PROTECTIVE ANTIBODY AFTER A 'ONE DOLLAR' HEPATITIS B VACCINE

Siripen Kalayanarooj[1], David W Vaughn[2], Churdchoo Ariyasriwatana[1] and Rapin Snitbhan[2]

[1]Children's Hospital, Bangkok 10400, Thailand; [2]Armed Forced Research Institute of Medical Sciences, Bangkok, Thailand

Abstract. The seropositivity rate of anti-HBs after hepatitis B vaccines, "Hepavax B", a one-dollar per dose vaccine produced by Korean Green Cross Corporation, Korea which were widely distributed and used for the first few years in the National Expanded Program on Immunization in Thailand were assessed in children who regularly came for immunization at the Well Baby Clinic at the Children's Hospital between June to December 1994. The schedule for hepatitis B immunization is at birth, 2 and 6 months of age. The seropositivity rate of anti-HBs at 6 months after the last dose were 86.3% and 87.7% at 12 months which was comparable to the seropositivity rate after other more expensive hepatitis B vaccines at 2 years (88.1%). This result should convince people that a one-dollar hepatitis B vaccine, "Hepavax" is immunogenic and expected to be as effective as other expensive hepatitis B vaccines. The marked reduce in the cost of hepatitis B vaccines will enable us to prevent and ultimately control of worldwide hepatitis B infections in the future.

INTRODUCTION

Hepatitis B is disease of global importance, with more than 300 million carriers of the virus worldwide. The hepatitis B virus (HBV) is one of the most important causes of persistent viremia in humans. The sequelae of this infection include chronic active hepatitis, cirrhosis and primary hepatocellular carcinoma (Maynard *et al*, 1989, 1990; Sherlock, 1990; Robinson, 1995 a, b; Thompson, 1995). The World Health Organization (WHO) Viral Hepatitis Control Program Technical Advisory Group on Viral Hepatitis (TAG) concluded in 1987 that the most important means of controlling hepatitis B on a global scale to reduce mortality due to sequelae is universal immunization of infants and young children. In hyperendemic regions where most infections are acquired early in life, the vaccine should be administered shortly after birth. Vaccination of all infants should be a major public health priority for populations with carrier rates > 10% (Ghendon, 1990).

Thailand is endemic for hepatitis B: the overall carrier rate in Thai people is estimated to be about 10% (Poovorawan, 1990; Kiatisevi, 1994). The Ministry of Public Health, Department of Communicable Disease Control adopted the TAG's recommendation in 1989 and implemented hepatitis B immunization in infants in two provinces (Chon Buri and Chiang Mai). They found that the "Hepavax-B" vaccine produced by the Korean Green Cross Corporation, which was available at one dollar per dose, was immunogenic and had good protective efficacy (Anonymous, 1990). So in 1992, hepatitis B vaccine was incorporated in the Expanded Program on Immunization (EPI) for all newborns, 10 µg intramuscular at birth and later at 2 and 6 months of age. At the beginning of this program, Hepavax-B vaccine was distributed for immunization. This study attempts to compare the immunogenicity of this 'one dollar' hepatitis B vaccine to another 'ten-dollar' commercially available hepatitis B vaccine. Serum collected as part of a study of immune response to polio and measles vaccines offered an opportunity to look at acquisition of antibodies against HBV following vaccination or natural exposure.

MATERIALS AND METHOD

Patient enrolment

Venous blood was obtained from infants and children attending the Well-baby Clinic at the Children's Hospital, Bangkok between June to December 1994. Most were from middle and low socioeconomic families residing in Bangkok, except a few of them who came from nearby provinces.

The subjects were divided into 3 groups as follows:

Group A included healthy 9-month-old infants coming for measles vaccination; Group B consisted of 18-month-old children presenting for DTP and OPV booster vaccination; Group C consisted of 48-month-old children coming for the second set of DTP and OPV booster vaccines.

Enrolment was offered at the visit for the infants and children who had complete immunization records. Blood was obtained 3 months later for group A and 1 month later for groups B and C.

Vaccines

All group A and B subjects received plasma-derived hepatitis B vaccine, Hepavax B, produced by Korean Green Cross Corporation, Korea, 10 μg → intramuscular. The vaccination schedule was at birth, 2 months and 6 months of age.

Group C subjects received recombinant DNA hepatitis B vaccines, either Engerix-B (SmithKline Biologicals, Belgium) or H-B-Vax II (Merck Sharp and Dohme, USA) 10 μg intramuscular. These subjects were born before hepatitis B vaccine was incorporated into the EPI, so they had their vaccinations at various ages, and the schedule of immunization was at 0, 1 and 6 months intervals.

Blood drawing

Upon completion of informed consent procedures, 3-5 ml of venous blood was drawn from each patient. Serum was separated and kept at -20°C until time of assay.

Serologic testing

Each specimen was tested using the following commercially available assay:

- anti-HBs using "AUSAB EIA", Abbott Laboratories, Chicago IL USA.
- anti-HBc (IgG) using "CORZYME EIA", Abbott Laboratories, Chicago IL USA.
- All specimens from Group C and specimens from groups A and B who had positive anti-HBc(IgG) were assayed for HBsAg by "AUSZYME EIA" Abbott Laboratories, Chicago IL USA.

All testing was performed in the Department of Virology, Armed Forced Research Institute of Medical Sciences (AFRIMS).

Statistical analysis

Chi-square and student's *t*-test were used to compare the categorial and continuous variables, respectively.

RESULTS

There were 73 infants in group A, 73 children in group B and 42 children in group C. The mean ages of those in group A, group B and group C were 12.49 ± 0.66 months (Range 10.3 - 15.4 months), 20.15 ± 1.49 months (Range 18.5 - 28.8 months) and 51.21 ± 2.37 months (Range 48.0 - 60.8 months), respectively. The male to female ratios for subjects in group A, group B and group C were 1 : 1.2, 1 : 1 and 1 : 1.1, respectively.

Number of subjects with Anti-HBs after "Hepavax B" vaccines

Sixty-three of 73 subjects in group A (86.3%) had anti-HBs (Table 1). The mean duration between the most recent dose of hepatitis B vaccine and venipuncture was 6.3 ± 1.6 months (range 3.5 - 13.0 months). Among these subjects who had anti-HBs, one had received 1 dose, 3 received 2 doses and 59 had received 3 doses of hepatitis B vaccine (Table 2). All ten subjects who failed to produce anti-HBs had received 3 doses of hepatitis B vaccines (Table 3).

Sixty-four of 73 subjects (87.7%) in group B had anti-HBs (Table 1). The mean duration between the most recent dose of hepatitis B vaccine and venipuncture was 13.3 ± 2.4 months (range 0.9 - 19.9 months). Among these subjects who had anti-HBs, 2 had received 1 dose, 1 received 2 doses, 57 received 3 doses and 4 received 4 doses of hepatitis B vaccine (Table 2).

Among participants without anti-HBs, one had received 2 doses and 8 had received 3 doses of hepatitis B vaccines (Table 3).

Table 1

Seropositivity rate of anti-HBs in each group of subjects.

	Group A	Group B	Group C	Total
Number	73	73	42	188
Anti-HBs	63	64	37	164
Percent	86.30	87.67	88.10	87.23

Table 2

Number of hepatitis B vaccinations in anti-HBs positive subjects.

	1 Dose	2 Doses	3 Doses	4 Doses	Total
Group A	1	3	59	0	63
Group B	2	1	57	4	64
Group C	1	5	26	5	37
Total	4	9	142	9	164

Table 3

Number of hepatitis B vaccinations in non-responder subjects.

	1 Dose	2 Doses	3 Doses	4 Doses	Total
Group A	0	0	10	0	10
Group B	0	1	8	0	9
Group C	0	0	4	1	5
Total	0	1	22	1	24

Table 4

Geometric mean titers (mIU/ml) of anti-HBs in group C subjects.

GMT (mIU/ml)	Number	Percent
> 10-100	11	30.56
> 100-500	11	30.56
> 500-1,000	5	13.89
> 1,000	9	25.00
Total	36	100.0

Number of children who had Anti-HBs after Engerix B/ H-B-Vax II vaccines

Thirty-seven of 42 subjects (88.1%) in group C had anti-HBs (Table 1). The mean duration between the most recent dose of hepatitis B vaccine and venipuncture was 24.8 ± 13.0 months (Range 2.7 - 49.3 months). Among subjects who had anti-HBs, one had received 1 dose, 5 received 2 doses, 26 received 3 doses and 5 received 4 doses of hepatitis B vaccines (Table 2).

Among participants without anti-HBs, 4 subjects had received 3 doses and 1 received 4 doses of hepatitis B vaccines (Table 3).

Geometric mean titers of anti-HBs in vaccinees after Engerix B/ H-B-Vax II vaccines

About two years after hepatitis B vaccination, 30% of group C subjects had geometric mean titers (GMT) of anti-HBs between 10 - 100 mIU/ml, another 30% had GMT between 100 - 500 mIU/ml and 39% of them had very high GMT of more than 500 mIU/ml (Table 4).

DISCUSSION

The rates of seropositivity of anti-HBs after the last dose of "Hepavax B" vaccines at 6 months (86.3%) and one year (87.7%) were comparable in this study ($p > 0.05$). These seropositivity rates were slightly lower than most of the previously reported series in which had more than 90-99% seroconversion rates after other hepatitis B vaccines (Zachoval *et al*, 1984; Jilg *et al* 1984; Davidson *et al*, 1985; Xu *et al*, 1985; Coursaget *et al*, 1986; Hollinger *et al*, 1986; Poovorawan *et al*, 1990; Andre', 1990; Stevens *et al*, 1992; Robinson, 1995 a, b; Overby, 1996). This may be explained by the difference in the populations studied and their differing immune responsiveness, as well as the different vaccines used. There was only one exceptional report of lower seropositivity rate (75%) than this study, that used hepatitis B vaccines produced by the Beijing Vaccine and Serum Institute (Xu *et al*, 1995).

The rate of seropositivity of anti-HBs after 2 years of "Engerix B"/ "H-B-Vax II" was 88.10% which was comparable to previous reports of 80-

94.2% at 5-6 years. This lower seropositivity rate had been reported when serologic testing was done > 12 months after the last dose of vaccine (Wainwright *et al*, 1989; Marion *et al*, 1994). The lower seropositivity rate also was reported to be associated with simultaneously administration of hepatitis B immune globulin (HBIG) (Xu *et al*, 1995 a, b). In this study, only one subject in group B and 4 subjects in group C had received HBIG.

About 10-13% of subjects in this study were non-responders to hepatitis B vaccines. Whether these non-responders should need booster doses of hepatitis B vaccine or not is still debatable. Some have suggested that if serologic testing was < 18 months after the last dose of vaccine, they should receive a booster immunization (Kohn *et al*, 1996). If the serologic testing was > 18 months after the last dose of vaccine, they may not need to have booster immunization because these non-responders might have had initial high antibody responses which declined over time. Many reports suggested that they might have undetectable levels of antibody and if hepatitis B infection should occur in these individuals, they would have subclinical infections without detectable serum HBsAg and the infections would be detected only by development of anti-HBc or by a rise in anti-HBs (Wainwright *et al*, 1989; Poovorawan *et al*, 1992; Stevens *et al*, 1992; Lieming *et al*, 1993; Robinson, 1995).

Two infants in group A (mean age 12.5 months) and 4 children in group B (mean age 20 months) had anti-HBc. All these 6 infants had antiHBs. These children were likely to have been exposed to natural HBV infections without clinical disease. Some of them, especially the younger children, might have had persistent maternal antibody. No children in group C (mean age 51 months) had HBsAg or anti-HBc. Overall, the children in this study, whether or not they had antibody, were healthy and there was no clinical or laboratory evidence of acute hepatitis.

Most of the subjects receiving "Engerix B" and "H-B-Vax II" who had antibody had high GMT, > 100 mIU/ml. These subjects who had high titers would have a longer period of protection and no need for booster immunization for at least 2 years or more (Jilg *et al*, 1984 a, b).

This successful incorporation of hepatitis B vaccine into the EPI was possible because of the marked reduction in the cost of the vaccine. The crude estimate elsewhere of the cost-effectiveness of adding hepatitis B vaccine (US$ 1.5-3 per dose) in the EPI was between US$ 75-359 (Maynard *et al*, 1989). Such integration is an effective approach to reducing the prevalence of acute hepatitis B infections, hepatitis B chronic carrier state, as well as significant control and prevention of mortality due to chronic sequelae of this infection, including primary hepatocellular carcinoma (Stevens *et al*, 1992; Mahoney *et al*, 1993).

Thus, the seropositivity rate of anti-HBs in vaccinees receiving "Hepavax B", a "one dollar" hepatitis B vaccine in the National EPI program was comparable to that using other more expensive hepatitis B vaccines. The protective efficacy of "Hepavax B" vaccine is expected to be as good as other hepatitis B vaccines because there was no history or clinical evidence of acute hepatitis B infections among vaccinees, whether or not they had protective levels of anti-HBs. The marked reduction in the cost of hepatitis B vaccine makes it possible to incorporate in the EPI

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REFERENCES

Anonymous. Control of hepatitis B infection. In: Pinyowiwat W, ed. Expanded Programme on Immunization 1990 (Thai language). Department of Communicable Disease Control, Ministry of Public Health, 1990: 53-4.

Andre' FE. Overview of a 5-year clinical experience with a yeast-derived hepatitis B vaccine. *Vaccine* 1990; 8 (suppl) : s74-8.

Coursaget P, Yvonne B, Lelyveld EH, *et al*. Simultaneous administration of diptheria-tetanus-pertussis-polio and hepatitis B vaccines in a simplified immunization program: immune response to diptheria toxoid, tetanus toxoid, pertussis, and hepatitis B surface antigen. *Infect Immun* 1986; 51 : 784-7.

Davidson M, Krugman S. Immunogenicity of recombinant yeast hepatitis B vaccine. *Lancet* 1985; 1 : 108-9.

Ghendon Y. WHO strategy for the global elimination of new cases of hepatitis B. *Vaccine* 1990; (suppl) : S129-33.

Hollinger FB, Troisi CL, Pepe PE. Anti-HB_s responses to vaccination with a human hepatitis B vaccine made by recombinant DNA technology in yeast. *J Infect Dis* 1986; 153 : 156-9.

Jilg W, Schmidt M, Deinhardt F, Zachoval R. Hepatitis B vaccination: how long does protection last? *Lancet* 1984a; 1 : 458.

Jilg W, Lorbeer B, Schmidt M, *et al.* Clinical evaluation of a recombinant hepatitis B vaccine. *Lancet* 1984b; 2 : 1174-5.

Kiatisevi F. Hepatitis B carrier. In: Kiatisevi F, ed. Viral Hepatitis, 5th ed (Thai language). Bangkok; Unity Publication 1994; 56-60.

Kohn MA, Farley TA, Scott C. The need for more aggressive follow-up of children born to hepatitis B surface antigen-positive mothers: lessons from the Louisiana perinatal hepatitis B immunization program. *Pediatr Infect Dis J* 1996; 6 : 53-40.

Lieming D, Mintai Z, Yinfu W, Shaochon Z, Weiquin K, Smego RA. ←A 9-year folow-up study of the immunogenicity and long-term efficacy of plasma-derived hepatitis B vaccine in high risk Chinese neonates. *Clin Infect Dis* 1993; 17 : 475-9.

Mahoney FJ, Woodruff BA, Erben JJ, *et al.* Effect of a hepatitis B vaccination program on the prevalence of hepatitis B infection. *J Infect Dis* 1993; 167 : 203-7.

Marion SA, Pastore MT, Pi DW, Mathias RG. Long-term follow-up of hepatitis B vaccine in infants of carrier mothers. *Am J Epidemiol* 1994; 140 : 734-46.

Maynard JE, Kane MA, Hadler SC. Global control of hepatitis B through vaccination: role of hepatitis B vaccine in the expanded programme on immunization. *Rev Infect Dis* 1989; 11 (suppl 3) : s574-8.

Maynard JE. Hepatitis B: global importance and need for control. *Vaccine* 1990; 8 (suppl) : s18-20.

Overby JK. Hepatitis B vaccine. In : Rodolph's Pediatrics, 20th ed. Rudolph, Hoffman and Rudolph eds. Prentice Hall International, 1996: 35-6.

Poovorawan Y, Sanpawat S, Pongpunlert, *et al.* Comparison of a recombinant DNA hepatitis B vaccine alone or in combination with hepatitis B immune globulin for the prevention of perinatal acquisition of hepatitis B carriage. *Vaccine* 1990; 8 (suppl) : s56-9.

Poovorawan Y. Hepatitis B. In : Liver Disease in Children (Thai language). Poovorawan Y Suwanagool P, eds. Bangkok : Chulalongkorn University Press, 1990: 94-107.

Poovorawan Y, Sanpavat S, Pongpunglert W, *et al.* Long term efficacy of hepatitis B vaccine in infants born to hepatitis B e antigen-positive mothers. *Pediatr Infect Dis J* 1992; 11 : 816-21.

Robinson WS. Hepatitis B virus and hepatitis D virus. In: Principles and Practice of Infectious Diseases. 4th ed. Churchill Livingstone. 1995a: 1406-28.

Robinson WS. Prevention of HBV infection. In: Principles and Practice of Infectious Diseases 4th ed. Churchill Livingstone. 1995b: 1428-31.

Sherlock S. Hepatitis B: the disease. *Vaccine* 1990; 8 (suppl): s6-9.

Stevens CE, Toy PT, Taylor PE, *et al.* Prospects for control of hepatitis B virus infection: implications of childhood vaccination and long-term protection. *Pediatrics* 1992; 90 : 170-3.

Thompson RF. Hepatitis B. In : Travel and Routine Immunizations. A Practical Guide for the Medical Office. Milwaukee, USA: Shoreland Medical Marketing 1995 : 31-8.

Wainwright RB, McMahon BJ, Bulkow LR, *et al.* Duration of immunogenicity and efficacy of hepatitis B vaccine in a Yupik Eskimo population. *JAMA* 1989; 261 : 2362-6.

Xu ZY, Lieu CB, Francis DP, *et al.* Prevention of perinatal acquisition of hepatitis B virus carriage using vaccine: preliminary report of a randomized, double-blind placebo-controlled and comparative trial. *Pediatrics* 1985; 76 : 713-8.

Xu ZY, Duan SC, Harold S, *et al.* Long-term efficacy of active postexposure immunization of infants for prevention of hepatitis B virus infection. *J Infect Dis* 1995; 171 : 54-60.

Zachoval R, Jilg W, Lorbeer B, *et al.* Passive/active immunization against hepatitis B. *J Infect Dis* 1984; 150 : 112-7.