Progress on the elimination of hepatitis B virus transmission in Micronesia and American Samoa

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Abstract

Hepatitis B virus (HBV) infection is highly endemic in Pacific populations and HBV-induced chronic liver disease is a leading cause of death among adults. Between 1986-89 hepatitis B vaccine was integrated into infant immunization schedules in the U.S.-affiliated Pacific Islands and catch-up vaccination programs were conducted for children up to 6 years of age.

To assess program activities, serologic surveys were conducted in Palau, Chuuk, CNMI and American Samoa, prior to and after program implementation. Immunogenicity studies were conducted to evaluate vaccine performance under 'field conditions'.

The prevalence of chronic HBV infection was low among children born after the integration of hepatitis B vaccine into infant immunization schedules. Vaccination programs in the Pacific should emphasize vaccination at birth and completing the series by 6 months of life.

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Introduction

The consequences of acute and chronic hepatitis B virus (HBV) infection are major public health problems throughout the world. Persons with chronic HBV infection are predisposed to the development of chronic liver disease and have a > 200 fold increased risk of hepatocellular carcinoma when compared to noninfected persons [1,2]. Approximately 45% of the world's population live in areas where the prevalence of chronic HBV infection is > 7% and the lifetime risk of HBV infection is >60%. In these communities, most HBV infections occur at birth or during the first decade of life when the risk of chronic infection is high. Because most early childhood HBV infections are asymptomatic, there is little recognition of acute disease but high rates of chronic liver disease and liver cancer among adults.

HBV is highly endemic in Pacific populations and HBV induced chronic liver disease is a leading cause of death among young adults [3-11]. Between 1987-89, there were 26 deaths due to cirrhosis of the liver or hepatocellular carcinoma in Chuuk State (population 45,000), Federated States of Micronesia (FSM). In a review of death certificates for the years 1986-91, chronic liver disease was the sixth leading cause of death in the FSM.

To prevent premature death due to chronic liver disease, the U.S. Public Health Service, in collaboration with the

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Pacific Island Health Officer's Association, and the U.S. Department of the Interior, implemented a comprehensive program to eliminate HBV transmission in the U.S.-affiliated Pacific Islands. This plan included the integration of hepatitis B vaccine into infant immunization schedules and "catch-up" vaccination programs for children 6 years of age.

Because the clinical manifestations of HBV infection are often absent among newborns and young children, routine surveillance for acute disease does not reflect early childhood transmission within a community. Baseline and follow-up seroprevalence surveys can be used to monitor the incidence of early childhood HBV infections and to evaluate the effectiveness of vaccination programs[11]. To monitor the effectiveness of hepatitis B vaccination programs in the Pacific, immunogenicity studies, vaccination coverage surveys, and seroprevalence surveys have been performed among children born since program implementation. This report summarizes the results of several studies which demonstrate a remarkable reduction in the prevalence of chronic HBV infection among children in the Pacific.

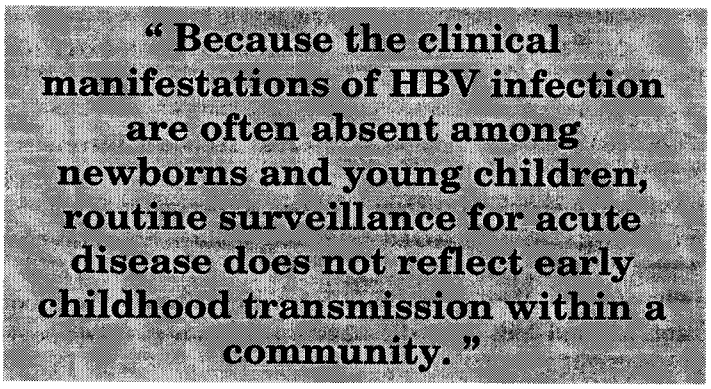
Methods

The U.S.-affiliated Pacific Islands are comprised of six diverse political entities geographically dispersed over the western and south Pacific Ocean. Guam, Commonwealth of the Northern Mariana Islands (CNMI), FSM, Republic of the Marshall Islands (RMI), and Republic of Palau (ROP) and American Samoa participated in the implementation of hepatitis B prevention programs. Due to competing public health priorities, RMI did not participate in the vaccination program at that time.

Program description: Between 1986-87, a comprehensive vaccination program was implemented in American Samoa using plasma-derived vaccine. This program included routine infant immunization, catch-up vaccination of all children ≤ 6 years of age, and serologic screening of the entire population > 6 years with vaccination of susceptible persons. Between 1988-89 hepatitis B vaccine was integrated into infant immunization schedules in the other Pacific countries with a recommended schedule using Recombivax-HB with 5 ug at birth, and 2.5 ug at 2 and 6 months of age. Catch-up vaccination programs were conducted for children up to 6 years of age between 1988-89 using 10 ug of Heptavax at a 0,1,6 month schedule. Some jurisdictions obtained additional vaccine and expanded the catch-up program for older children and Palau has implemented catch-up vaccination programs for the entire population. Because maternal screening for hepatitis B surface antigen (HBsAg) to prevent perinatal HBV transmission was not feasible and/or consistently done, specific programs to prevent perinatal HBV transmission were not recommended at the time of program implementation.

Baseline seroprevalence surveys: Serosurveys were conducted in American Samoa, CNMI (1985) and Palau (1990) on persons in randomly selected households from the general population. In FSM, sera was tested on a sample of children selected to participate in a survey to evaluate vitamin A deficiency in Chuuk State, FSM[12].

Immunogenicity studies: To evaluate the immunogenicity of vaccine under field conditions, studies were conducted in American Samoa (1992) and the Republic of Palau (1992-93). In American Samoa, serologic testing was offered to all 12-14 month children identified over a 1 month period on the capital island of Tutuilla. In Palau, serologic testing was conducted on 12-14 month old infants and their mothers over a one year period in an attempt to obtain serologic test results for the entire birth cohort of 1992.



Cross sectional seroprevalence surveys: To evaluate the long term effectiveness of infant vaccination programs, cross sectional seroprevalence surveys were conducted in American Samoa, CNMI, and FSM. All studies were approved by Institutional Review Boards and used methods to randomly select participants either through the use of birth registries, random selection from schools, or through field teams recruiting participants in randomly selected villages. Vaccination records of survey participants were reviewed and vaccination coverage at the time of the survey was calculated; children without records were classified as unvaccinated.

Evaluation of catch-up vaccination programs: To evaluate the effect of catch-up vaccination programs, cross-sectional studies were conducted among 6-11 year old children in American Samoa in 1990 and 3-6 year old children in Chuuk State, FSM, in 1992. These children were eligible to receive hepatitis B vaccine between the ages of 1-6 years in American Samoa and 1-3 years in Chuuk.

Laboratory methods: Serum samples were tested for total antibody to hepatitis B core antigen (anti-HBc) and antibody to hepatitis B surface antigen (anti-HBs). Samples positive for anti-HBc were tested for hepatitis B surface antigen (HBsAg). Persons were classified as to their hepatitis serologic test results as follows: past or present infection, anti-HBc positive with or without other markers; chronic infection, HBsAg-

Table 1. Immunogenicity of hepatitis B vaccine when integrated into infant immunization schedules of Pacific Island; 1992-94

Study	Schedule (months)	Vaccine/dose (ug)	No. of infants	Seroprotection %*	GMT**
Samoa	0.1 - 2, 6	Recombivax 5, 5, 5	115	95	486
Palau	0.1 - 2, 6	5, 2.5, 2.5	278	93	243

** Seroprotection indicates > 10 mIU anti-HBs.*
*** Geometric mean antibody titer in milli-international units among children who responded to vaccination.*

positive and IgM anti-HBc negative; or immune from vaccination, anti-HBc negative and anti-HBs 10 milli-international units per milliliter (mIU/ml).

Results

Baseline surveys: Baseline seroprevalence surveys revealed a rapid increase in the prevalence of antibody to hepatitis B core antigen between the ages of 1-10 years in all jurisdictions (Figure 1). The rate of increase appeared to be highest in Chuuk where> 70% of children were infected by 8-9 years of age. All surveys revealed a high prevalence of chronic HBV infection which ranged from 7% in American Samoa to 14% among children in Chuuk (Figure 2).

Immunogenicity studies: In American Samoa, 150 infants 12-14 month old were recruited to participate in the immunogenicity study. One infant was anti-HBc-positive and none were HBsAg positive. Overall, 115 noninfected infants received three doses of hepatitis B vaccine and had serologic testing within 7 months after the third dose of vaccine; 109 (95%) of these infants had anti-HBs titers ≥10 mIU/ml (Table 1). The geometric mean antibody titer among infants who responded to vaccination was 486 mIU.

noninfected infants received three doses of hepatitis B vaccine and had serologic testing within 7 months after receiving the third dose of vaccine; 261 (93%) infants had anti-HBs titers > 10 mIU (Table 1). The geometric mean antibody among infants who respond to vaccination was 243 mIU.

Serologic testing was also conducted on 329 mothers of these children; 54 (16%) were HBsAg-positive and 22 (40%) of HBsAg-positive mothers were hepatitis B e antigen (HBeAg) positive. Among infants born to HBsAg-positive women, there was no difference in the prevalence of chronic HBV infection in those who received hepatitis B immune globulin (HBIG) and vaccine at birth (0/25), compared to infants who received vaccine alone (1/21).

Cross sectional surveys: Cross sectional surveys were conducted in several countries to evaluate vaccination coverage and monitor serologic markers for HBV infection among children born after program implementation.

American Samoa: Participants were recruited by random selection from the birth registry (1991) or from schools (1995). Of the 95 three to four year old children sampled in 1991, 82% had received 3 doses of hepatitis B vaccine. Serologic testing revealed that 2 (2%) children were anti-

sitive. Of 435 7-8 survey, 87% had ccine. Overall, 11

Of the 358 infants recruited to participate in the immunogenicity study in Palau, 23 (6%) were anti-HBc positive and 4 (1%) were HBsAg-positive. Overall, 278

HBc positive, and none were HBsAg po year old children enrolled in the 1995 received three doses of hepatitis B vac

r program
0.5%
0.5%
1%
3%
0%

Table 2. Prevalence of chronic HBV infection among children born prior to and after the integration of hepatitis B vaccine into infant immunisation schedules in Pacific communities, 1990 - 96

Site	Follow-up year	No. tested	Age	Vaccination coverage	Chronic infection	
					Before program	Afte
Samoa	1996	435	7 - 8	87%	7%	
CNMI	1995	200	3 - 4	94%	9%	
Pohnpei	1994	364	3 - 4	82%	NA	
Chuuk	1992	544	2	40%	12%	
Samoa	1990	95	3 - 4	82%	8%	

Note: No. tested are the number of children enrolled in follow-up studies during the years indicated.

Table 3. Hepatitis B virus infection, by doses of hepatitis B vaccine received, Chuuk 1992

	Hepatitus B vaccine doses		
Serologic test results	0* (%) n = 114	1 (%) n = 116	2 - 3 (%) n = 312
Past infection	19 (17%)	12 (10%)	26 (8%)
Chronic infection	10 (9%)	3 (3%)	3 (1%)

** Includes children without vaccination records.*

(2.5%) children were anti-HBc positive and 2 (0.5%) were HBsAg-positive. One HBsAg-positive child was unvaccinated and the other had received one dose of vaccine in early childhood (not at birth). Children born after program implementation were less likely to be HBsAg-positive than similar-aged children at baseline (Table 2).

Chuuk: In January, 1992, survey teams visited all the villages on the capital island of Moen and the inhabited islands of Chuuk Lagoon and enrolled children born between January 1 and July 31, 1990. Of the 417 children for whom a vaccination record was located, 48% had received 3 doses of hepatitis B vaccine. Assuming that a child without a record had not been vaccinated, coverage decreased to 37%.

Serologic testing revealed that 57 (11%) children had evidence of HBV infection, and 16 (3%) had chronic infection. Of the 16 children with chronic infection, 2 had received vaccine at birth. In a comparison of vaccination status with serologic status, the prevalence of anti-HBc was inversely related to the number of vaccine doses a child had received (Table 3). Among children who had received two or more doses, 8% had evidence of HBV infection, compared to 10% of children who received one dose, and 17% of unvaccinated children ($p < .05$). In addition, among the 57 antiHBc-positive children, the prevalence of chronic HBV infection was 11% for children who had received two or more doses of vaccine, 25% for children that received one dose, and 60% for unvaccinated children ($p < .05$). Overall, the prevalence of chronic HBV infection was lower than similar-aged children tested at baseline (Table 2).

Serologic testing of 496 mothers of children in the survey revealed that 57 (12%) were HBsAg-positive and that 26% of HBsAg-positive mothers were HBeAg-positive.

Pohnpei and CNMI: Serologic testing was conducted on children enrolled in child health surveys in Pohnpei (1994) and CNMI (1995). Of the 364 children enrolled in the child health survey in Pohnpei, 82% had received three doses of hepatitis B vaccine. Overall, 13 (4%) children had evidence of past or current HBV infection and 4 (1%) children had chronic HBV infection. None of the HBsAg-positive children had received hepatitis B vaccine at birth.

Of the 200 children enrolled in the child health survey in CNMI, 94% had received 3 doses of hepatitis B vaccine. Overall, 4 (2%) children were anti-HBc-positive and 1 (0.5%) child was HBsAg-positive. The prevalence of chronic HBV infection was lower than similar-aged children tested at baseline (Table 2).

Several findings in the immunogenicity surveys and cross sectional studies emphasized the importance of beginning

Table 4. The prevalence of HBV infection among vaccinated children (3 doses) by the timing of the first dose of vaccine, 1990-96

Study / Schedule		Total No.	% HBSAG+	PR	95% CI
[redacted]					
First dose at birth	*No*	30	6.70%	11.4	1.1, 121.1
	Yes	323	0.60%	*ref*	
[redacted]					
First dose at birth	*No*	78	2.6%	*Und.*	0.8 ,
	Yes	217	0%	*ref*	

** 12-14 month old children*
*** 3-4 year old children*
PR - Prevalence ratio (prevalence not at birth/prevalence at birth)
CI - 95% Confidence interval

Table 5. Effect of early childhood hepatitis B vaccination programs on the prevalence of chronic HBV infection in American Samoa and FSM

Group	Age (years)	Before Program	After Program	Prevalence Ratio	95% CI
American Samoa	6-11	8/121 (7)	7/386 (2)	3.6	1.3, 9.8
FSM *	3-6	47/364 (14)	18/302 (6)	2.2	1.3, 3.7

** Chuuk State, Federated States of Micronesia*
Data are no. positive/total (%).
CI = 95% confidence intervals.

the vaccination series at birth. Of the 27 chronic HBV infections detected in all the various follow-up surveys, only 5 children had received vaccine at birth; 1 of these children did not complete the series and another had a prolonged interval between the first and second dose of vaccine. Among fully vaccinated children in Palau and Pohnpei, those who did not receive vaccine at birth were more likely to be HBsAg-positive than children who started the series in the first 3 days of life (Table 4).

Evaluation of catch-up vaccination programs: To evaluate the catch-up vaccination program, 386 children in American Samoa (1991) and 302 children in Chuuk (1992) were enrolled in cross-sectional surveys (Table 4). Overall,

Figure 1. Prevalence of HBV Infection (anti HBc) prior to implementation of Hepatitis B vaccination programs in Pacific communities

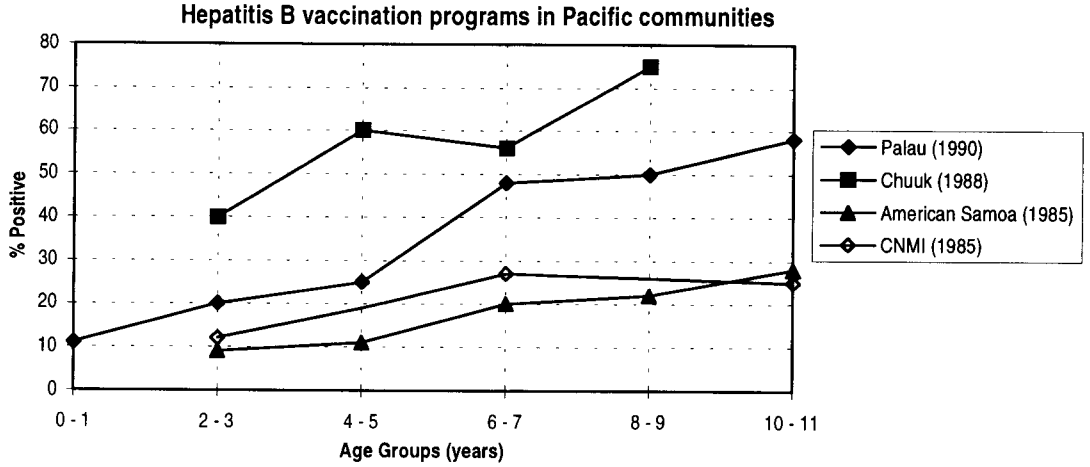
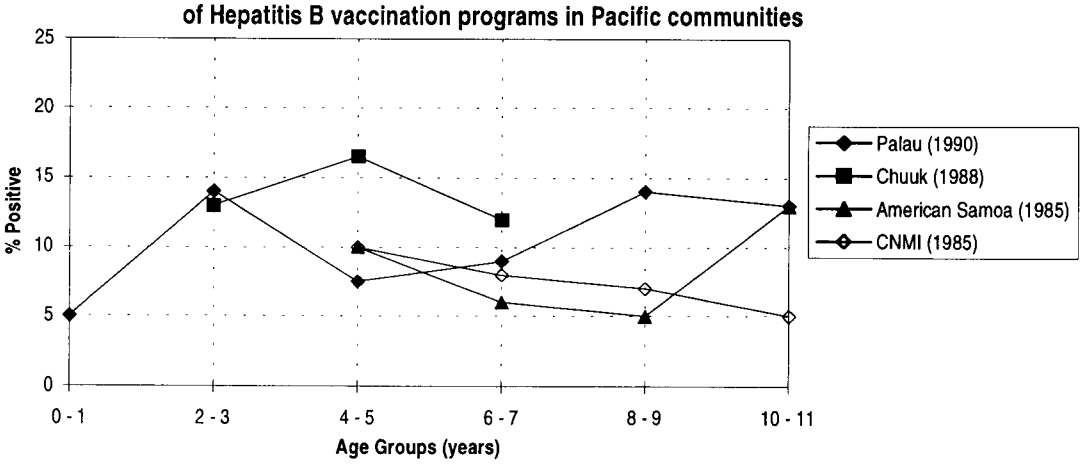


Figure 2. Prevalence of chronic HBV Infection (HBsAg) prior to implementation of Hepatitis B vaccination programs in Pacific communities



78% of children in American Samoa and 80% of children in Chuuk had received three doses of hepatitis B vaccine. The prevalence of chronic HBV infection was 2% among children in American Samoa and 6% among children in Chuuk. Children targeted for the catch-up program were less likely to be HBsAg-positive than similar-aged children tested at baseline (Table 5).

Discussion

The main adverse outcomes associated with HBV infection (cirrhosis and hepatocellular carcinoma) occur in persons with chronic HBV infection. The risk of developing chronic HBV infection varies inversely with age and is highest (up to 90%) for infants infected in the perinatal period[13, 14]. Between 25% and 50% of children infected between ages 1 and 5 years develop chronic infection whereas only 6%-10% of acutely infected older children and adults become carriers. Longitudinal studies of persons with chronic infection indicate 15-25% develop chronic liver disease during their lifetime[2, 15]. Thus, the prevention of chronic HBV infection is the key indicator of program success when evaluating vaccination activities in areas of high endemicity.

Surveys conducted prior to program implementation, revealed a high prevalence of chronic HBV infection among Pacific children, which was due in part to perinatal transmission. The high prevalence of HBsAg and HBeAg among pregnant women indicates a high degree of infectivity and suggests that the pattern of early childhood HBV transmission in the Pacific is similar to Asia's where perinatal HBV transmission accounts for a substantial proportion of the children with chronic HBV infection. Because of the high risk of chronic infection, prevention of perinatal HBV transmission was a high priority during program implementation. Therefore, recommendations included beginning the vaccination series at birth with a dose of vaccine appropriate for infants born to HBsAg-positive women.

"The strategy of routine infant immunization, combined with catchup vaccination of older children was designed to eliminate perinatal and early childhood HBV transmission and reduce the prevalence of chronic HBV infection among Micronesian children."

Several findings in the follow-up surveys indicate that perinatal HBV transmission is now rare or absent. Most survey participants were born prior to implementation of specific programs to prevent perinatal HBV transmission (HBsAg screening of pregnant women, the administration of HBIG and vaccine at birth, completion of the series by 6 months of life), however, few infections were detected among children who had started the vaccination series at birth. For example, in Pohnpei, where maternal HBsAg screening was not done, only 4 children were HBsAg-positive and none of these children started the series at birth. Since the prevalence of chronic infection among pregnant women in Pohnpei is 12%, it is likely that 40-50 of the survey participants were born to HBsAg-positive mothers, and 17-22 would have been infected if vaccine had not been given. In Palau, where maternal HBsAg screening was inconsistently done, the administration of HBIG provided little additional benefit in preventing perinatal HBV transmission. These data indicate vaccine alone (when started at birth) provides excellent protection for infants born to HBsAg-positive women and that specific programs designed to prevent perinatal HBV transmission may not be necessary.

In addition to high rates of perinatal HBV transmission, the baseline serologic surveys demonstrated high rates of early childhood HBV transmission. The implementation of routine infant immunization has resulted in a > 90% reduction in the prevalence of chronic HBV infection in communities where vaccination coverage was > 80%. The finding that 2-4% of children had serologic evidence of HBV infection (anti-HBc-positive) suggests that inapparent infections may occur as a result of residual perinatal or person to person transmission. However, these infections occur at a substantially lower rate than prior to 1986. There is no evidence that persons with asymptomatic HBV infection who do not progress to chronic infection, are at increased risk of chronic liver disease or primary hepatocellular carcinoma[2].

In Chuuk, where comprehensive coverage has been difficult to achieve, clinically significant HBV transmission continues to occur. However, a 75% reduction in the prevalence of chronic infection was still observed, despite vaccination coverage of < 40%. This may be related to several factors:

1. Vaccination records may have been lost and a child's vaccination status was misclassified.
2. Partial vaccination may provide some degree of protection. The immunogenicity studies revealed that under field conditions, the vaccines were highly immunogenic and provided some protection for partially vaccinated children (data not shown). In addition, among children who had received 1-2 doses, the prevalence of anti-HBc and HBsAg was significantly lower than the prevalence of those markers among unvaccinated children. Finally, among the anti-HBc-positive children, those who received 1 or 2 doses of vaccine were less likely to be HBsAg-positive than unvaccinated children. This suggests that partial vaccination may protect children from developing acute infection, as well as protect those

who develop acute infection from developing chronic infection.

3. Children born after program implementation may be less likely to be exposed to HBV than children tested at baseline. The mass catch-up vaccination campaign for older children was highly successful and reduced the prevalence of chronic HBV infection for a large cohort of children. In addition, vaccine-induced protection of at least some infants, may provide enough population-based immunity that children born after program implementation had infrequent exposure to HBsAg-positive children. It is anticipated that, over time, with a reduction in the prevalence of HBV infection and increased vaccination coverage, the prevalence of chronic HBV infection will continue to decline among children in Chuuk.

"It is a tribute to the enthusiasm and dedication of public health personnel in the region. Thanks to their efforts, HBV is a "demerging" pathogen in the Pacific."

The strategy of routine infant immunization, combined with catchup vaccination of older children was designed to eliminate perinatal and early childhood HBV transmission and reduce the prevalence of chronic HBV infection among Micronesian children. Findings from the follow-up surveys indicate that the key elements in program success include vaccination beginning at birth, and completion of the vaccination series by 6-8 months of age. Current studies indicate that the program has been highly successful. It is a tribute to the enthusiasm and dedication of public health personnel in the region. Thanks to their efforts, HBV is a "demerging" pathogen in the Pacific. Continued surveillance is needed to monitor long term protection after hepatitis B immunization and ensure the continued success of current activities.

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