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The effectiveness of the infant hepatitis B immunisation program in Fiji, Kiribati, Tonga and Vanuatu

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Abstract

The aims of this project were: (1) to determine the extent to which infant hepatitis B immunisation is preventing chronic hepatitis B infection in children living in a sample of Pacific Island countries; and (2) to identify factors associated with the successful prevention of hepatitis B infection in these populations. A regional hepatitis B immunisation project which supplied hepatitis B vaccine to 10 Pacific Island countries began in 1995. Seroepidemiological surveys were conducted in Fiji, Kiribati, Tonga and Vanuatu in early 1998. These included immunised pre-school children and their biological mothers, and a historical control group of unimmunised students. Prevalence rates for hepatitis B surface antigen (HBsAg) in the populations of students, mothers and their pre-school children were respectively: Fiji: 6.9, 6.6, 0.7%; Kiribati: 27.4, 15.1, 3.8%; Tonga: 11.1, 18.6, 3.8%; Vanuatu: 16.3, 12.3, 3.0%; and for all four countries: 13.2, 12.5, 2.6%. Compared to the historical control group of students, the pre-school population had a much lower probability of HBsAg positivity (relative risk [RR] = 0.19 [95%CI: 0.12–0.31]). Statistically significant differences in risk were apparent for all the countries: Fiji: RR = 0.10; Kiribati: RR = 0.14; Tonga: RR = 0.34; Vanuatu: RR = 0.19. This is equivalent to an overall program effectiveness of 81% (95%CI: 69–88%) in reducing chronic carriage. Also, the overall protective effectiveness against vertical hepatitis B transmission resulting in HBsAg positivity among children exposed to HBeAg positive and negative carrier mothers, was estimated to be 70%. By age 6 months, when all children should have had three vaccine doses, completed immunisation rates ranged from 22 (Fiji) to 84% (Vanuatu). Coverage of the first dose being given within 2 days of birth varied from 43% in Kiribati to 92% in Tonga. In conclusion hepatitis B immunisation of infants in these four countries is having a substantial beneficial effect in preventing chronic hepatitis B infection. Nevertheless, there is significant scope for further improving the timeliness of immunisation.

Keywords: Hepatitis B; Immunisation; Pacific

1. Introduction

Infection with the hepatitis B virus is highly endemic in the South Pacific with carrier rates among the highest in the world, as shown by studies in Micronesia [1–4], Melanesia [5–12] and Polynesia [13–20]. Many Pacific countries incorporated hepatitis B (HB) vaccination into their childhood immunisation schedules in the early 1990s. However, the supply of the vaccine was often not adequate or consistent. To address this, a project managed by UNICEF, with technical support from WHO began in 1995 in 13 Pacific Island

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Table 1
Reported immunisation coverage for third HB vaccine dose (%) in Pacific Island countries in which vaccine supply is supported by the current project, 1994–8 (based on routine data on all vaccinations from Maternal and Child Health clinics)

Country	Coverage		Change (absolute %)
	1994	1998	
Cook Islands	79	86	+7
Fiji	60	98	+38
Kiribati	36	89	+53
Niue	100	100	0
Samoa	94	99	+5
Solomon Islands	65	73	+8
Tokelau	0	100	+100
Tonga	90	93	+3
Tuvalu	17	96	+79
Vanuatu	66(1995)	75	+9

countries (PICs). The project is known as the Control of Hepatitis B Infection in Pacific Island Countries Project. This project supplies HB vaccine (initially fully-subsidised) and technical support for HB immunisation specifically, and the Expanded Program on Immunization (EPI) more generally. The Australian and New Zealand Governments provide donor support.

The project has ensured sufficient and consistent vaccine supply to 10 countries and immunisation coverage levels reported to UNICEF and WHO have improved substantially (Table 1). All of the countries schedule the first dose of HB vaccine at birth (Table 2). This study was undertaken to determine how effectively the HB immunisation program was reducing the risk of chronic infection. Relatively few data on HB immunisation effectiveness were available for PICs, and there had been concern raised about the immunogenicity of HB vaccines in some Pacific Island populations [21,22].

2. Methods

Countries that represented the various different population groups were selected: Fiji and Vanuatu (Melanesian), Kiribati (Micronesian) and Tonga (Polynesian). Table 2 outlines the HB immunisation schedules recommended in each country. Within each country the study areas were generally in and around the major city or town because of logistic considerations. However, one or more village areas outside the major centre were also included in each country. In Fiji only Melanesian Fijians and not Indo-Fijians were included as the latter have much lower HB infection rates. The survey was undertaken between February and April 1998.

2.1. Study populations

2.1.1. Recently immunised pre-school children

All the children on the records of the selected Maternal and Child Health (MCH) clinics aged between 12 and 24 months and regardless of vaccination status. (The HB vaccine became available under the current project in 1996.)

2.1.2. Historical control group of unimmunised students

A group of students aged 10–13 years who were old enough never to have received HB vaccine (vaccination first commenced in 1989 or 1990 in these four countries). These students attended schools in the same locality as that serviced by the MCH clinic used for identifying mothers and their pre-school children.

2.1.3. Mothers of the pre-school children

The biological mothers of the cohort of pre-school children. The mothers were interviewed and blood samples were taken at MCH clinics from them and their pre-school children.

Sample sizes necessary to detect significant differences in chronic HB virus infection between students and immunised pre-school children were estimated using data from previous studies in these countries. Demographic data were collected on all the populations and immunisation data were abstracted from the parent-held record card (or the actual MCH clinic records when the card was not available).

2.2. Vaccine

The vaccine used in all study countries over the relevant period was Korean Green Cross Corporation plasma-derived HB vaccine presented as one, two or

Table 2
Recommended hepatitis B immunisation schedules, survey countries

Dose	Fiji	Kiribati	Tonga	Vanuatu
Dose 1	Birth	Birth	Birth	Birth
Dose 2	2 months	6 weeks	6 weeks	6 weeks
Dose 3	Changed during 1997 from 8 months to 5 months	12 weeks	3 months after second dose	10 weeks

ten dose vials, each pediatric 0.5 ml dose containing 10 mcg HBsAg.

2.3. Ethical and consent procedures

Written approval for all the serological survey procedures was obtained from the Department of Health in each country. Written consent was provided by the parents of each of the students (on a form in the appropriate language). The mothers invited to participate were informed by the local nurses of the voluntary nature of the study, and their verbal consent relating to themselves and their pre-school children was obtained upon arrival at the MCH clinic.

2.4. Laboratory processing and testing

Blood samples were separated by centrifugation on the day of collection, and azide added as a preservative. Samples were transported to the Victorian Infectious Diseases Reference Laboratory (VIDRL) in Melbourne, Australia. At the VIDRL all sera were tested for total antibody to hepatitis B core antigen (anti-HBc) (Wellcozyme anti-HBc, Murex Diagnostics, Dartford UK); antibody to hepatitis B surface antigen (anti-HBs [non-quantitative]; Murex anti-HBs, Murex Diagnostics); and hepatitis B surface antigen (HBsAg; Murex HBsAg, Murex Diagnostics). All samples testing positive for HBsAg were confirmed by neutralisation using a Murex HBsAg confirmatory kit. Maternal samples positive for HBsAg were tested for hepatitis B e antigen (HBeAg), (IMx HBe 2, Abbott Laboratories, Chicago, Illinois, USA). All the epidemiological and laboratory data were made anonymous and entered onto a Microsoft Access database and analysed with Epi Info [23]. All the available data were examined to identify risk factors for HB infection and the impact of HB immunisation.

3. Results

3.1. Hepatitis B infection by age group and country

For all four countries the typical pattern of increasing HB markers with age was apparent. In the maternal group, the highest prevalence of total markers was in Kiribati at 94% with the lowest being in Fiji at 78% (Table 3). Similarly, Kiribati had the highest prevalence of total markers among the students and pre-school children while Fiji had the lowest. Rates of HBsAg positivity were higher in students than in mothers for all countries except Tonga (Table 3, Fig. 1). The overall level of HBeAg positivity was rela-

Table 3
Distribution of hepatitis B markers by population group and country

	HBsAg		HBeAg (of those who were HBsAg +ve)			Anti-HBs		Anti-HBc		All markers (HBsAg, anti-HBs, anti-HBc)[a]		
Population	%	No.	%	No.		%	No.	%	No.	%	No.	
Fiji[b]												
Students[c]	6.9	20/288	–		–	39.9	115/288	49.0	141/288	55.6	160/288	
Mothers	6.6	19/290	70.6	12/17		57.9	168/290	67.2	195/290	77.9	226/290	
Pre-school children	0.7	2/285	–		–	77.0	217/282	5.3	15/281	–		–
Kiribati												
Students	27.4	37/135	–		–	48.9	66/135	92.6	125/135	94.1	127/135	
Mothers	15.1	27/179	47.8	11/23		49.4	87/176	89.4	160/179	94.4	169/179	
Pre-school children	3.8	6/156	–		–	46.9	68/145	12.8	19/149	–		–
Tonga												
Students	11.1	25/225	–		–	43.8	96/219	45.0	99/220	57.3	126/220	
Mothers	18.6	40/215	47.5	19/40		60.5	130/215	84.7	183/216	89.4	193/216	
Pre-school children	3.8	8/211	–		–	59.9	121/202	12.3	25/203	–		–
Vanuatu												
Students	16.3	22/135	–		–	35.8	48/134	54.1	73/135	58.5	79/135	
Mothers	12.3	16/130	50.0	8/16		58.9	76/129	65.4	85/130	83.8	109/130	
Pre-school children	3.0	4/132	–		–	72.4	89/123	9.3	12/129	–		–
All four countries												
Students	13.2	103/783	–		–	41.9	325/776	56.3	438/778	63.4	496/782	
Mothers	12.5	102/814	52.1	50/96		56.9	461/810	76.4	623/815	85.5	697/815	
Pre-school children	2.6	20/784	–		–	65.8	495/752	9.3	71/762	–		–

[a] Past infection in these vaccinated pre-school children is indicated by the presence of HBsAg and/or anti-HBc since anti-HBs is associated with both vaccination and infection.
[b] Melanesian population only, ie, excluding Indo–Fijians.
[c] Including only the student population aged over 10 years (as for all the analyses in this report).

tively high at 52% of those mothers who were HBsAg positive (Table 3).

From ages 10 to 13 years among the students, the prevalence of HBsAg positivity increased by an absolute level of 3.1% per year (data not shown). The prevalence of total markers continued to increase among the mothers at around 0.7% per year (for the periods 20–24 and 40–44 years).

3.2. Effectiveness of hepatitis B immunisation

Of the pre-school children of HBeAg positive mothers in all countries combined, 27.1% of these children were found to be HBsAg positive (13/48). In contrast, of the children of carrier mothers who were HBeAg negative, none of these children were HBsAg positive (0/44). Of the children born to HBsAg positive mothers it is reasonable to assume that in the absence of immunisation, around 80% of these children would become chronically infected from exposure to their HBeAg positive mothers and 10% from exposure to their HBeAg negative mothers. These estimates are within the respective ranges of 70–90% and 5–10% described in a recent review [24]. Therefore, the results obtained for all the countries combined suggest a protective effectiveness of immunisation against HBsAg positivity of 66.2 and 100% for infants of HBeAg positive and negative mothers, respectively (and 69.6% overall for children of carrier mothers).

When the prevalence of HBsAg in the pre-school population was compared with that in the student population, the overall relative risk (RR) was 0.19 (95%CI: 0.12–0.31). Significant differences in risk were apparent for all the countries: Fiji: RR = 0.10, (95%CI: 0.02– 0.43); Kiribati: RR = 0.14, (95%CI: 0.06–0.32); Tonga: RR = 0.34, (95%CI: 0.16–0.74); Vanuatu: RR = 0.19, (95%CI: 0.07–0.53).

3.3. Risk factors for hepatitis B infection

A major risk factor for HBsAg positivity in pre-school children was having a mother who was HBsAg positive (RR = 14.9) (Table 4). Indeed, out of the 19 HBsAg positive pre-school children, 68% (13/19) had HBsAg positive mothers. Maternal HBeAg positivity was also a significant risk factor for HBsAg positivity in pre-school children. The only other significant risk factor for HBsAg positivity in any population was older age among students.

Significant risk factors for past or current infection (total markers) in pre-school children were maternal HBsAg or HBeAg positivity, being female and only having had two doses of HB vaccine (as opposed to three doses). Significant risk factors for past or current infection in students were being male and being older. Older age was also a significant risk factor for the maternal population.

There were no significant associations between infection in pre-school children and their age, their mother's age, or the number of children that their mother had. There was no evidence that the timing of the first or second dose affected the risk of infection in pre-school children (regardless of their mother's HBsAg status). Although pre-school children who had evidence of past infection (and who had HBsAg negative mothers) had a longer mean delay before their first dose of vaccine than children with no evidence of past infection (5.7 vs 15.8 days) this was not at a significant level ($p = 0.5$).

3.4. Immune response to immunisation

The levels of anti-HBs positivity for fully immunised children with no evidence of past infection infection were 48.6 (Kiribati), 62.2 (Tonga), 72.7 (Vanuatu), and

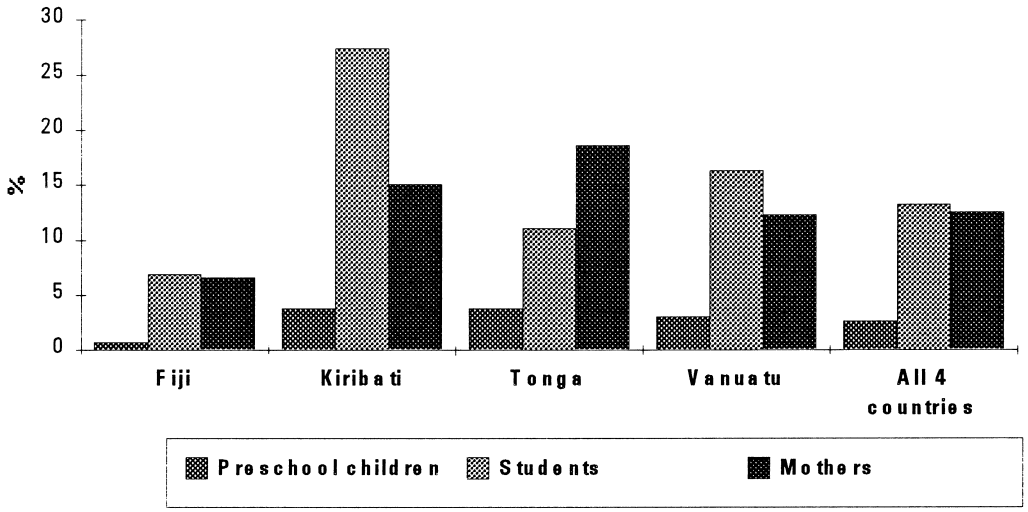

Fig. 1. Prevalence of HBsAg positivity.

Table 4
Potential risk factors for current or past infection with hepatitis B (all countries combined)

Potential risk factor (referent)	Current infection (HBsAg)		All markers (HBsAg, anti-HBs[a], anti-HBc)	
	RR[b] (95%CI)	p for trend	RR (95%CI)	p for trend
Pre-school children				
Mother HBsAg positive (negative)	14.92 (5.81–38.35)		2.68 (1.68–4.30)	
Mother HBeAg positive (negative)	RR not calculated[c] ($p = 0.0002$)		8.06 (1.98–32.75)	
Female (male)	1.37 (0.98–1.91)		1.33 (1.09–1.63)	
Three doses of vaccine (two doses)	0.41 (0.06–2.89)		0.30 (0.14–0.66)	
Increasing age		$p > 0.05$		$p > 0.05$
Mothers				
Live in or around a main town (rural village)	1.05 (0.93–1.19)		1.13 (0.98–1.29)	
Increasing age		$p > 0.05$		$p = 0.001$
Students				
Male (female)	1.21 (0.84–1.73)		1.18 (1.06–1.32)	
Live in or around a main town (rural village)	1.07 (0.96–1.20)		1.01 (0.92–1.10)	
Increasing age		$p = 0.019$		$p = 0.002$

[a] Anti-HBs was not included in the analyses for pre-school children.
[b] RR = relative risk, with the 95% confidence interval (CI) in brackets.
[c] Relative risk could not be calculated as a cell value equalled zero.

79.1% (Fiji). However, these results are not strictly comparable, as the schedule varied between countries. These results also do not constitute seroconversion rates, as the age of the infants and the interval between the last vaccine dose and blood sampling also varied.

3.5. Timeliness of vaccinations

The coverage for the three doses of HB vaccine was very high (over 95% in all the countries) and all the pre-school children had at least one dose (Fig. 2). There was significant variation in the rates of the first HB vaccination given on the day of birth between the countries (22% in Fiji to 90% in Tonga; Table 5). Coverage rates for the first HB vaccine dose being given within the first 2 days of life ranged from 43% in Kiribati, to 92% in Tonga.

The timeliness of the second HB vaccination ranged from 46 (Tonga) to 76% (Fiji) (for within 2 weeks of the due date). By age 6 months, when all pre-school children in each country should have been fully immunised, coverage for three vaccine doses was 22 (Fiji), 46 (Tonga), 56 (Kiribati) and 84% (Vanuatu) (Fig. 2). However, the result for Fiji is distorted by the change in the immunisation schedule in 1997.

4. Discussion

The high prevalence of HB markers among the maternal population in these four countries is consistent with the findings of previous studies. The high prevalence rate of total markers among mothers in Kiribati (94%) was matched by the high rate among students (94%). This suggests relatively high rates of horizontal transmission among young people, prior to the onset of significant sexual activity.

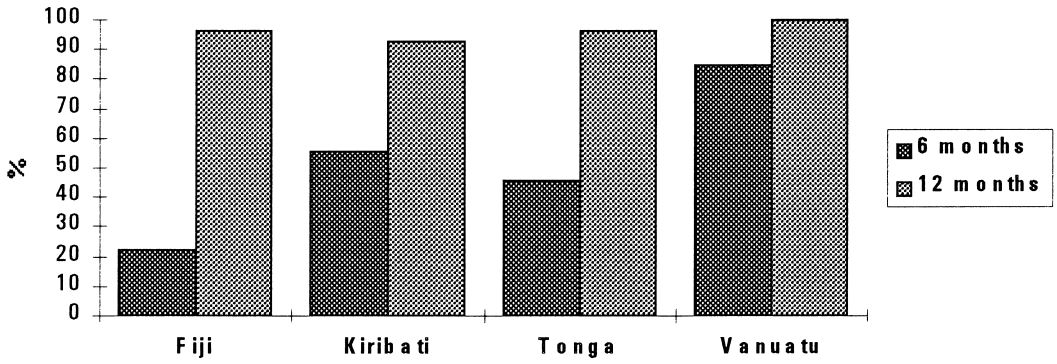

Fig. 2. Proportion of children fully vaccinated (third dose of hepatitis B vaccine) by age.

4.1. Effectiveness of hepatitis B immunisation

4.1.1. Prevention of infection from HBsAg positive mothers

The overall protective effectiveness of immunisation in children born to carrier mothers at 69.6% is an encouraging result. However, this finding was only based on 92 cases.

4.1.2. Prevention of perinatal infection overall

When compared to the historical control group of students, the pre-school population had a much lower probability of HBsAg positivity (RR = 0.19; 95%CI: 0.12–0.31)). These groups are not strictly comparable as it is plausible that the prevalence of chronic infection in the pre-school child cohort could continue to rise over the next decade of life (due to the ongoing risk of infection combined with vaccine failure). However, the evidence from other studies suggests that there is almost no increase in the prevalence of HBsAg positivity in immunised cohorts 10–15 years following immunisation [25–29]. Thus the reduction in HBsAg positivity in immunised pre-school children compared with the control group of 81% (95%CI: 69–88%) provides the best available estimate of program effectiveness over the study period.

Additional evidence favouring a benefit from immunisation in these populations was the significantly reduced risk of past infection (HBsAg or anti-HBc) among pre-school children who had received three as opposed to two doses of vaccine.

4.2. Immune response to immunisation

The significant variation in the anti-HBs results between the four countries among fully immunised pre-school children with no evidence of infection, and antibody prevalence rates lower than observed in recently immunised children in carefully controlled settings, are commonly observed in field settings in developing countries. The most likely explanation is variations in vaccine storage and handling, particularly those allowing vaccine freezing to occur. While quite heat stable, like other alum-adjuvanted vaccines, HB vaccine is damaged by freezing. While formal data on frequency of vaccine freezing in Pacific Island countries is lacking, field experience indicates that the potential for vaccine freezing to occur is common. Despite these results, it is reassuring to find that on the measure that really counts, immunisation is providing a relatively high level of protection from chronic infection.

Table 5
Coverage of the first hepatitis B vaccination by time

	Fiji	Kiribati	Tonga	Vanuatu
On birth date (%)	21.7	34.8	90.1	60.4
On day after birth (%)	62.9	7.8	1.9	17.9
Day 2–5 (%)	10.4	9.2	1.4	18.6
Days 6–30 (%)	2.5	19.1	2.4	0.7
> 30 days (%)	2.4	29.1	4.2	2.2
Median (days)	1	5	0	0
Range (days)	0–53	0–354	0–78	0–89

4.3. Timeliness of vaccinations

The high level of coverage for three doses of HB vaccine in the pre-school population is not surprising. This is because these figures represent the children of a group of mothers who continue to be in contact with the local MCH clinic and who were willing to participate in this survey (those with incomplete vaccination status may have been less willing to participate).

The large variation in the timing of the first vaccine dose is of concern, given that virtually all the births of these pre-school children would have occurred in hospital facilities. This suggests that there is significant scope for increasing the proportion of first doses given within 24 h of birth. This could be achieved by administering this dose in the labour ward, for example, at the same time as the vitamin K injection. It is possible that one of the factors in the relatively lower success of Kiribati in preventing perinatal infection is the lower rate of administering the first dose during the 1st week of life (but the relationship in this study was not statistically significant).

Screening of pregnant women for HBsAg and administration of HB immune globulin (HBIG), in addition to vaccine to infants of carrier mothers, is conducted on an incomplete basis in Fiji, but not in any of the other countries included in this survey. In this study, HBIG was given to only five (1.7%) of children surveyed in Fiji, whereas 19 (6.6%) of mothers were found to be HBsAg positive. Universal HB immunisation with vaccine, commencing at birth, is highly acceptable and the most effective strategy to prevent vertical HB transmission, whether or not maternal screening and use of HBIG occur [30,31]. This is because vaccines containing at least 10 mcg of HBsAg are associated with a protective efficacy of over 90% in the highest risk infants, those born to HBeAg positive carrier mothers [32]. The addition of HBIG increases protective efficacy by only 2–5% [32].

Other studies have shown that administration of the first vaccine dose soon after birth is the key to preventing vertical HB transmission [33]. For no other EPI vaccine is early administration so important. The timeliness of the second and third doses of HB vaccination also varied substantially between countries. Indeed, all four countries could benefit from improving the timeliness of these doses.

4.4. Cost–effectiveness of immunisation

Using an estimated overall protective effectiveness of 80% (within the range of 69–88% estimated in this study), it is possible to roughly estimate the cost–effectiveness of HB immunisation. For the four countries combined, the vaccination of 100 infants will prevent 10 of them becoming carriers at a cost of US $37 per prevented carrier (using a vaccine price of $US 5.50 per 10 dose vial [assuming 50% wastage] and $US 0.13 per autodestruct syringe). Even if the additional vaccination delivery costs by the health sector were as high as $US 10 per child for HB vaccination (the "basic" EPI package costs $15 per fully immunised child on average), this suggests an undiscounted cost of around $US190 per premature death prevented (assuming that around 25% of carriers will suffer premature death from HB associated sequelae). Such a result suggests that HB vaccination is an extremely cost–effective intervention in these countries.

4.5. Limitations and generalisability of these results

Due to HB vaccination being introduced nationwide in all four countries, this study was limited by the absence of age-comparable control groups with whom to compare immunised pre-school children. Because of this, the impact of immunisation has had to be assessed by examining the impact on vertical transmission and on comparisons with an older historical control group. Another limitation was the urban bias of the sample sites. Also of note is that this study has assumed that all HBsAg positive results represent chronic infection whereas a very small percentage may in fact represent acute infection, some of which would resolve.

These results reflect the impact of immunisation amongst a group of pre-school children of whom all had at least one dose of HB vaccine and 97% had three doses. However, the mean vaccination coverage rates for each country in 1996, the year most of these children were born, (66% in Kiribati, 68% in Vanuatu, 82% in Fiji, and 94% in Tonga) suggest that the effectiveness of the vaccination programs in each country might be significantly lower than indicated by the results of these serosurveys. Nevertheless, there were further improvements in coverage levels by 1998 (Table 1).

The islands selected in this study represent Melanesian populations (Fiji and Vanuatu), a Micronesian population (Kiribati) and a Polynesian population (Tonga). These results and the other evidence of the impact of HB vaccination in other parts of the Pacific [4,13,34,35], provide compelling evidence that HB vaccines are effective in Pacific populations and that universal infant HB immunisation, commencing at birth, is of great benefit to all South Pacific peoples.

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