Long term hepatitis B vaccine in infants born to hepatitis B e antigen positive mothers

Yong Poovorawan, Suvimol Sanpavat, Saowani Chumdermpadetsuk, Assad Safary

Abstract

Neonates of hepatitis B surface antigen (HBsAg) positive and hepatitis B encoded antigen (HBeAg) positive mothers received 10 µg of recombinant hepatitis B vaccine at months 0, 1, 6, or 0, 1, 2, 12, with or without immunoglobulin at birth, and were followed up to the age of 8 years for HBsAg, anti-HBc, and anti-HBs. Some were boosted at month 60. The overall vaccine protection at month 12 was 96.2%. No child became a chronic carrier beyond the age of 3 years, showing that this vaccine provides immediate protection against HBsAg carriage, and long term protection against fetally acquired HBsAg. After month 60 hepatitis B serological markers without disease, indicating re-exposure to HBV, reappeared in comparable numbers among boosted and non-boosted children (5 for a total of 167 children).

This vaccine provides long term protection against hepatitis B chronic carriage and infection in high risk neonates with or without a month 60 booster. A booster at the age of 5–6 years or 11–12 years would reduce HBV infection, viral circulation and transmission, while ensuring long term antibody persistence.

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Keywords: hepatitis B vaccine; transmission; boosters; long term efficacy

Hepatitis B virus (HBV) is a ubiquitous organism that leads to a wide range of liver diseases which often result in chronic or fatal outcomes. It has been estimated that there are about 400 to 500 million HBV carriers in the world, and globally, each year more than a million deaths are attributed to the consequences of HBV infection.

Transfer of HBV perinatally from infected mother to child represents a major mode of disease transmission, and is responsible for 35–40% of HBV infections every year worldwide. Women who are seropositive for both hepatitis B surface antigen (HBsAg) and hepatitis B encoded antigen (HBeAg) have high HBV titres and carry a greater risk of infecting their children. Neonates of such mothers are at considerable risk of contracting hepatitis B, with 65–93% becoming chronic HBV carriers within 12 months of age. In Asia the risk of HBV infection persists well into childhood for neonates of HBsAg positive mothers not already infected in the first year of life. By the time these neonates have reached 4 years of age, 40% born to HBeAg positive mothers, and 75% born to HBeAg positive mothers, show signs of HBV infection.

To reduce and eventually eliminate hepatitis B from mankind, the adoption of universal hepatitis B vaccination in neonates is an imperative strategy to prevent perinatal transmission of HBV, and thus reduce the pool of chronic carriers responsible for spreading HBV. This requirement has been recognised by the World Health Organisation, which has recommended that all countries should adopt such an immunisation strategy by 1997.

Hepatitis B vaccines must therefore demonstrate high and long lasting protection in neonates of HBsAg and HBeAg positive mothers if the ultimate goal of hepatitis B eradication is to be achieved. In 1986 we initiated three prospective clinical trials to investigate the reactivity, immunogenicity, and protective efficacy of a recombinant DNA hepatitis B vaccine in high risk neonates. The results of these trials up to 48 months after the first dose have been published elsewhere. We present the follow up to 96 months, and investigate the effect of booster administration at month 60, on anti-HBs titres.

Methods

IMMUNOPROPHYLAXIS SOLUTIONS

A recombinant DNA hepatitis B vaccine (Engerix B), manufactured by SmithKline Beecham Biologicals in Rixensart, Belgium, was used. Each 0.5 ml dose contained 10 µg of HBsAg adsorbed on to 0.25 mg of aluminium as hydroxide salt, with thimerosal at a concentration of 1:20 000 as preservative. The specific hepatitis B immunoglobulin (from Bern on in Switzerland) administered to some of the neonates, depending on the study protocol, was at a concentration of 100 U/0.5 ml. The vaccine was administered either in the deltoid muscle or the anterolateral thigh. Whenever immunoglobulin and vaccine were administered simultaneously at birth, they were injected in opposite limbs.

STUDY OBJECTIVES

The primary objective was to measure the long term protective efficacy of this recombinant hepatitis B vaccine against chronic carriage in neonates of mothers seropositive for HBsAg and HBeAg using two different immunisation schedules, either with booster (B) or no booster (NB) administration at month 60. Secondary objectives included the assessment of long term persistence of anti-HBs and prevention of hepatitis B infections without progression to carrier state in these neonates.
A chronic carrier was defined as being HBsAg positive for an interval of six months or more. The protective efficacy at month 12 was calculated using 65% as a conservative rate of chronic carriage occurring in unvaccinated neonates of mothers positive for HBsAg and HBcAg up to 12 months of age.² The protective efficacy was therefore worked out as: 65% minus the chronic carriage (%) in the vaccinated group, divided by 65, and multiplied by 100 to give a percentage.

For HBsAg-negative non-carrier children, a silent infection was defined as persistence of anti-HBc beyond 3 years of age, or permanent reappearance of anti-HBc after having become negative (defined as a minimum of two successive anti-HBc reappearances only without subsequently becoming negative for anti-HBc), or temporary reappearance of anti-HBc if associated with a rise in anti-HBs titre (> fourfold) to a titre of at least 10 mU/ml, and if accompanied at the same time by an increase in anti-HBs to a titre of >10 mU/ml. An infant with a rise in anti-HBs titre was defined as having been exposed to HBV leading to a “natural booster.”

**STATISTICAL ANALYSIS**

Statistical analyses were not performed for seropositivity rates (% seropositivity) or GMTs and so the immunogenicity results are descriptive in nature. Protective efficacy rates were compared among groups and immunisation schedules using Fisher’s exact test with an α level of 0.05.

**Results**

The details of the immunisation schedules with or without immunoglobulin at birth are shown in table 1. Overall, 254 analysable neonates were enrolled into the three studies.

At 12 months of age, 2.5% (6/243) of the neonates were positive for HBsAg, and remained so during the follow up period (tables 1 and 2). The protective efficacy of the recombinant hepatitis B vaccine at month 12 is also shown in table 1. The overall protective efficacy is 96.2%; that for the neonates immunised at 0, 1, and 6 months with or without immunoglobulin is 96.1%; and the protective efficacy is 96.3% for the neonates vaccinated at 0, 1, 2, and 12 months with or without immunoglobulin, with no significant difference in protective efficacy between the two immunisation schedules (P = 1.0). At month 24 in group 4 NB, one infant out of 41 became HBsAg positive and was not included in the protective efficacy calculation at month 12 (table 2). The protective efficacy at month 24 in group 4 was 92.8% (table 1).

**ANTI-HBs IMMUNOGENICITY**

One month after completion of the 0, 1, 2, and 12 month immunisation course, the seropositivity rates in groups 1 and 2 were 100%, with GMTs of 3341 and 4703 mU/ml; when measured at month 9 after vaccination at months 0, 1, and 6, the percentage seropositivity for group 3 and 4 was 98.2% and 96.6%, respectively, with GMTs of 507 and 317 mU/ml.

The percentage seropositivity and GMTs in all groups tended to decrease with time, as

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Table 1. Protective efficacy (PE) against HBsAg chronic carriage for each group, and overall

<table>
<thead>
<tr>
<th>Groups</th>
<th>Immunoglobulin administration</th>
<th>Chronic carrier rate* at month 12</th>
<th>PE† (%) at month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0, 1, 2, 12, (60) No</td>
<td>2/59</td>
<td>94.8</td>
</tr>
<tr>
<td>2</td>
<td>0, 1, 2, 12, (60) Yes</td>
<td>1/65</td>
<td>97.6</td>
</tr>
<tr>
<td>3</td>
<td>0, 1, 6, (60) No</td>
<td>3/59</td>
<td>92.2</td>
</tr>
<tr>
<td>4</td>
<td>0, 1, 6, (60) Yes</td>
<td>0/60</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>6/243</td>
<td>96.2</td>
</tr>
</tbody>
</table>

* Based on: two chronic carriers in group 1 B confirmed at month 9, one in group 3 NB confirmed at month 12, two in group 3 NB and one in group 2 NB confirmed at month 24, and one in group 4 NB confirmed at month 36.
† Assuming a 65% rate of chronic carriage at 12 months of age in unvaccinated neonates. At month 24, one of 41 infants in group 4 became a chronic carrier: this gives a PE of 92.8% assuming a 34% rate of chronic carriage between 1 and 2 years of age in unvaccinated infants. Using Fisher’s exact test, there was no significant difference in PE rates among the four groups (P=n.s.27).

**STUDY POPULATION AND DESIGN**

Prospective mothers who had been pregnant for 6–7 months were screened for hepatitis B infection markers at the antenatal clinic of Chulalongkorn University in Bangkok, as described in detail elsewhere. All enrolled neonates had a minimum birthweight of 2 kg and a 5 minute Apgar score of at least 7 at birth. The study protocols were approved by the Ethics Committee of the Faculty of Medicine at Chulalongkorn Hospital, and were conducted according to the Declaration of Helsinki and its amendments. Informed consent was given by the parents of the neonates before enrolment into the study.

The details of the study design are shown in table 1. The first two studies (groups 1 B, 1 NB, and 2 NB) were open in design. The neonates were vaccinated at birth, then at months 1, 2, and 12 (365 ± 30 days after the first dose) of age. Group 2 NB neonates also received immunoglobulin at birth. The neonates enrolled into the third study were randomised and administered either vaccine only (group 3 NB), vaccine only with a booster at month 60 (group 3 B), vaccine with immunoglobulin at birth (group 4 NB), or vaccine with immunoglobulin at birth and a vaccine booster at month 60 (group 4 B), all four following initial immunisation at months 0, 1 (30 ± 10 days after the first dose), and 6 (180 ± 30 days after the first dose). In all three studies further vaccination of the neonates at month 60 was offered to parents who agreed to return to the study centre with their children at this time. The children were followed up by correspondence with their parents or guardians.

**LABORATORY ANALYSIS**

Each blood sample was tested with commercially available test kits (Abbott Laboratories, Chicago, Illinois). HBsAg was measured using Auszyme II/Austria II (monoclonal antibody based), HBcAg by HBe, total anti-HBc with Corab (monoclonal antibody based), and anti-HBs by Ausab (polyclonal antibody based). Anti-HBs titres were expressed in mU/ml and calculated using a World Health Organisation standard.²⁵ The assay cutoff was set at > 1 mU/ml, and seropositive titres were defined as > 10 mU/ml. The mean GMTs of serum anti-HBs titres (GMTs) were determined solely for infants who were negative for HBsAg and with titres > 1 mU/ml.
measured between months 12 and 60; at month 12, 98.3% (232/236) of infants had anti-HBs titres >10 mU/ml at month 24, 95.7% (199/208) had titres >10 mU/ml by the time of booster administration at month 60, 89.8% (159/177) of infants had anti-HBs titres >10 mU/ml. When measured at month 61, a sharp increase in both percentage seropositivity and GMTs was observed in the children who received a booster vaccination at month 60. For the groups of infants who were revaccinated at this time, the percentage seropositivity increased to 100% (62/62), with anamnestic rises in GMTs. For the 18 infants with anti-HBs titres <10 mU/ml at month 60, seven received no booster and 11 were boosted at month 60. The seven without booster were either lost to follow up or remained with anti-HBs <10 mU/ml beyond month 60; for the 11 who were boosted at month 60, all had anti-HBs titres >10 mU/ml at month 61, with a rise in GMT from 4 to 619 mU/ml.

**LOSS OF PASSIVELY ACQUIRED ANTI-HBC:**

At birth, all neonates except two in group 1 NB were anti-HBC positive. The seven HBsAg chronic carriers were anti-HBC positive for all the blood samples drawn during the follow up period. For the continuing 247 neonates, nine stayed anti-HBC positive while being lost to follow up within the first two years, and one subject lost anti-HBC between months 24 and 60. For those who were followed up until at least month 36, six stayed anti-HBC positive, one remained positive for anti-HBC until month 60 and became negative at month 61, and the remaining neonates lost their anti-HBC within the first three years of age.

**SILENT INFECTIONS IN HBsAg NEGATIVE BABIES**

The six subjects who remained positive for anti-HBC during the follow up were considered to have been infected at birth or during infancy, although the exact time of infection could not be assessed from these results. For the 231 neonates who did become anti-HBC negative during the study, anti-HBC reappeared in 14 blood samples among 6.1% (14/231) of subjects (tables 3 and 4). Therefore, when considering the number of subjects who were either continuously anti-HBC positive or who had reappearance of anti-HBC, 20 silent infections occurred during the follow up. Five of the 14 anti-HBC reappearances were without a simultaneous anti-HBs rise (table 3): one child in group 1 B was positive at months 60 and 61; one child in group 1 NB was positive at months 60, 84, and 96; another in group 2 NB was positive at months 24, 36, 48 and then lost to follow up; and the remaining two children (in groups 2 NB and 3 NB) were positive at months 36, 60, and subsequently lost to follow up (table 3). In the five blood samples from five neonates before the reappearance of anti-HBC, 60% (3/5) had anti-HBs titres below 100 mU/ml, with a GMT of 75 mU/ml. In the nine neonates who had an anti-HBC reappearance also accompanied by an anti-HBs rise (table 4), 78% (7/9) had anti-HBs titres <100 mU/ml with a GMT of 36 mU/ml.

**CHANGES IN ANTI-HBS TITRES**

For the blood samples taken at yearly intervals during follow up in the HBsAg negative children who also lost their passively acquired maternal anti-HBC, all rises in anti-HBs titres that were not associated with vaccine administration were recorded. Overall, anti-HBs rises were shown in 33 blood samples from 31 children. A more than fourfold increase in anti-HBs was observed in 28 serum samples from 27 children (11.7%), and a greater than 10-fold increase in anti-HBs was noticed in 16 blood samples taken from 16 children (6.9%).

Nine of these anti-HBs rises occurred in the children who had a concomitant anti-HBC reappearance at some stage during follow up, the details of which are also shown in table 4. For the remaining 24 anti-HBs rises reappearing in 23 children that were not accompanied by either anti-HBC or HBsAg, the blood samples before the anti-HBs rises showed a GMT of 34 mU/ml, with 83% (20/24) having anti-HBs titres of less than 100 mU/ml. For these 23 children, one neonate in group 3 NB who had an anti-HBs rise from 4 to 45 mU/ml between months 9 and 12 was transiently positive for HBsAg at month 6, and also had a transient anti-HBC reappearance at month 60 together with a rise in anti-HBs from 14 to 17 mU/ml. Two other children with anti-HBs only reappearances also experienced anti-HBC only temporary reappearances, but at different times. One of these infants (in group 1B) had only an anti-HBs rise from month 24 to month 36 (29 to 720 mU/ml), with the reappearance of anti-HBC only at month 84; the other (in group 4 NB) only had an anti-HBs rise from month 24 to 36 (11 to 323 mU/ml) with anti-HBC only reappearing at month 60.

**Discussion**

These three studies show that 10 µg of recombinant hepatitis B vaccine is effective at preventing high risk neonates born to mothers positive for both the hepatitis B surface and HBc antigens from becoming infected with hepatitis B during the first eight years of life. To

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### Table 2: Anti-HBs (in mU/ml), anti-HBC, and HBsAg serological details for the seven chronic HBsAg carriers

| Group | 0 | 1 | 2 | 4 | 6 | 9 | 12 | 13 | 24 | 36 | 0 | 1 | 2 | 4 | 6 | 9 | 12 | 13 | 24 | 36 |
|-------|---|---|---|---|---|---|----|----|----|----|---|---|---|---|---|---|----|----|----|----|----|----|
| 1 B   | <1 | <1 | <1 | <1 | <1 | <1 | <1 | <1 | <1 | <1 | 4  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| 1 B   | <1 | <1 | <1 | <1 | <1 | <1 | <1 | <1 | <1 | <1 | 4  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| 2 NB  | <1 | 77 | 36 | 7  | <1 | <1 | <1 | <1 | <1 | <1 | 4  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| 3 NB  | <1 | 120| 34 | <1 | <1 | <1 | <1 | 1.5 | 11 | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| 3 NB  | <1 | <1 | <1 | 25 | 12 | 56 | 25 | <1 | <1 | <1 | 4  | 7  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| 3 NB  | <1 | <1 | <1 | <1 | 2  | 4  | 7  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| 4 NB  | 7  | 65 | 26 | 3  | 6  | <1 | 8  | 4  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |

To
our knowledge, this is the longest follow up performed to date which shows the protective efficacy of recombinant hepatitis B vaccines in such neonates. The protective efficacy was similar in all groups at month 12 with no significant differences between the groups (table 1).

From initiation of vaccination at birth until 8 years of age, only six out of 243 (2.5%) neonates became chronic carriers within the first year of life. This low rate of overall chronic carriage is equivalent to the protective efficacy achieved at 12 months of age in a similar population of neonates who received 10 µg of the same vaccine at months 0, 1, 2, and 12, together with immunoglobulin at birth (2.5% vs 2%).

In addition, the 2.5% rate of chronic HBsAg carriage compares favourably with those of chronic carriage achieved with other recombinant hepatitis B vaccines administered to neonates of mothers positive for HBsAg and HBeAg. In one study where 2.5 µg of another recombinant vaccine was administered at months 0, 1, 2 and 12 without immunoglobulin, 30.4% (7/23) became chronic carriers by month 13. In two further studies where 5 µg doses of this different recombinant hepatitis B vaccine were administered at months 0, 1, and either 6 or 9, concomitantly with immunoglobulin at birth, 10.5% (2/19) and 5.4% (1/35) became hepatitis B carriers.

The high anti-HBs titres achieved after completing a full immunisation course with this vaccine persist well beyond the period of follow up. Overall, the percentage of neonates with anti-HBs ≥ 10 mIU/ml was 89.8% (159/177) at month 60 before booster administration. Furthermore, in the group of neonates (group 1 NB) who were not boosted at month 60 and followed up to month 96, the percentage seropositivity was still 95.5% (116-1115).

Table 3  Anti-HBs titres for neonates in each group

<table>
<thead>
<tr>
<th>Group</th>
<th>Month</th>
<th>9</th>
<th>12</th>
<th>13</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>61</th>
<th>72</th>
<th>84</th>
<th>96</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 B</td>
<td>N</td>
<td>50</td>
<td>57</td>
<td>56</td>
<td>48</td>
<td>49</td>
<td>45</td>
<td>46</td>
<td>20</td>
<td>20</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>% SP (95% CI)</td>
<td>100</td>
<td>98.2</td>
<td>100</td>
<td>97.9</td>
<td>100</td>
<td>100</td>
<td>93.5</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GMT (mIU/ml)</td>
<td>91.1-100</td>
<td>89.3-99.9</td>
<td>92.0-100</td>
<td>87.5-99.9</td>
<td>90.9-100</td>
<td>90.2-100</td>
<td>93.5-99.8</td>
<td>80.0-100</td>
<td>80.0-100</td>
<td>78.1-100</td>
<td>75.9-100</td>
</tr>
<tr>
<td>1 NB</td>
<td>N</td>
<td>236-451</td>
<td>121-226</td>
<td>2264-4931</td>
<td>233-621</td>
<td>214-526</td>
<td>112-266</td>
<td>97-250</td>
<td>2996-14907</td>
<td>390-3182</td>
<td>306-1862</td>
<td>143-1510</td>
</tr>
</tbody>
</table>

Table 4  Vaccinated neonates experiencing permanent anti-HBs re-emergence (AR) without an accompanying rise in anti-HBs

<table>
<thead>
<tr>
<th>Immunisation group</th>
<th>No of subjects</th>
<th>Sex</th>
<th>Time of AR (months)</th>
<th>Anti-HBs titre (mIU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 B (n=20)</td>
<td>1 M</td>
<td>60</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>1 NB (n=40)</td>
<td>1 F</td>
<td>60</td>
<td>290</td>
<td>18</td>
</tr>
<tr>
<td>2 NB (n=53)</td>
<td>2 F</td>
<td>24</td>
<td>990</td>
<td>120</td>
</tr>
<tr>
<td>3 NB (n=34)</td>
<td>1 F</td>
<td>36</td>
<td>34</td>
<td>33</td>
</tr>
</tbody>
</table>

% SP = seroprotection rate (10 mIU/ml); GMT = geometric mean titre.
either a different recombinant hepatitis B vacci-
cine or a plasma derived vaccine, 44% (19/43) of
the recombinant vaccine recipients, and
83% (33/40) of the plasma derived vaccine
recipients had anti-HBs <10 mIU/ml at month
60.23 In these two studies as well as ours, the
anti-HBs titres were measured using the same
serological test. These results have important
implications for the long term implementation
of effective immunisation programmes against
hepatitis B.

There were only 20 silent infections in the
HBsAg negative neonates during the first eight
years of follow up. In these subjects with sero-
logical indication of infection, all became posi-
tive for anti-HBc without detectable titres of
HBsAg or clinical hepatitis. Therefore, in high
risk neonates this vaccine seems to provide
lasting protection against horizontally acquired
virus.

After month 60, five children showed
evidence of re-exposure to HBV: one had
re-emergence of anti-HBc with a simultaneous
rise in anti-HBs, two children experienced
>4-fold increases in anti-HBs titres, and two had
>10-fold anti-HBs rises. Four re-
exposures occurred in groups that did not
receive a booster dose at 5 years of age, from a
total of 204 blood samples (2.0%) taken from
105 (3.8%) children. The remaining re-
exposure, a >4-fold rise in anti-HBs from
151 blood samples, overall (0.7%), occurred in
62 (1.6%) children who did receive a month 60
booster. Therefore, after month 60, although
the frequency of anti-HBs “natural boosters” is
comparable between vaccinees who do and do
not receive an additional vaccination at month
60, in order to overcome hepatitis B from an
epidemiological point of view, a booster at 5–6
or 11–12 years old would reduce HBV
infection, viral circulation, and transmission
substantially.

As interruption of HBsAg carriage is the
primary aim of immunisation programmes in
high risk neonates, it could be argued that booster
administration is not necessary at month 60.
Nevertheless, such children could be at a
higher risk for chronic HBsAg reappearance later
on in life—for example, when these children
become adolescents and become sexually active, a
known risk factor for hepatitis B infection.
Moreover, these children are already at increased risk of horizontal hepatitis
infection, as they were born to mothers positive
for both HBsAg and HBeAg, and therefore
other family members or siblings would
probably also be positive for hepatitis B mark-
ers. It would thus seem advisable to follow up
all neonates of HBsAg and HBeAg positive
mothers who have received their full immuni-
sation course against hepatitis B to ensure that
these neonates maintain protective anti-
HBs levels and do not become infected with the
hepatitis B virus.

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