# Efficacy of yeast-recombinant hepatitis B vaccine in prevention of perinatal transmission in Saipan

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## Abstract

A yeast-recombinant hepatitis B (HB) vaccine has been produced commercially since 1987. In formal trials in infants of mothers at highest risk of transmitting infection this new vaccine has appeared to be comparable to plasma-derived HB vaccine in effectiveness. To assess the newer vaccine under field conditions we compared the prevalence of markers of HB infection in three to four year old children on the island of Saipan before and after the addition of yeast-recombinant HB vaccine to the schedule of routine infant immunizations. The children in the post-vaccine sample were less likely to have serologic evidence of previous HB infection (4/200 vs. 13/124; prevalence ratio {PR}=0.19, 95% confidence interval {CI}=0.01 to 0.43) or chronic infection (1/200 vs. 11/124; PR=0.06; CI=0.01-0.43). Yeast-recombinant HB vaccines is highly effective in preventing the peri-partum transmission of HB virus under field conditions

## Introduction

The hepatitis B virus (HB) has proven to be the most important cause of chronic liver disease, cirrhosis, and liver cancer throughout much of the world[1,2,3,4,5]. There is considerable evidence that plasma derived HB vaccine is effective in decreasing the occurrence of infection under research[6,7,8,9,10,11] and field conditions[12,13] while there is less evidence for the effectiveness of newer yeast-recombinant vaccine[14,15], especially under field conditions. There is concern that lower antibody titers produced by the newer vaccine may confer less protection than that afforded by the older vaccine[16].

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In the Pacific HB and its sequelae are highly prevalent[17,18,19,20]. Vertical transmission and horizontal transmission during the first few years of life are thought to account for the large majority of these infections[21,22]. In the Northern Mariana Islands the point prevalence of hepatitis B surface antigen (HBsAg) among pregnant women is 7.5%[23].

In 1988 a program of universal infant hepatitis vaccination was begun in the Commonwealth of the Northern Mariana Islands (CNMI), using yeast-recombinant vaccine (Recombivax, Merck, Sharp and Dohme; 5mcg, 2.5mcg and 2.5mcg, within 12 hours and at 1 month and 6 months after delivery). Screening of pregnant women for HBsAg and administration of HB immune globulin (HBIG) to selected infants were not performed as part of the program during the study period. The present study was performed to assess the effectiveness of universal infant HB vaccination with yeast-recombinant vaccine under field conditions in the cohort of children who were vaccinated in the first two years of the program.

## Method

The baseline data in 1984 were collected by household survey in which the island of Saipan was divided into numerous sectors of approximately equal population and all households within randomly chosen sectors were sampled. The follow-up sample in 1994 was obtained by randomly choosing 200 three and four year old children (out of a total cohort of approximately 3000) on Saipan from the computer database of the Commonwealth Health Center in the CNMI. This database contain identifiers for all children known to have been born in the CNMI as well as any child who has ever visited the government hospital, emergency room, or outpatient clinics (these clinics provide over 90% of the primary care services in the island). Homes of the children were visited where blood samples were collected by venipuncture and a standardized questionnaire administered to the child's parents. Care taken was such that immunization status of each child was determined by review of vaccination records.

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Serum samples were tested for HB markers by enzyme linked immunoabsorbent assay. Each sample was tested for hepatitis B core antibody (HBcAb) and hepatitis B surface antibody (HBsAb). Samples positive for HBcAb were also tested for HBsAg.

Children who were HBcAb positive were considered to have been infected at some time with HB. Those who were HBsAg positive were considered to have current (and probably chronic) infection. Those with negative HBcAb and positive HBsAb were considered to be uninfected and to have responded to the vaccine, while those with negative HBcAb and HBsAb were considered to be uninfected and to have not responded or to have had antibody response which had waned beyond the limit of detectability since vaccination.

**" Compared with children in the baseline survey, those in 1994 were significantly less likely to have been ever infected, ie. to be HBcAb positive ... or to be currently infected, ie. HBsAg positive ... "**

The prevalence of a HB marker was taken as the number who tested positive for that marker divided by the total number tested. Prevalence ratios were computed as the prevalence of the marker in 1994 divided by that in 1984. 95% confidence intervals were computed for prevalence ratios using EpiInfo software[24].

## Results

A total of 124 three and four year old children (76 male, 48 female) were sampled in the baseline (1984) survey. Of these, 13 (10.5%) were positive for HBcAb while 11 of these children (9%) were positive for HBsAg. There was no significant difference in the prevalence of these markers by sex.

Of the 200 children in the follow up (1994) survey 111 were male and 89 female. All of the 200 children received at least one dose of HB vaccine and all had received their first dose in the hospital within 24 hours of birth. Five of the children had received only this first dose while seven others had received only two doses of vaccine. The other 188 children (94%) had received all three doses of vaccine within the first year of life. None of the children in the follow-up survey had a history of symptomatic hepatitis B infection. Of all 200 children 173 (86.5%) had received all of the childhood vaccines used at that time in the CNMI (four DPT, three OPV, one MMR, three HepB). Four children (2%) were positive for HBcAb while one child (0.5%) was also positive for HBsAg. All of these four children were male and all had received three doses of hepatitis B vaccine. One hundred and seventy three children (86.5%) were negative for HBcAb and positive for HBsAb, while 23 (11.5%) were negative both for HBcAb and HBsAb. The profile of HBsAb titers of children in the sample is shown in Table 1. Of subjects without evidence of previous infection, 19% of the males and 31% of the females had absent or low (<10mlUml) titers of HBsAb, a difference which did not attain statistical significance.

Compared with children in the baseline survey, those in 1994 were significantly less likely to have been ever infected, ie. to be HBcAb positive (PR=0.19; CI=0.06-0.57) or to be currently infected, ie. HBsAg positive (PR=0.06; CI=0.01-0.43).

**Table 1: Hepatitis B surface antibody titre of 200 children on Saipan Island,1994**

| Titre(mIU/ml) | Number |
|---|---|
| 0 | 23* |
| >0-10 | 21** |
| <10 | 156*** |
| **Total** | **200** |

** Includes one child with positive HBsAg.*
*** Includes one incompletely immunized child (two doses HB Vaccine).*
**** Includes 11 children who were incompletely immunized (five with one dose and six with two doses of HB vaccine) and three other children with positive HBcAb.*

## Discussion

The hepatitis B (HB) vaccination program in the CNMI has been very successful in attaining a high level of vaccine coverage among three-four year old children and in decreasing the prevalence of markers for past and chronic HB infection in these children by 81% and 94% respectively. Part of this success may be attributed to the centralization of health services and the conduct of nearly all births within the hospital in the CNMI. This has allowed for universal administration of the first dose of vaccine very soon after delivery, a practice which is crucial for prevention of peripartum transmission of HB[25].

Of the children in the follow up survey, 10.5% had low levels of HBsAb (between 0 and 10mlU/ml), indicating that they did respond to the vaccine but had waning immunity, while 11.5% had levels that were undetectable. Though these children lack sufficient titers of antibody to reliably protect them should they be exposed to HB, they are already past the age when most infections occur[26,27]. Since members of their cohort have very low rates of chronic infection these children are also at much lower risk of horizontal infection than the generations of children who came before them[28]. Even if they do become infected they run a much lower risk beyond preschool age of

developing chronic infections than had they been infected as infants[13]. The reduction in markers of hepatitis B infection in this study closely parallels the results of a similar study performed in American Samoa using the plasma-derived vaccine in which the rate of HBsAb and HBsAg carriage rates declined 85% and 100% respectively, in three and four year old children following the introduction of infant vaccination[29]. This suggests that the protection afforded by the two vaccines is similar, at least to the age of four years.

The budget for HB vaccination program in the CNMI in 1990 and 1991 (the years that the children in the 1994 survey were vaccinated) was $66,000 (US dollars). Extrapolating to the entire cohort of 3000 three and four year old children residing on Saipan on 1994 a total of 252 chronic infections (CI=156-267) were prevented in this cohort for a cost per chronic infection averted of $261. An estimated 8 children (CI=1-69) in the cohort have chronic infections which were not prevented by the program. Of these infections, 75% might have been prevented by screening pregnant women for chronic infection and giving HBIG at birth to infants of those who are infected[31]. The addition of such screening and administration of HBIG when indicated would have added $38,400 to the cost of the program over two years (at $10 per HBsAg test and $40 per dose of HBIG) at an estimated cost of $6400 per chronic infection averted.

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In communities where health services are less centralized than in the CNMI, the logistics of program administration and corresponding costs are likely to be greater. In populations with a higher prevalence of chronic HB infection among pregnant women, the costs per chronic infection averted in children will be less than these figures, since the total program costs are fixed (with the exception of HBIG, more doses of which will be required in higher prevalence populations). Conversely, the cost per chronic HB infection averted will be much higher in very low prevalence populations.

Each day in the hospital and clinics HB vaccine is administered to infant in the CNMI. Because of the vaccine, the efforts of the staff in these clinics, local appropriations and support from the Centers for Disease Control, many people and their families are spared chronic HB infection each year. Quietly, a public health program in the Marianas Islands is making a difference.

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**" Vaccination is the medical sacrament corresponding to baptism "**

*Samuel Butler (1835 - 1902)*