long-term efficacy of continuing hepatitis B vaccination in infancy in two Gambian villages. *Lancet*, 1995;345:1089-1092
- 6 Xu ZY, Chao HL, Liu CB, Yang JY, Yan TQ, Shun YD. A cross-sectional study of long-term effectiveness of universal infant hepatitis B vaccination program. *Chin J Experiment Clin Virol*, 1995;9:13-16