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1 Efficacy of a Locally-Manufactured Hepatitis B Vaccine on Newborns in the Taiwanese Mass Hepatitis B Vaccination Program
11 Cases of Notifiable and Reportable Diseases, Taiwan-Fukien Area

# Efficacy of a Locally-Manufactured Hepatitis B Vaccine on Newborns in the Taiwanese Mass Hepatitis B Vaccination Program

Abstract

In September 1987, Taiwan began to use, in its mass vaccination program against Hepatitis B, a plasma-derived hepatitis B vaccine manufactured locally by Lifeguard Pharmaceutical, Inc. To assess both the immunological and the protective effects of this domestically-manufactured hepatitis B vaccine used in the program, the vaccinated children, all aged two years, were grouped into three categories according to the degree of hepatitis B infectivity of their mothers.

A total of 1,079 children were selected by the stratified random sampling method, and their blood specimens were collected for HBsAg, anti-HBs and anti-HBc testing. A total of 471 children were born to highly infectious mothers (HBeAg positive or HBsAg titers by RPHA method >1:2,560); these children had received, on schedule, both HBIG and four doses of the domestically-manufactured vaccine. Their HBsAg positive rate had declined from 90% (historical control) to 15%, achieving a protective efficacy of 83.3%. Another 351 children, born to less-infectious mothers (HBeAg negative or HBsAg titers by RPHA method <1:2,560), had received, on schedule, four doses of the vaccine. Their HBsAg positive rate had decreased to 1%, reflecting a protective effect of 93.3%. The remaining 257 children were born to HBsAg-negative mothers and had received, on schedule, four doses of the hepatitis B vaccine. None of them became hepatitis B carriers, and 91% of them developed antibodies. The geometric mean of the titer of hepatitis B surface antibody in each group was more than 100 mIU/mL.

These results correspond to findings from studies of parental plasma vaccines manufactured by the Pasteur Institute[1]. It can therefore be concluded that the plasma hepatitis B vaccine manufactured by the local factory, that was used in the mass vaccination program against hepatitis B in Taiwan, has produced a protective effect, by preventing hepatitis B infection and eliminating the risk of

**prevention and control of hepatitis B in Taiwan.**

## Introduction

Hepatitis B infection and its sequelae are important public health issues in Taiwan where, for the general population, the hepatitis B carrier rate is as high as 15-20%[2,3], the highest in the world. Chronic hepatitis is also prevalent. Cirrhosis of the liver and hepatoma are the major causes of death here[4,5] and evidence shows that chronic carriers are closely associated with these liver diseases[6-8]. Prevention and control of hepatitis B infection have, therefore, become an imperative public health issue in Taiwan.

In Taiwan, vertical transmission of hepatitis B from mothers to children is common. Of children born to carrier mothers, 40% are found to be infected and themselves also become chronic carriers[9]. In mothers with high infectivity (HBeAg positive), the chance of their children being infected and remaining chronic carriers is 86%-96%[9-11]. Studies have shown that hepatitis B vaccination can effectively prevent vertical transmission from mothers to children[12-14].

A program to implement mass hepatitis B vaccination in Taiwan was started on July 1, 1984. Initially, babies born to HBsAg positive mothers were given the plasma hepatitis B vaccine manufactured by the Pasteur Institute of France. Beginning in September 1987, the hepatitis B vaccine used in the program has been that manufactured by the local Lifeguard Pharmaceutical, Inc. utilizing technology transferred by the Pasteur Insitute. To better assess and understand the locally-produced vaccine's effect, the present study followed up 1,079 2-year-old children who had received four doses of the Lifeguard hepatitis B vaccine.

## Materials and Methods

Subjects for Study:

In the period between September 1990 and February 1991 all had received four doses of plasma hepatitis B vaccine manufactured domestically by Lifeguard Pharmaceutical, Inc.

Study groups:

"Vaccination-on-schedule" means that the four doses should be given successively as follows:

The first dose was administered within one week after birth or within eight days, but not including the eighth day. The second dose was administered within a 4-6 week (or 28-42 day) period after the first dose The third dose was administered at the same interval, but after Dose II The fourth dose was administered within a 9-11

month (or 271-330 day) interval, but after the third dose. For children born to highly-infectious mothers, in addition to the four doses described above, HBIG had also been given within 24 hours after birth.

The study groups were defined in the following table:

| Group | Hepatitis B Test Results of Mothers | Vaccination Status |
|---|---|---|
| A | HBsAg(+) and HBeAg(+) or HBsAg titer by RPHA > 1:2,560 (high infectivity) | HBIG and vaccine on schedule |
| B | HBsAg(+) but HBeAg(−) or HBsAg titer by RPHA < 1:2,560 (low infectivity) | vaccination on schedule |
| C | HBsAg(−) (non-carrier) | vaccination on schedule |

Size of Samples:

Using the formula $n = \frac{Z^2 \cdot P(1-P)}{d^2}$ to calculate the needed sample size for each study group we assumed that; (1) the expected positive rates (P) of the surface antibody in each of the A, B and C groups were 91%, 85% and 90%, respectively; (2) the difference (d) between the actual surface antibody positive rate and the expected one was ±5%; and (3) the two-tailed test $\alpha$ was 0.05. The minimum size of samples in each of A, B and C groups was then calculated to be 500, 400 and 300, respectively. To make up for refusals to be vaccinated and replace any missing cases, 20% more subjects were added to make the actual corresponding sampling sizes of 600, 477 and 358. The National Hepatitis B Program Data Bank, sponsored by the Department of Health, maintains the records of pregnant women and vaccinated newborns. Using this database, random samples were selected monthly to allow follow-up visits and blood collection from September 1990 to February 1991.

Blood collection and Serum Testing:

Each of the newborns randomly sampled by the above method was visited by a local public health nurse who interviewed the parents, using a standard questionnaire. That questionnaire noted reasons for any interview failure, refusals to be interviewed, blood collection results and any other findings from the visit. From each infant 5 ml of venous blood was taken. After separation, the serum samples were sent to the Hepatitis Research Center at National Taiwan University Hospital and tested with radioimmunoassays, for HBsAg, anti-HBc, anti-HBs and surface antibody titer. Reagents used were Ausria II, Ausab and Corab, all from Abbott Laboratories, North Chicago, Illinois.

Statistical analysis:

Data collected from the questionnaire interviews and laboratory tests were filed in computers. Pairwise differences in positive rates among groups were tested either with chi square tests or Z tests for two binomial propartions. Differences in the average values of surface antibody potency were compared with Student's *t*-tests.

## Results

Of the children aged two years in the period between September 1990 and February 1991 who had received four doses of domestically- manufactured serum hepatitis B vaccine, 1,435 were randomly selected (see Table 1). From those, 1,301 interviews were conducted (90.1%); 1,133 (87%) agreed to participate in the survey; 170 (13%) refused to be involved. Reasons given for refusal were that: 18% were "not feeling well"; the parents of 45% refused to allow blood to be taken; 32% were lost to follow-up; 3% had already participated in other related study projects; and 2% for other various reasons.

**Table 1. Children in the Study by Group**

| | Group | | | |
|---|---|---|---|---|
| Status of mothers | A | B | C | Total |
| e Antigen | + | — | — | |
| surface antigen titer* | ≥2,560 | <2,560 | — | |
| Vaccination | | | | |
| HBIG | yes | no | no | |
| vaccination on schedule | yes | yes | yes | |
| Children | | | | |
| sample size | 600 | 477 | 358 | 1,435 |
| No. interviewed | 543 | 441 | 319 | 1,303 |
| No. enrolled | 490 | 377 | 266 | 1,133 |
| No. laboratory tested | 471 | 351 | 257 | 1,079 |
| male | 246 | 189 | 134 | 569 |
| female | 225 | 162 | 123 | 510 |

* by RPHA method

The serum specimens from the 1,079 children among the 1,133 whose blood had been taken were adequate for testing. Of these subjects, 569 were male and 510 female (see Table 1). There were no significant differences in sex and age distribution between groups. The average age was 2.1±0.1 years.

Findings of laboratory testing for HBsAg, anti-HBs and anti-HBc are shown in Table 2. HBsAg positive rates were 15%, 1% and 0%; anti-HBs positive rates, 78%, 84% and 91%; anti-HBc positive rates 30%, 4% and 2%; and rates without serum marks were 7%, 14% and 9% in groups A, B and C , respectively. Among these three groups, 900 cases (83%) were surface antibody positive. Of those, 899 cases had sufficient sera for testing surface antibody titer, with findings shown in Figure 1. Groups A, B and C, 12%, 13% and 9%, respectively, gave a surface antibody potency lower than 10 mIU/mL; 38%, 35% and 32% of the children showed a potency of 11-100 mIU/mL; 36%, 33% and 39% of them, a potency of 101-1,000 mIU/mL; and 14%, 19% and 20% of them, a potency higher than 1,000 mIU/mL. The geometric mean titers of surface antibody potency in each group (102±7, 126±8 and 163±8 mIU/ml, respectively) were higher than 100 mIU/mL. The difference among the Groups was all statistically significant ($p<0.001$).

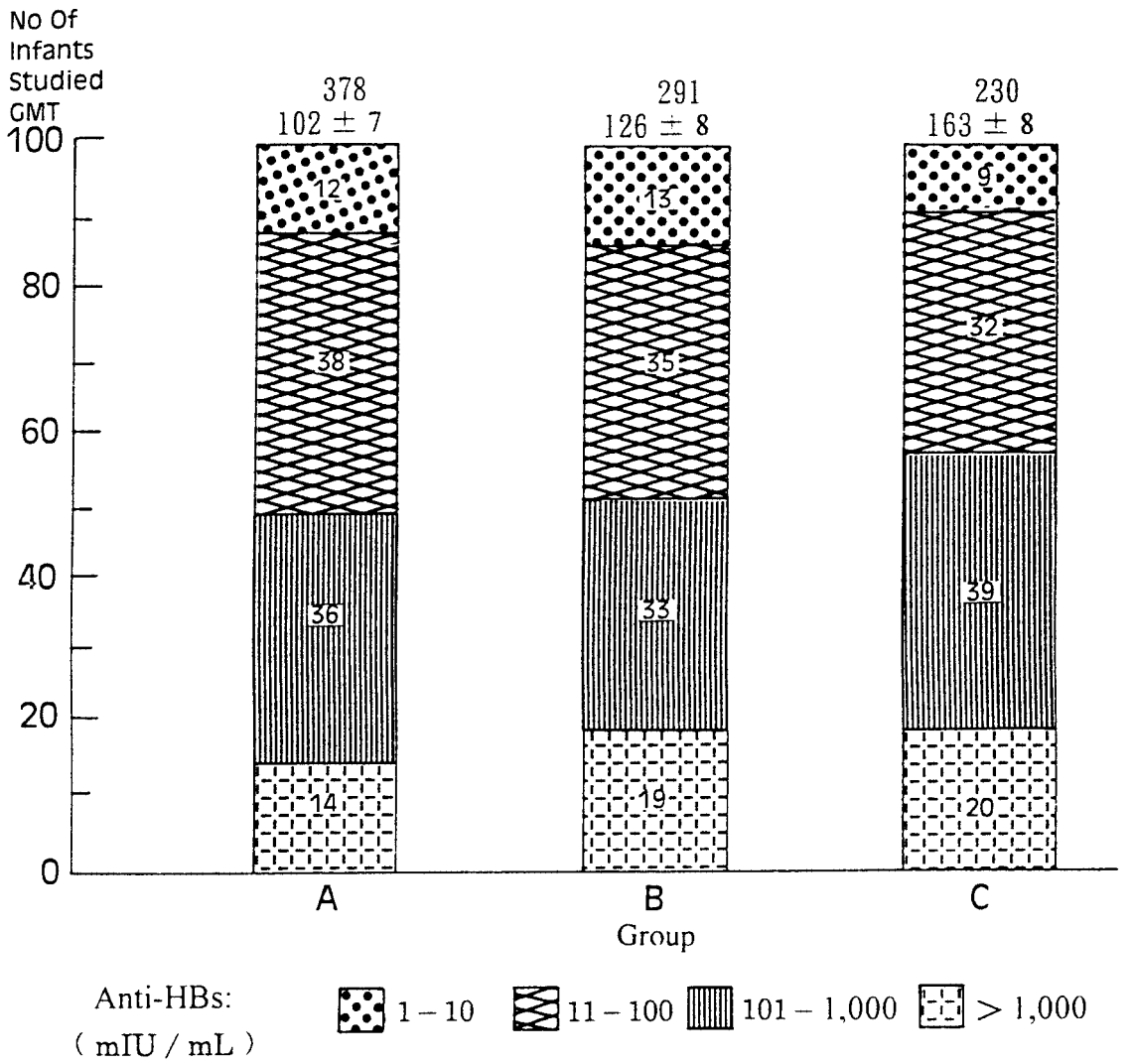
**Table 2. Results of Serological Testing**

| Serological Testing | | | Group | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | A | | B | | C | | | |
| HBsAg | anti-HBc | anti-HBs | No. | % | No. | % | No. | % | No. | % |
| — | + | — | 3 | 1 | 0 | 0 | 0 | 0 | 3 | 0 |
| — | + | + | 66 | 14 | 12 | 3 | 6 | 2 | 84 | 8 |
| — | — | + | 302 | 64 | 285 | 81 | 229 | 89 | 816 | 75 |
| + | + | — | 68 | 15 | 3 | 1 | 0 | 0 | 71 | 7 |
| + | — | — | 1 | 0 | 1 | 0 | 0 | 0 | 2 | 0 |
| — | — | — | 31 | 7 | 50 | 14 | 22 | 9 | 103 | 10 |
| Total | | | 471 | 100 | 351 | 100 | 257 | 100 | 1,079 | 100 |

## Discussion

A mass vaccination program against hepatitis B began in Taiwan on July 1, 1984. The program, aimed primarily at the prevention of hepatitis B in infants and children, was initiated because Taiwan has always been a high hepatitis B infection

**Figure 1. Geometric Average of Surface Antibody Potency (mIU/mL) by Group**



area and those infected with the hepatitis B in early life easily become chronic carriers. The program required pregnant women to accept ante-natal testing for HBsAg. Those found to be positive were further tested for HBeAg or RPHA potency of HBsAg. Babies born to women of high infectivity (HBeAg positive or RPHA potency of HBsAg $\geq$1:2,560) were given HBIG within 24 hours after birth, and then one dose each of vaccine within 3-5 days after birth, at one month, two months and one year. Babies born to either low-infectivity carrier mothers (HBeAg negative or RPHA potency of HBsAg 1:2,560) or non-carrier mothers were given only four doses of the vaccine. The Department of Health maintains a national database of hepatitis B testing of pregnant women and of the vaccination of infants against hepatitis B. The present study used stratified random sampling from these data to identify two-year-old infants who had received four doses of the serum hepatitis B vaccine domestically-manufactured by Lifeguard Pharmaceutical, Inc. Thus, assessment of the immunological and preventive effects of this vaccine as it was used in a mass vaccination program against hepatitis B was possible. The subjects of this study were representative of the population-at-large.

Carrier mothers' children, if tested positive for HBsAg, are likely to be chronic carriers. Therefore, in the present study, two-year-old HBsAg positive children were considered to be chronic carriers. Carrier rate after hepatitis B vaccination is much lower than the rate after spontaneous infection[10,11,13,14]. The 471 babies born to mothers of high infectivity were given both HBIG and four doses of vaccine on schedule (passive and active immunity); they had a 15% carrier rate. Previous studies have shown that their carrier rates would have been as high as 86%-96% had they not been given hepatitis B vaccine[10,11]. Taking this group as historical controls, it was estimated that passive and active vaccinations on schedule must have produced an efficacy as high as 83%-84%. This efficacy is slightly lower than findings of some small-scale clinical trials[13,19,20], but it is similar to the findings of some other studies[14,21,22] and to another study which had used a similar vaccination schedule[14]. It can, therefore, be concluded that children born to mothers of high infectivity can be effectively prevented from hepatitis B infection through vaccination.

Chances of HBeAg negative mothers or carrier mothers of low HBsAg titer transmitting the disease to the newborn are as low as 10%-21%[10,11]. Of the 351 children in Group B, the number of carriers was 4 (1%), giving a protective efficacy of 90%-95%. Of these four cases, three mothers had tested as HBsAg positive and HBeAg negative with either EIA or RIA methods; one tested with RPHA method as HBsAg positive, but with a titer lower than 1:2,560. Testing methods of different accuracy could have read an HBeAg positive as negative. A potency of lower than 1:2,560 found by RPHA method exempted the child from HBIG and thus may reduce the protective effect. Children born to mothers of low infectivity could still become carriers, and highly fatal fulminant hepatitis often occurs in children of this category[23,24]. Vaccination should also be given for them. After vaccination, 84% of the two-year-olds still had high surface antibody potency and could be protected from hepatitis B infection in the future. None of the 257 children born to surface antigen negative mothers (Group C) became carriers, and 91% of them produced hepatitis B surface antibodies.

The present study also showed that some children, despite having been vaccinated against hepatitis B, were infected by hepatitis B virus. Of the 471 children born to mothers of high infectivity (Group A, vaccinated on schedule), 30% were anti-HBc positive and half of them were carriers. Maternal anti-HBc which had passed through the placenta disappeared when the children were two years old. The existence of anti-HBc in these two-year-old children meant that they had been infected by hepatitis B virus. The rest of the children were not infected and they produced a relatively high level of surface antibodies and had immunity.

In general, 83% of children aged two years had produced surface antibodies one year after the completion of the four doses of the hepatitis vaccine. Of them, 89% had a surface antibody higher than the protective potency (10 mIU/mL). Though the level of potency varied, the average potency in each group was higher than 100 mIU/mL. Further studies, however, are needed to understand whether children who have lost surface antibodies are still protected and whether spontaneous re-infection will stimulate the immune system to develop higher antibody. In the present study, 10% of the children did not carry any hepatitis B virus markers in their sera. This percentage, slightly higher than the findings of some pilot studies[13,19,21], was in line with other studies[20,22]. These children either did not develop immunological reactions to hepatitis B, or the reaction was weak and the antibodies had disappeared by two years of age and then became undetectable.

In conclusion, the locally-manufactured plasma hepatitis B vaccine, made by Lifeguard Pharmaceutical, Inc. and used in Taiwan's mass vaccination program of children against hepatitis B, has produced a satisfactory efficacy. Therefore, the goal of preventing chronic hepatitis B virus infection and the related liver diseases could be reached in the near future.

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