

# Comparison of Immunogenicity of Hepatitis B Vaccine Between Low and Normal Birth Weight Infants

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Hepatitis B virus (HBV) infection is endemic in Southeast Asia and tropical Africa. Chronic carriers of HBsAg are at high risk of chronic persistent hepatitis, chronic active hepatitis and primary hepatocellular carcinoma.<sup>1-3</sup> In countries where HBV is endemic, transmission from carrier mothers to their infants has been estimated to be the cause of about 20 to 40 per cent of all chronic carriers.<sup>4</sup> Such transmission might account for as many as fifty million carriers throughout the world. In addition, chronic HBV carriers serve as a continuing source of infection to others. Thus, prevention of the vertical transmission of HBV should be one of the top priorities in the control and prevention of HBV infection and its associated sequelae.

Hepatitis B vaccine alone or in combination with hepatitis B immunoglobulin (HBIG) has been shown to be very effective in the prevention of vertical transmission of HBV in normal birth weight infants.<sup>5-9</sup> So far, there have been no comparative studies assessing the immunogenicity of hepatitis B vaccine in low birth weight (less than 2,500 g) infants, since in most of the studies, low birth weight was a criterion of

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**SUMMARY** A comparative study was conducted to evaluate the immunogenicity of hepatitis B vaccine in low and normal birth weight infants. Hepatitis B vaccine (Hevac B Pasteur®) was given to 50 low birth weight infants and 50 controls, matched by sex and date of delivery. The vaccine was given at birth, 1, 2 and 12 months of age. HBsAg and anti-HBs were assessed at birth, 4, 9 and 13 months of age by the micro-ELISA technique. Using the geometric mean titre of anti-HBs and the seroconversion rate as indicators, the immunogenicity of hepatitis B vaccine in low birth weight infants was as good as in normal birth weight infants.

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exclusion. The objective of this study was to assess the efficacy of Hepatitis B vaccine (Hevac B Pasteur®) in low birth weight infants, with reference to normal birth weight infants.

## MATERIALS AND METHODS

The study group was comprised of 50 healthy low birth weight (1,800-2,499 g) infants born at Srinagarind Hospital, Khon Kaen University. The inclusion criteria included: 1) the mother's serum at the antenatal clinic was negative for HBsAg; 2) informed consent of the parents was obtained. The exclusion criteria included: 1) Apgar score < 4, 2) clinical sepsis, 3) respiratory distress syndrome, 4) major congenital malformation, 5) mother received steroids for acceleration of fetal lung maturity and 6) history

of rupture of membranes more than 24 hours before delivery.

The control group consisted of 50 normal birth weight infants (birth weight > 2,500 g) matched with the study group by sex and date of delivery within one month. The same inclusion and exclusion criteria were also applied to the control group. Our study has an 80% power to

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detect a 25% difference in the seroconversion rate, given an alpha error of 0.05 and a 95% seroconversion rate in the normal birth weight group.<sup>10</sup>

Each infant received a 10- $\mu$ g dose of plasma-derived hepatitis B vaccine (Hevac B Pasteur®) intramuscularly in the anterolateral thigh within 7 days after birth, at 1, 2 and 12 months of age. Blood samples were drawn from all infants before the first dose of vaccine, at 4, 9 and 13 months of age for HBsAg and anti-HBs assessment by enzyme linked immunosorbent assay (Enzygnost® -Beringwerke AG Marburg, West Germany). An adequate antibody response was defined as antibody titre  $\geq$  10 milliinternational units (mIU)/ml. At each follow-up visit, the parents were asked about reactions that occurred within one week after vaccination. DTP, OPV and measles vaccine were given to every infant according to the regular schedule.

Differences in seroconversion rate between groups were tested for statistical significance by McNemar Chi-square and Mantel-Haenzel statistics. The geometric mean titres were compared by using paired *t* test.

## RESULTS

From January 1988 to October 1990, fifty low birth weight and fifty matched normal birth weight infants were recruited into the study. The low birth weight infants were selected to be equally distributed in each birth weight range. There were 15 infants between 1,800-1,999 g, 17 infants between 2,000-2,199 g and 18 infants between 2,200-2,499 g. The average birth weight in the low birth weight group was 2,147 g (range 1,810-2,480 g), while that of the normal birth weight group was 3,145 g (range 2,670-3,920 g). Thirty-six per cent (18 out of 50) of the infants in the low birth weight group, and 2% (1 out of 50) of the infants in the normal

birth weight group were less than 37 weeks gestational age at birth.

At birth there were 10 and 7 infants in the low birth weight and normal birth weight groups, respectively, who had positive anti-HBs, passively transferred from their mothers. At 4, 9 and 13 months of age, the percentages of infants in the low birth weight group who had anti-HBs were 68.3%, 70.7% and 91.7%, respectively. The corresponding rates in the normal birth weight group were 65.1%, 72.5% and 89.2%, respectively (Table 1). There was no statistically significant difference between the 2 groups at all months of the test. The geometric mean titres (mIU/ml) of anti-HBs in the low birth weight group were 219, 166, 123 and 1,479 at birth, 4, 9 and 13 months of age, respectively. The corresponding figures

in the control group were 186, 166, 120 and 1,698, respectively (Table 2). There was also no statistically significant difference between the 2 groups at each month of the test. A two-way ANOVA repeated measure was tried to assess the overall difference. Because of the irregularity in the follow up of the infants in the two groups, there were only 11 pairs of infants who came to every scheduled visit, this statistical procedure could not be carried out.

Concerning the side effects, reactions occurring within one week of vaccination included low grade fever of less than 24 hours duration in 11 infants in each group (22%) and loose stool in 2 infants in the normal birth weight group. All infants were healthy at the 13<sup>th</sup> month of follow up.

**Table 1.** Positive anti-HBs rate (%) after hepatitis B immunization in low birth weight (< 2,500 g) and normal birth weight (> 2,500 g) infants

BW (g)	% Positive anti-HBs at month			
	0	4	9	13
< 2,500	20.0 (10/50)*	68.3 (28/41)	70.7 (29/41)	91.7 (33/36)
> 2,500	14.0 (7/50)	65.1 (28/43)	72.5 (29/40)	89.2 (33/37)

\*No. positive/No. tested

**Table 2.** Geometric mean titres of anti-HBs (mIU/ml) after hepatitis B immunization in low birth weight (< 2,500 g) and normal birth weight (> 2,500 g) infants

BW (g)	GMT at (month)			
	0	4	9	13
< 2,500	219	166	123	1,479
> 2,500	186	166	120	1,698

## DISCUSSION

Our study indicates that low birth weight infants respond to hepatitis B vaccine as well as normal birth weight infants. The seroconversion rates and anti-HBs levels are comparable in both groups.

There were no other comparative studies assessing the immunogenicity of hepatitis B vaccine in low birth weight infants. One descriptive study, assessing the immunogenicity to recombinant yeast-derived hepatitis B vaccine in 25 premature infants, showed a 88% seroconversion rate and a geometric mean titre of 542 IU/l at 9 months. The vaccines were given at 0, 1, 6 months of age.<sup>11</sup>

The hepatitis B vaccine used in our study was a plasma-derived vaccine, which will probably be of limited use in the near future because of the availability of the recombinant yeast-derived vaccine. However, previous studies have indicated that plasma-derived and recombinant yeast-derived vaccines have comparable immunogenicity.<sup>12,13</sup> Therefore, it is very likely that the immunogenicity of recombinant yeast-derived hepatitis B vaccine in low birth weight infants will also be very good and comparable to that of normal birth weight infants.

The World Health Organization has concluded that the simplest and most effective strategy for the control and eventual eradication of HBV infection would be to immunize all infants with hepatitis B vaccine (Ghendon, Y. 1989; unpublished

observations). The data from our study give assurance that this recommendation will have a protective effect against HBV for both normal and low birth weight infants. Therefore, the standard dose of hepatitis B vaccine should be given to all infants in endemic areas regardless of their birth weight.

## ACKNOWLEDGEMENTS

The authors thank Pasteur Vaccins for its supply of vaccines and financial support, Professor Direk Pongpipat for his laboratory support, Mr. Aroon Chirawatkul and Mrs. Malinee Laopaiboon for statistical advice, and Mr. David Narot for editorial assistance.

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