



Hepatitis B surface antigen seroprevalence among pre- and post-vaccine cohorts in Cambodia, 2017



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ARTICLE INFO

Article history:

Received 12 December 2018

Received in revised form 24 May 2019

Accepted 24 June 2019

Available online 5 July 2019

Keywords:

Hepatitis B virus

Cambodia

Seroprevalence

Vaccine

ABSTRACT

Background: Hepatitis B virus (HBV) infection is highly endemic in most low income countries including Cambodia. This nationwide serosurvey was conducted to assess the impact of hepatitis B vaccination and to determine whether Cambodia met the WHO regional 2017 target of hepatitis B surface antigen (HBsAg) seroprevalence less than 1% in five-year-old children.

Methods: A cross-sectional multi-stage cluster survey was conducted among children born during 2010–2012 and their mothers in Cambodia. HBsAg prevalence was estimated by rapid point-of-care testing, and demographic data, including vaccination history, was collected. Vaccine coverage in children and the prevalence of HBsAg among children and mothers was calculated taking into account the complex survey design. Factors associated with children's failure to receive timely (within 24 h) vaccination were analysed by multivariate logistic analysis.

Findings: A total of 2,520 children 5–7 years old and 2,028 mothers were recruited. In total, 78.4% of children received hepatitis B vaccination birth-dose (HepB-BD); of these, 58.7% were administered \leq 24 h. Birth at home or "other" location were independent risk factors for children's failure to receive timely HepB-BD. Overall HBsAg seroprevalence was 4.39% (95%CI: 3.53%–5.45%) among mothers and 0.56% (95%CI: 0.32%–0.98%) among children. The prevalence among children without hepatitis B vaccination was 4.62% (95%CI: 1.31%–14.97%). Among children with a HBsAg-positive mother, prevalence was 10.11% (95%CI: 5.41%–18.11%).

Interpretation: Having achieved the 2017 target of less than 1% HBsAg prevalence among 5 years old children, Cambodia can now focus on eliminating mother-to-child transmission of HBV. Moreover, the high HBsAg prevalence among mothers suggests that routine screening with proper linkage to care and treatment is needed. Strengthening measures to improve vaccination coverage further and eliminate mother-to-child transmission by coordinated programming with other services offering additional HBV interventions will help move towards the global goal of hepatitis B elimination by 2030.

Funding: As per sources of funding.

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Abbreviations: HBV, Hepatitis B virus; HBsAg, hepatitis B surface antigen; WHO, World Health organization; HepB-BD, hepatitis B birth dose vaccine; HepB, hepatitis B vaccine.

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<https://doi.org/10.1016/j.vaccine.2019.06.073>

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1. Research in context

1.1. Evidence before this study

Prior to the implementation of widespread use of hepatitis B vaccination (HepB) in children, hepatitis B virus (HBV) infection was a major public health concern in most low income countries of Asia, including Cambodia. In 2006, a nationally representative serosurvey in Cambodia conducted among 5 years old children born before HepB introduction revealed a 3.5% prevalence of chronic HBV infection. Pilot studies implemented in Siem Reap Province during 2009–2016 documented a hepatitis B surface antigen (HBsAg) prevalence of 4.6% among the general population (18 ~ 89 years old) and 2.02% among schoolchildren (8 ~ 11 years old). However, there has been no nationally representative hepatitis B serosurvey among children born after HepB introduction into Cambodia's National Immunization Program in 2005.

1.2. Added value of this study

This is the first large scale nationally representative serosurvey to assess the impact of HepB and to determine whether Cambodia met the WHO regional 2017 target of HBsAg prevalence <1% in 5 years old children.

This nationally representative serosurvey estimated the HBsAg prevalence among ≥ 5 years old children who represent a post-vaccine cohort as well as among their mothers who represent a pre-vaccine cohort. The HBsAg prevalence among mothers was 4.39% and that among ≥ 5 years old children was 0.56%. High prevalence of 10.11% (95% CI: 3.85–16.38) was found among children with HBsAg-positive mothers. Factors associated with children's failure to receive timely (within 24 h) hepatitis B birth-dose vaccine (HepB-BD) included home birth or birth at "other" location.

1.3. Implications of all available evidence

This nationwide survey indicates that Cambodia has achieved the 2017 regional target of HBsAg prevalence <1% in 5 years old children. Additionally, it assessed factors associated with the children's failure to receive the vaccination in a timely manner. The high prevalence of HBsAg among mothers indicates the need to improve timely HepB-BD coverage and 3 dose coverage. Further research is needed on the impact of additional HBV interventions to prevent mother-to-child transmission to help move towards the global goal of HBV elimination by 2030.

2. Introduction

Chronic hepatitis B virus (HBV) infection affected an estimated 257 million people globally in 2015, and the Western Pacific Region had an estimated 45% of all person with chronic HBV infection despite only having approximately 25% of the global population [1]. Approximately three-quarters of all deaths related to HBV in the Western Pacific Region occur in individuals infected perinatally or during early childhood (before 5 years of age) [2], making routine infant vaccination beginning at birth essential to interrupt both vertical and horizontal HBV transmission. In 2013, all 37 countries and areas in the Western Pacific Region, which includes Cambodia, agreed to a target of reducing hepatitis B surface antigen (HBsAg) prevalence to less than 1% by 2017 in five-year-old children born after vaccine introduction. [3,4].

With a nationally estimated burden of chronic HBV infection of 8.2% before hepatitis B vaccine introduction [5], the government of Cambodia began geographically phasing in hepatitis B vaccination

for infants beginning in 2001. Since 2005, hepatitis B vaccine has been included in the national immunization schedule for all infants, with the first dose given at birth, followed by 3 doses of hepatitis B-containing pentavalent vaccine administered at 6, 10 and 14 weeks.

In 2006, a nationally representative serosurvey conducted among 5 years old children born before hepatitis B vaccine introduction revealed a 3.5% (95% Confidence Interval (CI): 2.4%–4.8%) HBsAg prevalence [6]. In Siem Reap, the HBsAg prevalence was reported as 2.02% (95% CI: 0.27–3.77%) among children born from 1999 to 2005 [7]. A three province survey among children born from 2006 to 2007 showed the HBsAg prevalence was 0.33% in Phnom Penh, 1.41% in Kratie and 3.45% in Ratanakiri [8].

This nationally representative survey was conducted in 2017 to provide an accurate estimation of chronic HBV infection burden in Cambodia and to determine whether Cambodia has met the WHO regional target of <1% HBsAg prevalence in 5 years old children, and to identify appropriate additional strategies needed for hepatitis B prevention and control.

3. Methods

From March to April 2017, a nationally representative cross-sectional survey using a multi-stage sampling strategy was conducted to assess prevalence of HBsAg among two groups: (1) children 5–7 years old who were born after hepatitis B vaccination had been incorporated into Cambodia's national immunization schedule; and (2) their mothers, who represent a pre-vaccine cohort. Children born between March 2010 and February 2012 were eligible for inclusion. Exclusion criteria included children who were not able to give blood because of severe illness or hemophilia, and children whose caregivers did not provide consent for blood sampling. The survey design was based on WHO guidance for performing hepatitis B immunization surveys [9].

3.1. Sample size and sampling

Target sample size for the number of mothers and children to be enrolled was calculated using the formula as follows:

$$n = \frac{cz_{1-\frac{\alpha}{2}}^2 p(1-p)(1-ICC)}{cd^2 - z_{1-\frac{\alpha}{2}}^2 p(1-p)ICC}$$

where n = sample size; $Z_{1-\alpha/2}$ = critical value of normal distribution for 95% confidence; the expected HBsAg seroprevalence (p) = 1%; the absolute precision (d) = 0.5%; the probability of achieving the precision (α) = 0.05; an intra-class correlation coefficient (ICC) of 0.015; and the number of primary sampling units (c) = 70. For the study, 70 primary sampling units (PSUs) were set a priori, since that was the maximum number of PSUs that could be managed logistically. An initial sample size of 2240 was calculated and then adjusted to 2472 to account for 10% nonresponse. Dividing this final sample into 70 primary sampling units sets the target number of children to be approximately 36 per primary sampling unit, which translates into a final sample size of 2,520 mother-child pairs, for a total number of 5,040 participants.

Multi-stage sampling strategy with random selection at each stage was applied (Fig. 1). Assuming a target enrollment of 9 children and their mothers per cluster, a total of 280 clusters were required. We selected three strata (Phnom Penh, urban areas and rural areas). Seventy communes were selected among the three strata using the probability proportional to size. From each commune, four villages were randomly selected with replacement and probability proportional to size, resulting in 280 clusters selected from 269 separate villages. If a commune had less than

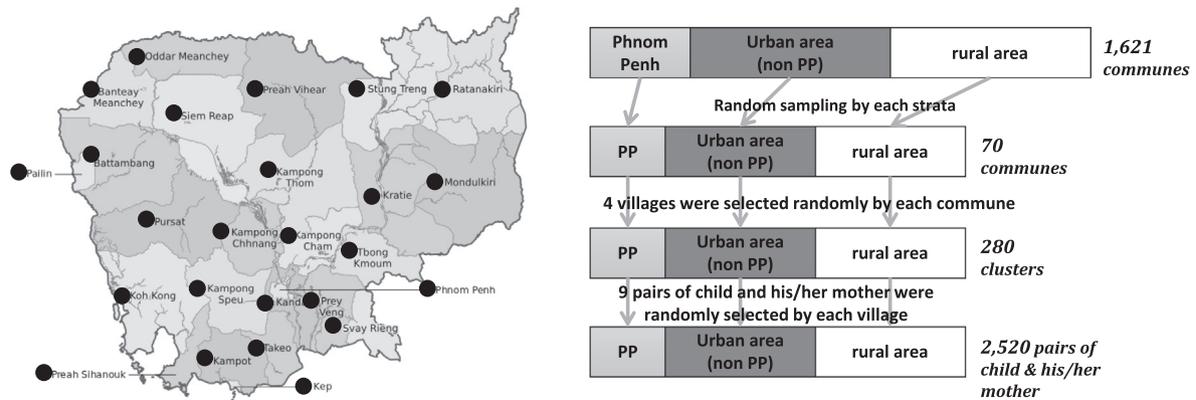


Fig. 1. Multi-stage stratified random sampling. Study subjects were selected from all provinces by multi-stage stratified random sampling.

four villages, other villages were selected from neighboring communes.

In each village, after picking a random start point, survey teams went house to house to identify and enroll the required number of age eligible children and their mothers. For 12 villages that did not have enough children to meet the required sample size, the remaining number of children was randomly selected from a neighboring village. Teams attempted to enroll mother and child pairs whenever possible, but to avoid potential bias in the selection of children enrolled, eligible children whose mothers were not present (e.g. deceased, away from village for work or other reasons) were enrolled as long as a parent/caretaker was present to provide consent.

3.2. Data collection

When consent was obtained, parents or caretakers of 5–7 years old children were asked to complete a brief face-to-face interview to provide general demographic information and vaccination history. Mothers of the children were asked additional questions about their vaccination history. The questionnaires were developed in English and then translated into Khmer version for the use in field work and back translated into English for countercheck. The protocol of this study prescribed the acquisition process of the vaccination history as follows: the survey team checks the immunization card first. If the immunization card is not available, go to the local health facility to check the vaccination registries. If there is no registry at the local health facility, record the verbal responses of the caretakers.

3.3. Specimen collection and testing

Approximately 50 μ L of blood was collected by finger prick from each study participant and tested in the field using the Alere Determine™ HBsAg point-of-care test strip (reported sensitivity: 95%–100%; reported specificity: 96%–100%).

3.4. Data management and analysis

All data were analyzed using JMP version 11 (SAS Institute, Cary, NC, USA). Proportions and accompanying Wilson 95% confidence intervals (CI) were calculated, accounting for the complex survey design. Hepatitis B vaccination coverage was calculated for all children who had a vaccination card, health facility vaccination records, or verbally reported vaccination history. To clarify the risk factors independently associated with children's failure to receive hepatitis B birth dose vaccination (HepB-BD) within 24 h after birth, multivariate logistic regression analysis using the step-

wise selection method was performed among 12 variables of the questionnaire which included mother's age, race, and education background; type of roof on house (as a measure of socioeconomic status [10,11]); occupation of head of household; total number of children; mother's knowledge about hepatitis B virus, vertical transmission of hepatitis B virus, and prevention by hepatitis B vaccine; mother's knowledge about her own hepatitis B status; whether the mother received any hepatitis B vaccine (self-reported); and place where the child was born. The risk factors independently associated with children's failure to receive any hepatitis B birth dose vaccination, whether within 24 h or given later, were also analysed in the same way. When evaluating potential factors related to vaccination history and seropositivity, vaccination data from all sources (immunization cards, health facility vaccination records and oral reports) were included. For all analyses, $p < 0.05$ was considered statistically significant.

3.5. Human subjects rights and ethics

Informed consent was obtained from the mother for her child and herself; if the mother was absent, the father or other caretaker was asked to provide consent for the child. Informed assent was obtained from all children in the study. All specimens and questionnaire data were de-identified, with reference only to a unique identifier. The study protocol was approved by the Cambodia National Ethics Committee for Human Research (392NECHR), the Ethics Review Committee for the WHO Western Pacific Region and the Ethical Committee for Epidemiology of Hiroshima University (E-573). This activity was reviewed in accordance with CDC human research protections procedures and was determined to be human subject research, but CDC involvement did not constitute direct engagement in human subject research.

3.6. Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

4. Results

A total of 2,520 children and 2,028 mothers consented to participate in this survey. Of the 2,520 enrolled children, 1,275 (50.6%) were male and the number of 5, 6 and 7 years old children were 1,237 (49.1%), 1,200 (47.6%) and 83 (3.3%) respectively (Table 1).

Table 1
Characteristics of enrolled children and their mothers, Cambodia, 2017.

CHILDREN (n = 2,520)		Number	%
Gender	Male	1,275	50.6
	Female	1,245	49.4
Age	5 years old	1,237	49.1
	6 years old	1,200	47.6
	7 years old	83	3.3
Region	Phnom Penh	144	5.7
	Urban	216	8.6
	Rural	2,160	85.7
Location of birth	Public hospital	512	20.3
	Community health center	1,271	50.4
	Home	486	19.3
	Other	248	9.8
Immunization Card	Available	1,846	73.3
	Seen vaccination record at Health Center	155	6.2
	Not available	519	20.5
Clinic where children received vaccine	Public Hospital	73	2.9
	Health Center	1,864	74.0
	Private Clinic	8	0.3
	Other	520	20.6
	Don't know	20	0.8
	Never received any vaccine	35	1.4
Vehicle for visiting clinic for receiving vaccine	By automobile (bus or car)	10	0.4
	By motorbike	1,609	64.7
	By bike	176	7.1
	On foot	542	21.8
Time spent travelling to the clinic to receive the vaccine	Other	148	6.0
	<15 min	1,245	50.1
	15–29 min	628	25.3
	30–44 min	417	16.8
	45–59 min	34	1.4
	>60 min	147	5.9
	No data	14	0.6
Percutaneous Exposures	Body or ear piercing	1,143	45.4
	Surgery	68	2.7
	Blood transfusion	29	1.2
	Tattooing	1	0.0
MOTHERS (n = 2,028)			
Maternal Education	No education/Primary School	1,468	72.4
	Secondary school/High school	438	21.6
	College or University	122	6.0
	Occupation of Head of Household	Farmer	963
Occupation of Head of Household	fisherman	70	3.5
	Laborer	349	17.2
	Other	646	31.9
	Roof of house	Tile	504
Roof of house	Metal/Aluminum	1276	62.9
	Other	248	12.3

Very few of 7-year olds were enrolled because in most cases 7 years old children were in the elementary school when we visited their home. Geographical distribution of children from selected areas in this survey was urban-Phnom Penh ($n = 144$; 5.7%), urban-non-Phnom Penh ($n = 216$; 8.6%) and rural ($n = 2,160$; 85.7%). A total of 1,783 children (70.7%) were born in a health facility (community health center or hospital), 486 (19.3%) were born at home and 248 (9.8%) in some other non-specified location. For the 737 children born outside a health center or a public hospital, 363 (49.3%) reported having a skilled birth attendant present (Table 1). Among the 2,028 participating mothers, virtually all (99.1%) were of Khmer nationality and ranged in age from 19 to 61 years with an average of 32.5 ± 6.1 years. Mothers reported a mean of 2.8 children (median: 2) with a range of 1–12 children. Among participating mothers, 1,468 (72.4%) had up to a primary school education, 438 (21.6%) had up to a high

school education and 122 (6.0%) had a college education (Table 1). The most common occupations reported for the heads of these households included farmers and fishermen (50.9%) and labourers (17.2%).

Immunization cards / vaccination records were available for review for 2,001 (79.4%) children. The vaccination history for the remaining 519 (20.6%) children was recorded based on parental/caretaker oral report (Table 1). In total, 74.0% of children (1,864) received vaccines at their local health centre, 2.9% received them at a hospital, <1% at private facilities and 20.6% were reported as receiving them at other non-specified places. To receive vaccinations, children and their caretakers typically travelled for 0–30 min (mean: 19 min, median: 12 min), with travel times beyond one hour reported for 5.9% of children. The most common mode of transportation to the vaccination site was by motorbike (64.7%) or on foot (21.8%). Combining information from immunization cards, clinical records and parental/caretaker oral reports, 78.4% (1,976/2,520, 95% CI: 74.2%–82.1%) reportedly received a HepB-BD: 1,145 (45.4%) children were reported as having received a timely HepB-BD (defined as administered within 24 h of birth), 737 (37.8%) within 1–7 days of birth, and an additional 60 (3.1%) greater than 7 days after birth (Table 2). Two thousand four hundred twelve (95.7%) children were reported to have received at least one dose of pentavalent vaccine. Three-dose pentavalent vaccine coverage was 88.7% (2,235/2,520, 95%CI: 86.4%–90.7%). Excluding histories based on caretakers' recall only, 1,621/2,001 (81.0%, 95%CI: 77.0%–84.5%) received a HepB-BD and 1,846/2,001 (92.3%, 95%CI: 90.3%–93.8%) received three doses of pentavalent vaccine (Table 2). Children born at home were statistically significantly less likely to receive a timely HepB-BD within 24 h (87/486; 17.9%) and to receive both a timely HepB-BD within 24 h and 3 doses of pentavalent vaccine (81/486; 16.7%) compared to children born at other places ($p < 0.0001$, respectively).

For multivariate logistic regression analysis involving the factors associated with receipt of HepB-BD within 24 h after birth (timely HepB-BD), 5 of 12 questionnaire variables were selected by the stepwise selection method ($p < 0.25$). Compared with children born at a public hospital, children born at home and “other” location were significantly less likely to receive timely HepB-BD (Birth at home: adjusted OR 0.26, 95% CI: 0.17–0.41, $p < 0.0001$, Birth at “other” location: adjusted OR 0.65, 95% CI: 0.43–0.99, $p = 0.0435$), and children born at health centres were significantly more likely to receive timely HepB-BD (adjusted OR 1.94, 95% CI: 1.46–2.58, $p < 0.0001$). (Table 3).

Among 2,520 children and 2,028 mothers, one mother's result of rapid point-of-care testing was invalid and one mother refused blood testing. Therefore, HBsAg status of 2,520 children and 2,026 mothers was determined by rapid point-of-care testing. The prevalence of HBsAg among children was 0.56% (95% CI: 0.32–0.98) and among mothers was 4.39% (95% CI: 3.53–5.45) (Fig. 2). HBsAg positivity among children varied greatly, depending on the mother's status ($p < 0.0001$); HBsAg positivity among mothers did not vary by age (Fig. 2). For all children, HBsAg positivity was as low as 0.17% (95%CI: 0.05–0.63) among those who received a timely birth dose. However, the prevalence among children was about the same as that of their mothers when they had not received any dose of HepB (4.62%, 95%CI: 1.31–14.97) (Fig. 3.1). Among children with HBsAg-negative mothers ($n = 1,937$), three children (0.15%, 95%CI: 0.05–0.46) were HBsAg-positive (Fig. 3.2). Among these children, the prevalence was 0.11% (95%CI: 0.02–0.65) if they had received a timely HepB-BD within 24 h and was 3.57% (95%CI: 0.63–17.71) if they had not received any HepB vaccination (Fig. 3.2). Among the 89 children whose mothers were HBsAg positive, nine were HBsAg-positive (10.11%, 95%CI: 5.41–18.11). Among these children, the prevalence was 3.13% (95%CI: 0.53–16.35) if they had received a timely HepB-BD, but was

Table 2
Hepatitis B vaccination coverage by questionnaire.

Type of vaccine	All subjects (N = 2,520)		Subject excluding oral report (N = 2,001)	
	N	(%, 95%CI)	N	(%, 95%CI)
HepB-BD				
Received	1,976	(78.4, 74.2–82.1)	1,621	(81.0, 77.0–84.5)
Timely (within 24 h)	1,145	(45.4, 42.1–48.9)	849	(42.4, 38.4–46.5)
1 – 7 days after birth	737	(29.2, 25.9–32.8)	691	(34.5, 30.6–38.7)
7 days and over after birth	60	(2.4, 1.7–3.4)	54	(2.7, 1.9–3.9)
Unknown/Other	34	(1.3, 0.9–2.0)	27	(1.3, 0.9–2.0)
Never received	544	(21.6, 17.9–25.8)	380	(19.0, 15.5–23.0)
Pentavalent (DTP-Hib-HepB)				
Received	2,412	(95.7, 94.4–96.7)	1,958	(97.9, 96.8–98.6)
3 dose and over	2,235	(88.7, 86.4–90.7)	1,846	(92.3, 90.3–93.8)
2 dose and under	177	(7.0, 5.7–8.7)	112	(5.6, 4.4–7.1)
Never received Pentavalent	108	(4.3, 3.3–5.6)	43	(2.1, 1.4–3.2)

Table 3
Multivariate logistic regression analysis for birth dose vaccination within 24 h.

Factor		n	AOR	95%CI	p-value	
Mother's race	Khmer	2,010	0.67	0.22	2.06	0.4783
	Other(reference)	18	1.00			
Roof of house	Tile(reference)	504	1.00			0.0673
	Metal/Aluminium	1,276	0.78	–	1.02	
	Cement/Bricks	38	0.61	–	1.25	
	Other	210	0.77	–	1.16	
Mother knows own infection status	Yes, infected	14	1.76	–	6.25	0.3758
	Yes, not infected (reference)	234	1.00			
	No/No answer/Do not know	1,780	0.75	–	1.11	
Place where child was born	Public hospital (reference)	408	1.00			<0.0001
	Health center	1,000	1.94	–	2.58	
	Home	415	0.26	–	0.41	
	Other	205	0.65	–	0.99	
Occupation of the head of household	Farmer	963	0.88	–	1.08	0.2179
	Other	1,065	1.00			

R² = 0.12, p < 0.0001, N = 2028.

AOR, adjusted odds ratio; CI, confidence interval.

Among 12 variables, 5 variables were selected by stepwise method (p < 0.25).

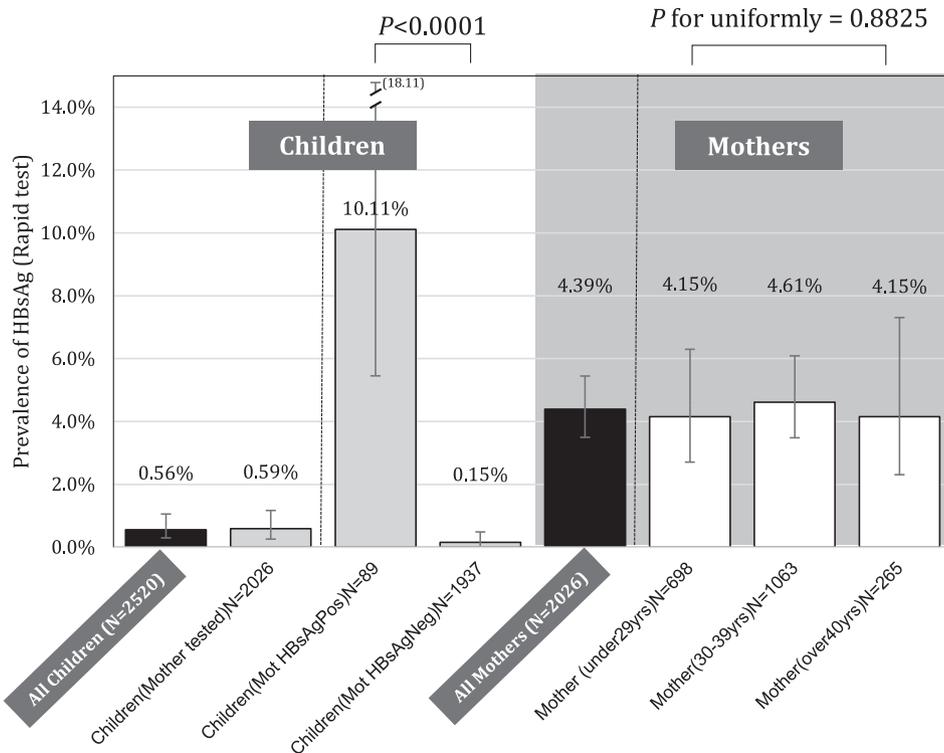
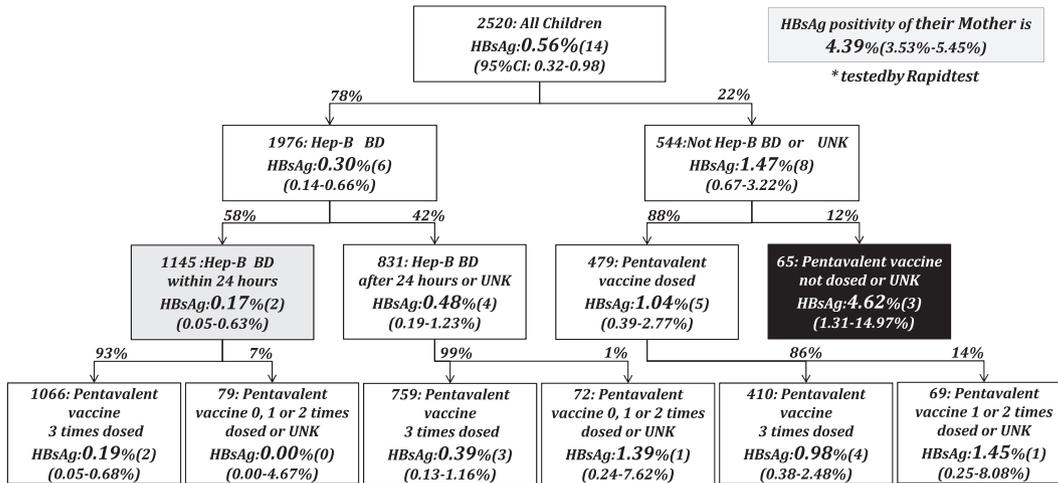
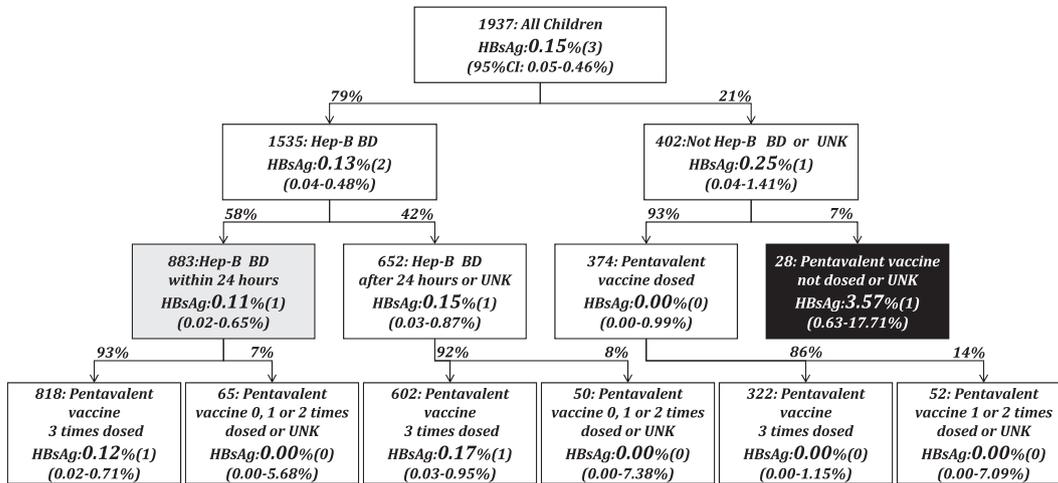


Fig. 2. HBsAg prevalence among children and their mothers. Prevalence of HBsAg is shown among children as follows: all children, children whose mother participated, children whose mothers were HBsAg-positive, and children whose mothers were HBsAg-negative. Age-specific prevalence of mothers is also shown. HBsAg: Hepatitis B surface antigen.

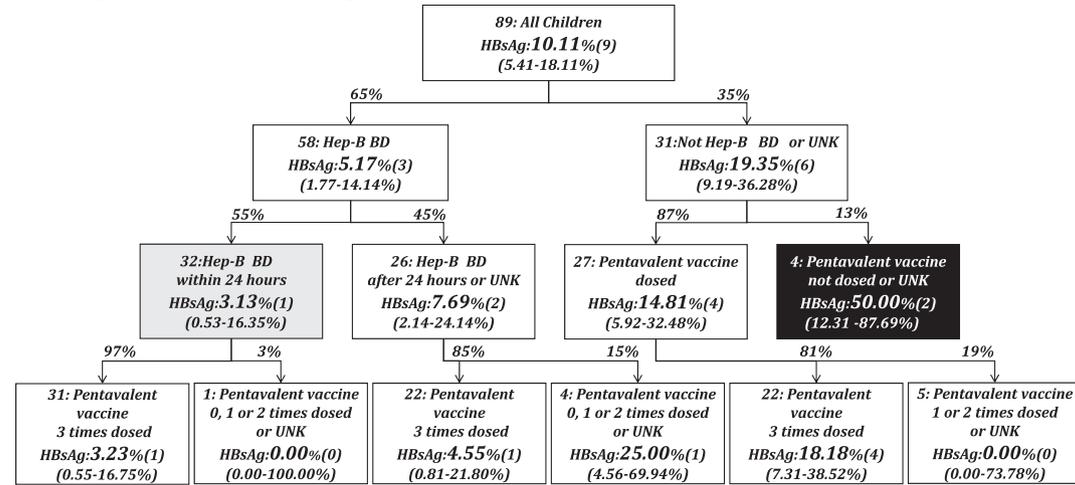
1) Among 2,520 children



2) Among 1,937 children with HBsAg negative mother



3) Among 89 children with HBsAg positive mother



HBsAg: Hepatitis B surface antigen
UNK: Unknown

Fig. 3. HBsAg positivity of children by Hepatitis B vaccine status. (1) HBsAg positivity of 2,520 children by Hepatitis B vaccine status. Prevalence of HBsAg among 2,520 children is shown by hepatitis B vaccine status based on classification tree. HBsAg: Hepatitis B surface antigen, UNK: Unknown. (2) HBsAg positivity of 1,937 children with HBsAg negative mother by Hepatitis B vaccine status. Prevalence of HBsAg among 1,937 children with HBsAg negative mothers is shown by Hepatitis B vaccine status based on classification tree. HBsAg: Hepatitis B surface antigen, UNK: Unknown. (3) HBsAg positivity of 89 children with HBsAg positive mothers by hepatitis B vaccination status. Prevalence of HBsAg among 89 children with HBsAg positive mothers is shown by Hepatitis B vaccine status based on classification tree. HBsAg: Hepatitis B surface antigen, UNK: Unknown.

50.0% (95%CI: 12.31–87.69) if they had not received any HepB vaccine (Fig. 3.3).

5. Discussion

This study represents the first nationally representative serosurvey conducted in Cambodia to evaluate the impact of hepatitis B vaccine introduction since 2005. Among 2,028 mothers enrolled in this survey, all were born before national vaccine introduction and 4.39% (95% CI: 3.53%–5.45%) were HBsAg-positive. Among the 2,520 children 5–7 years old enrolled in this survey, 88.7% received 3 doses of pentavalent vaccination from all sources (immunization cards, health facility vaccination records and oral reports); 78.4% received HepB-BD vaccine and 45.4% received a timely birth dose within 24 h; and only 0.56% (95% CI: 0.32%–0.98%) were HBsAg-positive.

There are some limitations for this study. First, we could not review immunization records for 22% of participants, whose vaccination history was obtained by oral reports. It is true that there is a possibility of recall bias, but in this study protocol, as a standard practice, it was prescribed to obtain verbal responses from subjects whose vaccination card nor vaccination registry was not available. As shown in Table 2, vaccination coverage in all subjects was slightly lower than in subjects excluding verbal responses. This result suggests that the analysis for vaccination efficacy in this study targeting all subjects is not overestimated. Second, the self-reported mother's hepatitis B vaccination history could also include recall bias. Third, since other HBV serum markers were not evaluated, it could not be accurately determined whether the HBsAg-positive mother's infection was acute or chronic. However, it was probabilistically considered to be a chronic infection. Fourth, the 95% sensitivity of point of care HBsAg rapid test used in this study may underestimate the true seroprevalence.

Even with these limitations, this study allowed us to assess HBsAg prevalence both in the pre- and post-vaccine introduction cohorts. We could not get all the children's mothers data but this study provides a snapshot of the efficacy of the Cambodia's national immunization program in reducing HBsAg prevalence from over 4% to less than 1% in just one generation. Based on the prevalence of HBsAg determined by this nationwide sero-epidemiological study and accompanying nationally reported data, Cambodia was subsequently verified by the WHO Western Pacific Region's independent Hepatitis B Immunization Expert Resource Panel in 2018 as having met the regional hepatitis B control goal of reducing the prevalence of HBsAg among children to less than 1% by 2017, and it joins 20 of 37 other countries and areas in the region that have reached the target [12,13].

Since including hepatitis B vaccine into the national immunization schedule for all infants in 2005, Cambodia's HepB-BD coverage has steadily increased from 25% in 2007 to 83% in 2016, with 3-dose pentavalent vaccination coverage remaining above 90% since 2008 and above 95% since 2014 [14]. The results of HBsAg positivity of children by hepatitis vaccine status in this study suggested the importance of receiving a HepB-BD, especially timely birth dose, and 3-dose pentavalent vaccine. Based on the result of the multivariate analysis, birth at home or "other" location were independent risk factors for children's failure to receive a timely HepB-BD. According to the Annual Operational Plan of National Immunization Program (NIP), Cambodia's Ministry of Health performed numerous communication efforts to reach target families and to train midwives and new health facility staff on the importance of hepatitis B vaccination in 2015. Cambodia's Ministry of Health has also advocated for and made concerted activities to promote delivery in health facilities or by trained health care workers [15]. This includes midwives and skilled birth attendants, who are

given a \$15 USD centrally-funded financial incentive for delivery at health centers. This financial incentive better ensures that newborns receive a hepatitis B birth dose within 24 h of birth and has served to better coordinate postnatal care services between maternal, newborn and child health and national immunization programmes. As a result of these efforts, health facility birth rates increased from below 20% in 2006 to 85% in 2016 [16]. In addition, families bringing in their newborns to receive a HepB-BD are also encouraged to have infants complete the 3 doses of HepB and subsequent routine immunizations. In this study, 70.7% of children born in 2010–2012 were reported to have been born in a health facility (health center or hospital) and children who were born at home were significantly less likely to receive birth dose vaccination or 3-dose vaccination. These results suggested that Cambodia's measures described above have been successful. Therefore, if Cambodia maintains and increases facility births, it is expected that it would be on track to eliminate mother-to-child transmission (MTCT) of HBV as a result of an increase in timely hepatitis B birth dose coverage.

On the other hand, the high HBsAg prevalence of 4.39% among mothers suggests the need to include additional interventions to reduce the chronic hepatitis B burden. Currently, Cambodia lacks a strategy or national policy on screening pregnant women for hepatitis B. While pregnant women are routinely screened for HIV and syphilis at no cost during antenatal visits, hepatitis B screening of pregnant women is largely paid out of pocket.

In order to make future progress in Cambodia towards the global goal of 0.1% prevalence among children by 2030 and the regional goal of eliminating mother-to-child transmission of HBV [17,18], routine antenatal screening for HBsAg at no cost should be considered if additional hepatitis B interventions, including providing hepatitis B immunoglobulin for newborns of infected mothers, and potential antiviral treatment for mothers with high viral loads are available. However, expansion of these services should be provided through a coordinated and incremental approach, ensuring and building upon high immunization coverage and determining expansion based upon the country's context as well as empiric data that shows the cost per perinatal infection prevented for each intervention. Although coverage with birth dose has increased to 78.4%, timeliness is still an issue. Population coverage with timely birth dose within 24 h was 45.4%, so improving timely HepB-BD coverage should be given attention especially since the regional goal for timely HepB-BD is $\geq 95\%$. Triple elimination of mother-to-child transmission of HIV, hepatitis B and syphilis proposes a coordinated approach under the shared Maternal, Newborn and Child Health platform so that immunization, screening, HBIG administration, and treatment can be administered more efficiently and cost-effectively to achieve regional MTCT elimination targets for HIV, hepatitis B and syphilis [18].

Author contributions

Prof. Junko Tanaka has full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Junko Tanaka, Md. Shafiqul Hossain, Joseph Woodring, Ork Vichit, Annemarie Wasley. Management of study implementation: Junko Tanaka, Ork Vichit, Md. Shafiqul Hossain, Joseph Woodring, Annemarie Wasley. Conducting the study and training of field staff: Ork Vichit, Md. Shafiqul Hossain, Joseph Woodring, Junko Tanaka, Annemarie Wasley, Shintaro Nagashima, Chikako Yamamoto, Chuon Channarena, Masayuki Ohosa, Tomoyuki Akita, Ko Ko, Mao Bunsoto. Data management: Mao Bunsoto, Masayuki Ohisa, Junko Tanaka. Data analysis: Tomoyuki Akita, Junko Tanaka. Interpretation of data: Junko Tanaka, Joseph Woodring, Md. Shafiqul Hossain, Ork Vichit.

Manuscript development: Joseph Woodring, Md. Shafiqul Hossain, Aya Sugiyama, Junko Tanaka. Critical revision of the manuscript for important intellectual content: Junko Tanaka, Joseph Woodring, Md. Shafiqul Hossain. Study supervision: Junko Tanaka.

Declaration of Competing Interest

The author declares no conflict of interests.

Acknowledgments

The authors are grateful to the following collaborating researchers and private donors:

Dr Shunji Mishiro for his invaluable help via the AAOHELP (Asia-Africa-Oceania Hepatitis Expert Linkage Promotion) project of Viral Hepatitis Research Foundation of Japan; Dr Keiko Katayama and Dr Tomoki Sato for participation in this survey; Professor Vonthanak Saphonn, Rector of the University of Health Science, Cambodia, for cooperation on this survey; and Dr Terumi Kaishima, Dr Toshiko Fujii and Dr Ayako Tabuchi for their generous donations for this survey.

Sources of funding

This study was financially supported by.

- 1) Hiroshima University, Department of Epidemiology, Infectious Disease Control and Prevention, Japan.
- 2) Project Research Centre for epidemiology and prevention of viral hepatitis and hepatocellular carcinoma, Hiroshima University, Japan (Director: J. Tanaka)
- 3) World Health Organization: WHO, The Expanded Programme on Immunization (EPI).
- 4) Viral hepatitis Research Foundation of Japan (AAOHELP: Asia-Africa-Oceania Hepatitis Experts Linkage Promotion)
- 5) National Center for Global Health and Medicine: NCGM (Contact Number: 29-2)

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.06.073>.

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