Hepatitis B Surface Antigen Seroprevalence among Children in Papua New Guinea, 2012–2013

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Abstract. Approximately 8% of the population in Papua New Guinea (PNG) has chronic hepatitis B virus (HBV) infection. To decrease the burden of chronic HBV infection, a national 3-dose infant hepatitis B vaccination program was implemented starting in 1989, with a birth dose (BD) added to the schedule in 1992. To assess the impact of the hepatitis B vaccination program, we conducted a serosurvey among children born after vaccine introduction. During 2012–2013, a cross-sectional stratified four-stage cluster survey was conducted to estimate hepatitis B surface antigen (HBsAg) prevalence among children 4–6 years of age. We collected demographic data, vaccination history, and tested children for HBsAg. Of 2,133 participants, 2,130 children had vaccination data by either card or recall: 28% received a BD; 81% received ≥ 3 vaccine doses. Of 2,109 children providing a blood sample, 60 (2.3%) tested positive for HBsAg. This is the largest, most geographically diverse survey of hepatitis B vaccination and HBsAg seroprevalence done in PNG. Progress has been made in PNG toward the Western Pacific Regional goal to reduce the prevalence of chronic HBV infection to $< 1\%$ by 2017 among 5-year-old children. Vaccination efforts should be strengthened, including increasing BD coverage and completing the 3-dose series.

INTRODUCTION

Globally, an estimated 240 million people have chronic hepatitis B virus (HBV) infection and an estimated 600,000 die each year from the consequences of this infection.^{1,2} The burden of disease is greatest among those living in the Western Pacific Region, most of whom acquire the infection from perinatal or horizontal transmission occurring during the first 5 years of life.^{3,4} Papua New Guinea (PNG) is considered highly endemic for chronic HBV infection; the World Health Organization (WHO) Regional Office for the Western Pacific (WPR) estimates that 8% of the general population has hepatitis B surface antigen (HBsAg).⁵

To decrease the burden of chronic HBV infection in PNG, hepatitis B vaccine was introduced for all infants starting in 1989 with the inclusion of the birth dose in 1992. Currently, the schedule has been a birth dose within 24 hours of birth, and doses at 1, 2, and 3 months of age as a combination vaccination. In 2012, national birth dose coverage was 35% and 3-dose hepatitis B vaccination coverage (HepB3) was 63%; reported coverage has remained stagnant during the past 10 years.⁶ For birth dose, the national program procures 10-dose vials of hepatitis B monovalent vaccine from Serum Institute of India; for subsequent doses, the national program procures single-dose DTP-HepB-Hib vials from Crucell/Berna Biotech Korea and Serum Institute of India. The approach to preventing perinatal HBV transmission in PNG is through birth dose administration followed by at least two more doses; mothers are not routinely screened for HBsAg, and hepatitis B immunoglobulin is not routinely administered to newborns.

To assess the progress of the national immunization program in decreasing the burden of disease, we conducted a serosurvey to determine the HBsAg seroprevalence among children born after the national implementation of the hepatitis B vaccina-

tion program. The secondary objective was to assess the hepatitis B vaccination coverage in the surveyed population and assess risk factors for failure to receive a birth dose.

METHODS

From November 2012 to May 2013, we conducted a four-stage cross-sectional cluster survey among children 4–6 years of age. The survey design was based on WHO guidance for performing hepatitis B immunization surveys.⁷

Sample size and sampling. We calculated a minimum sample size of 1,667 on the basis of an expected HBsAg seroprevalence of 7%, a two-sided precision of $\pm 1.5\%$, a 95% probability of achieving that precision, and a design effect of 1.5. We factored in a 20% nonresponse rate and targeted 2,084 children aged 4–6 years of age for enrollment.

The 2011 national census was chosen as the sampling frame; the lowest population unit available was the local-level government unit (LLG). *A priori*, 18 (5%) of the 334 LLGs were excluded because they were difficult to access or had small populations; this accounted for 0.8% of the total population of the country. Sampling was done in four stages. In the first stage, six districts were chosen in each of the four regions (Highlands, Southern, Momase, and Islands) by probability proportional to estimated size (PPES), resulting in 24 primary sampling units (PSUs). In the second stage, three LLGs were chosen in each of the districts by PPES with replacement. Sixty-two LLGs were chosen once; in each of these LLGs, three villages were chosen randomly for the third stage. Five LLGs were sampled twice; in each of these LLGs, six villages were chosen randomly for the third stage. In total, 216 villages were selected. If an LLG was unable to be visited because of access or insecurity issues, an attempt was made to visit three villages in a comparable nearby LLG. In the fourth stage, in most villages, all children 4–6 years of age were eligible for enrollment. If the village was large and had a health center, two segments were created. The first segment was those who lived within a 3 km radius of the health center; the second segment was those who lived > 3 km radius from the health

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center. In each of these segments, five children in the target 4- to 6-year old age group were chosen.

Staff selection and training. To assure high data quality, University of Medical and Health Sciences of PNG staff who had experience with other health-related surveys that included blood drawing were chosen to be field investigators and supervisors. All survey staff attended a 2-day training course led by WHO, which covered consent, child selection, data collection, and how to perform a rapid test. Supervisors were in charge of verifying test results and ensuring accurate data recording and completeness.

Data collection. Upon visiting a household, the field investigator sought to find out if a child in the target age group was in the household, and if the parent or caregiver would agree to participate. A brief questionnaire collecting demographic and vaccination history was administered to participating caregivers. If written vaccination history from the vaccination card was unavailable, we obtained vaccination history based on caregiver recall.

Specimen collection and HBsAg testing. Approximately 50 μ L of blood was collected from each child by finger prick and was tested in the field using the Alere Determine HBsAg point-of-care test strip (reported sensitivity: 95–100%; reported specificity: 96–100%).^{8–10} The test reports either a positive or negative result. If no control line appears, the test is considered invalid.

Data management and analysis. The data were entered and stored in Epi-Info 7 (Atlanta, GA). Data were analyzed in SAS v9.3 (Cary, NC). Stratum-level weights accounted for the equal allocation of PSUs to the four regions in the first stage. Children within each stratum were assumed to have the same probability of selection. Weighted proportions were calculated for population characteristics, vaccination status, and HBsAg seropositivity. The HBsAg tests that were invalid were excluded from the analysis. Because of the high number of missing and replaced clusters, the representativeness of the sample cannot be assumed and therefore confidence intervals for the seroprevalence and coverage estimates are not presented. Rao-Scott chi-square (χ^2) *p* values were calculated for categorical comparisons as were unadjusted odds ratios (OR) and 95% confidence intervals (CI), taking into account the stratification, first stage clusters, and stratum-level weights. When evaluating potential factors related to vaccination history and seropositivity, vaccination data among card holders and vaccination data among both card holders and those only providing recall are presented. We defined “timely birth dose” as a dose of hepatitis B vaccine given within 24 hours of birth.

Human subjects rights and ethics. We obtained informed consent from the parents or caregivers of all participants. The study protocol was approved by the Medical Research Advisory Committee of the Government of PNG (No. 54-6-2) and the Ethics Review Committee at the WHO Regional Office for the Western Pacific. The U.S. Centers for Disease Control and Prevention (CDC) determined the activity to be human subject research but CDC involvement did not constitute engagement in human subjects research and thus did not require CDC Institutional Review Board review.

RESULTS

Challenging field conditions, such as inaccessibility caused by unsurpassable terrain and insecurity, resulted in a failure

TABLE 1
Characteristics of enrolled children, Papua New Guinea, 2012–2013

Characteristics	Number	Total	Weighted %
Male	1,091	2,117	51
Age			
4 years of age	724	2,133	34
5 years of age	743	2,133	34
6 years of age	666	2,133	32
Region			
Highlands	550	2,133	43
Islands	487	2,133	14
Momase	596	2,133	25
Southern	500	2,133	18
Maternal education			
No education	630	2,133	35
Primary school	1,070	2,133	46
Secondary school	345	2,133	15
University or higher	42	2,133	2
Unknown	46	2,133	2
Caregiver heard about hepatitis B	411	2,118	18
Location of birth			
Health Facility	1,322	2,103	64
Home with SBA	88	2,103	3
Home without SBA	648	2,103	31
Home but unclear status of SBA	45	2,103	2

SBA = skilled birth attendant.

to visit 19 (28%) of the 67 LLGs selected; five of these LLGs were substituted with neighboring LLGs with similar populations estimates. The remainder could not be visited. In total, 2,265 children were identified for potential enrollment in the study; families of 2,164 (96%) children provided consent. On review of these 2,164 children, 31 children were outside the targeted age group of 4–6 years of age and were excluded from analysis, leaving data from 2,133 eligible children with questionnaire data for analysis. Of these, 17 (Highlands *n* = 2; Islands *n* = 10; Momase *n* = 0; Southern *n* = 5) children had invalid results for the rapid test; seven (Highlands *n* = 0; Islands *n* = 2; Momase *n* = 4; Southern *n* = 1) children refused the finger prick.

Of the children enrolled, 1,091 of 2,117 (51%) were male; approximately equal numbers of children were enrolled in each age category and region (Table 1). Of 2,133 mothers of enrolled children, 1,457 (63%) had at least a primary school education (Table 1). Among the 2,103 caregivers reporting location of the child's delivery, 1,322 (64%) were born in a health facility, and 781 (36%) were born at home (88 [3%] with a trained healthcare professional (also known as a skilled birth attendant or SBA), 648 [31%] without a SBA, and 45 [2%] with an unclear status of SBA) (Table 1). The most common reported reasons for delivering at home included lack of transportation to health facility (408 of 781, 50%), long distances to health facilities (310 of 781, 38%), cost of delivering at a health facility (170 of 781, 19%), and other children were born at home (58 of 781, 7%).

Vaccination cards were available for 1,141 (49%) of the 2,130 children with vaccination data; those providing data by recall reported higher birth dose coverage (Table 2). By either card or recall, 560 (28%) children received a timely birth dose; an additional 389 (20%) children were reported to receive a birth dose but timing was unknown. Of those with cards with available dates, 23% (265 of 1,137) indicated timely birth dose, compared with 52% (295 of 604) among those who reported timing by recall. Among those with any vaccination history, 1,693 (81%) of the children received at

TABLE 2
Hepatitis B vaccination coverage among 4–6 year olds, Papua New Guinea, 2012–2013

	Children with vaccination cards			Children without cards (recall)			All children (card or recall)		
	No. vaccinated	Total	%	No. vaccinated	Total	%	No. vaccinated	Total	%
Timing of first dose of hepatitis B vaccine*									
< 24 hours	265	1,141	23	295	989	32	560	2,130	28
2–7 days	168	1,141	14	84	989	7	252	2,130	10
8–30 days	229	1,141	22	68	989	6	297	2,130	14
> 30 days	475	1,141	42	157	989	17	632	2,130	29
Unknown timing	4	1,141	0.3	385	989	39	389	2,130	20
Total hepatitis doses									
0	8	1,141	1	87	989	9	95	2,130	5
1	152	1,141	13	98	989	6	250	2,130	10
2	63	1,141	5	29	989	4	92	2,130	5
3	320	1,141	27	92	989	10	412	2,130	18
4	598	1,141	54	683	989	71	1281	2,130	63
BD ≤ 24 hrs + 2 or more doses†	219	1,137	19	265	604	48	484	1,741	30
BD ≤ 7 days+2 or more doses†	363	1,137	31	341	604	58	704	1,741	42

* Percentages do not add up to 100% because of rounding.

† 389 reporting a birth dose but with an unknown timing excluded.

BD = birth dose.

least three doses of hepatitis B vaccine; this was similar among card holders and those who only provided recall data ($p = 0.96$), though more non-cardholders received four doses, compared with card holders (Table 2). One hundred and fourteen caregivers provided reasons for their children being under-vaccinated (< 3 doses): 30 (24%) reported no access to

health facilities, 21 (19%) reported not being in the area when vaccine was due, 20 (13%) reported lack of vaccine at the facility, and 19 (17%) forgot it was time for the vaccine dose.

We evaluated factors potentially affecting timely birth dose vaccination. Awareness of hepatitis B was low (18%, Table 1), but was unrelated to vaccination coverage (data not shown).

TABLE 3
Factors potentially associated with hepatitis B surface antigen positivity among 4–6 year olds, Papua New Guinea, 2012–2013

	No. HBsAg positive	Total tested	% HBsAg positive	χ^2 P value	Unadjusted odds ratio (95% CI)
Characteristics of HBsAg-positive children					
Sex					
Female	26	1020	2.0	0.21	Reference 1.3 (0.8–2.2)
Male	34	1074	2.6		
Age					
4 years of age	12	712	1.4	0.11	Reference 1.7 (0.8–3.5) 2.3 (0.98–5.3)
5 years of age	20	736	2.3		
6 years of age	28	661	3.2		
Caregiver knowledge of Hepatitis B					
Caregiver has NOT heard about hepatitis B	38	1,687	1.9	0.33	Reference 2.2 (0.7–6.8)
Caregiver has heard about hepatitis B	22	407	4.0		
Birth location					
Born at home	25	769	2.6	0.29	Reference 0.8 (0.5–1.2)
Born in a health facility	34	1,311	2.1		
Hepatitis B Vaccination History (CARD ONLY)					
Number of routine hepatitis B doses					
Received 3 + doses	26	907	2.3	0.15	Reference 0.5 (0.1–1.7)
Received < 3 doses	3	221	1.1		
Birth dose timing and number of hepatitis B doses					
24-hour birth dose (BD) timing*					
Received BD ≤ 24 hrs + 2 more doses	4	214	1.6	0.46	Reference 1.4 (0.5–4.2)
Did NOT receive BD ≤ 24 hrs + 2 more doses	25	910	2.2		
7-day BD timing*					
Received BD ≤ 7 days + 2 more doses	6	356	1.3	0.16	Reference 1.9 (0.7–4.7)
Did NOT receive BD ≤ 7 days + 2 more doses	23	768	2.5		
Hepatitis B Vaccination History (CARD OR RECALL)					
Number of routine hepatitis B doses					
Received 3 + doses	46	1,672	2.2	0.52	Reference 1.3 (0.6–2.8)
Received < 3 doses	14	434	2.8		
Birth dose timing and number of hepatitis B doses					
24-hour BD timing*					
Received BD ≤ 24 hrs + 2 more doses that are positive	7	478	1.2	0.07	Reference 2.2 (0.96–5.1)
Did NOT receive BD ≤ 24 hrs + 2 more doses that are positive	40	1,245	2.7		
7-day BD timing*					
Received BD ≤ 7 days + 2 more doses that are positive	10	695	1.2	0.01	Reference 2.6 (1.4–4.9)
Did NOT receive BD ≤ 7 days + 2 more doses that are positive	37	1,028	3.0		

* Excludes those with an unknown BD timing.

BD = birth dose; CI = confidence interval; HBsAg = Hepatitis B surface antigen.

FIGURE 1. Hepatitis B surface antigen seroprevalence among 4–6 year olds for each local level government unit (LLG) by region, Papua New Guinea, 2012–2013.¹¹ Fourteen selected clusters were not visited nor replaced: 6 in the Islands, 4 in the Southern region, 3 in the Highlands, and 1 in Momase.

Among those with vaccination cards, children born in health facilities were more likely to receive a timely birth dose (229 of 659, 35%, odds ratio [OR] 7.2 [95% CI 4.1–12.5]) compared with children born at home with a SBA (4 of 54, 7%, OR 1.0 [95% CI 0.4–2.7]) and children born at home without attendance by a SBA (26 of 387, 7%, reference).

Of 2,109 children with valid results for HBsAg, 60 (2.3%) were positive for HBsAg. If the 17 children with invalid test results were assumed to all be negative, seropositivity would remain 2.3%; if they were assumed to be positive, seropositivity would increase to 2.9% (77 of 2,126). When stratified by age, 12 (1.4%) of 712 4 year-olds, 20 (2.3%) of 736 5 year-olds, and 28 (3.1%) of 661 6 year-olds were seropositive for HBsAg (Table 3). Heterogeneity was seen among the regions; Figure 1 shows HBsAg seropositivity for each of the selected and replacement LLGs by region.

Potential risk factors related to HBsAg seropositivity were evaluated (Table 3). Among card holders, failure to receive three doses of hepatitis B vaccination, regardless of timing of the first dose, was not associated with HBsAg seropositivity. Among all children (with both written and recalled vaccination history), failing to receive a timely birth dose plus two additional doses of hepatitis B was not significantly associated with being seropositive (OR 2.2 [95% CI 0.96–5.1]), though failing to receive a birth dose within 7 days of birth plus two additional doses of hepatitis B vaccine was significantly associated with being seropositive (OR 2.6 [95% CI 1.4–4.9]). Failure to receive at least three doses, regardless of timing of the first dose, was not associated with HBsAg seropositivity.

DISCUSSION

It has been over 18 years since the last publication on the burden of HBsAg in PNG; furthermore, there has been no burden survey among those born after vaccine introduction.¹¹ This is the largest, most geographically diverse survey of hepatitis B vaccination and HBsAg seroprevalence done to date in Papua New Guinea. Among the children 4–6 years of age enrolled in this survey, 28% received a timely birth dose, 81% received at least three doses of hepatitis B vaccine, and 2.3% were HBsAg positive. Progress has been made in PNG

toward the WPR goal to reduce the prevalence of chronic HBV infection to < 1% by 2017 among children 5 years of age, because children in this survey had a lower HBsAg prevalence than previous serosurveys conducted in PNG.^{11–19} In this study, failure to receive a birth dose within 7 days followed by at least two subsequent doses was associated with being seropositive; however, failure to receive at least three doses was not associated with being seropositive. In PNG, it appears that perinatal HBV transmission is a key factor contributing to the burden of chronic HBV infection among young children; thus, increasing birth dose coverage is critical to achieving the < 1% HBsAg prevalence goal. In addition, 3-dose hepatitis B vaccination coverage needs to be increased.

Because of the remoteness of much of the country and low rates of institutional delivery, birth dose administration in PNG is challenging, however potential solutions do exist. As in a study from Cambodia, this study found that a timely birth dose was more likely to be administered to children born in health facilities.²⁰ Improving health facility delivery rates should improve the national timely birth dose coverage and provide other benefits to mothers and newborns, though real access challenges exist to accomplishing this in PNG as lack of transportation and long distances to health facilities were the two most common reasons women delivered at home. However, in this study, even among the children born in health facilities, only 35% received a birth dose, signifying that increasing facility delivery rates alone will not solve the problem without systematic improvements in birth dose administration in facilities. Neonatal health care providers should strive to achieve 100% coverage among health facility births; a previous survey among five PNG hospitals found that beliefs in false contraindications by healthcare workers and lack of access to the vaccine in the maternity unit were barriers to birth dose administration.²¹ Other potential barriers for timely birth dose administration in health facilities, such as lack of a functioning cold chain, vaccine stock outs, and failure to integrate the maternal health and the immunization sectors also need to be addressed. An evaluation of birth dose implementation is being conducted in health facilities throughout the country to help determine why birth dose coverage in health facilities is below 100%. PNG should work to ensure collaboration exists

between the maternal health and immunization sectors and that hepatitis B vaccine is available at every health facility. Not every health facility has a functional cold chain, and using hepatitis B vaccine in a controlled temperature chain, where vaccine is stored at ambient temperature for a defined period of time, could be an option for facilitating a timely birth dose in these facilities.^{22,23} Improving health facility coverage to 100% will only affect the 52% of children born in health facilities.²⁴ Children born at home must be reached by improved timely postnatal outreach visits. Another option is expansion of a successful pilot whereby trained village health volunteers stored hepatitis B vaccine in a controlled temperature chain in their homes, and administered the birth dose using Uniject (Bio Farma, Bandung, Indonesia), which is a prefilled simple injection device that requires minimal training.²⁵ Indonesia has been successful in reaching children born in rural areas by providing community midwives with Uniject, which is stored in a controlled-temperature chain in the midwife's home.^{26,27}

Three-dose coverage also has room for improvement, as birth dose alone is insufficient to prevent perinatal and early childhood HBV transmission.^{28,29} In this study, the most common reasons for being under-vaccinated include poor access to healthcare services and not being home when vaccination was due. Because of the challenges of the terrain, PNG's routine immunization system relies heavily on outreach to deliver routine vaccines to eligible children. To improve routine vaccination coverage in this challenging environment, a concerted effort has been made in PNG to transition from the "Reach Every District" immunization strategy to "Reach Every Child."³⁰ The main focus of the Reach Every Child strategy is to provide on-the-job supportive supervision to the health care staff to improve the quality of the routine immunization program, and to improve vaccination rates and decrease dropout rates by creating a system to track every newborn and child for vaccination. Implementing these improvements will not only increase hepatitis B coverage but also increase coverage of other critical vaccinations.

This study found different factors were associated with HBsAg seropositivity among card holders and among all children. In the cardholder analysis, power is limited as the number of seropositive children is small. Second, in this study, the quality of the vaccination data among both card holders and those providing recalled data could both be biased. Traditionally, vaccination data from cards is considered to be more reliable than recall, which frequently suffers from over-reporting; in this study, we saw that reported timely birth dose coverage was significantly higher among those providing recalled data leading us to question the validity of the data.³¹ However, anecdotal information from immunization supervisory visits suggests that cards are filled out incompletely at vaccination visits; thus card data might be underestimating the vaccination coverage in this population. Even with the lack of evidence of hepatitis B vaccination impact among card holders in this study, evidence from other studies has shown the significant impact of hepatitis B vaccination.^{32–34}

This study had several limitations. First, the rapid test used in this study has a reported sensitivity of 95%; therefore, the HBsAg prevalence in this study might be lower than the true seroprevalence.⁹ Additionally, 17 children had invalid results, potentially increasing the prevalence to 2.9%. Although sampling was intended to be representative, field conditions, such as inaccessibility caused by the terrain, and insecurity made it

challenging to visit all selected LLGs. Thus, these results might not be generalizable to the population of children 4–6 years of age living in PNG. Vaccination data collected by recall are not as reliable as vaccination card data, especially since we asked questions to the parents about an event that happened 4 to 6 years ago. We assumed that vaccination card data represented the true vaccination history of the child, but this might not be the case in PNG. We assessed only a few risk factors for HBsAg seropositivity; factors such as low socioeconomic status and household crowding were not assessed.^{32,35–38} Finally, some data, such as vaccination history, were incomplete for some children.

Efforts to improve vaccination coverage should be prioritized if PNG hopes to achieve the WPR 1% control goal, and future work should entail a nationally representative serosurvey to assess PNG's national prevalence after improvements are made in vaccination coverage.

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