Title

Assessment of the Anti-HBs Antibody Response in Beninese Infants Induced by a Scheme of 4 Doses of HBV Vaccination with a Birth Administration in Comparison to the Routine Scheme of 3 Doses; A Cross-sectional Survey.

Authors

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Abstract

Hepatitis B virus (HBV) infection is still one of the major neglected health issues worldwide with high endemicity in sub-Sahara Africa (SSA) settings where more than 8% of the population remain chronic HBV carriers. Recently, WHO recommends that all infants should receive their first dose of HBV vaccine as soon as possible after birth. However, HBV birth dose has not been implemented in most SSA countries through the expanded programme immunization (EPI). From April to September 2017, a cross-sectional survey conducted in two vaccine units located in Southern Benin, we have assessed the sustainable anti-HBs antibody response in infants induced by a standard scheme of 3 doses of HBV vaccination (6, 10, 14 weeks) in comparison to a scheme of 4 doses with a birth dose (0, 6, 10, 14 weeks). Blood samples were systematically collected in the first 140 children at age 9 months and in their mothers who had consented to participate during the study period. The prevalence of HBV infection among infants and mothers was 2.2% and 7.1% respectively. The geometric mean anti-HBs antibody level was 174.1 UI/L. Infants with 4 doses of HBV vaccine had an anti-HBs antibody level significantly higher than those with 3 doses of vaccine (557.9 UI/L vs. 386.9 UI/L, respectively, *P*=0.03). After considering potential confounding factors, we showed that the scheme of 4 doses with a birth administration was significantly associated with a higher sustainable protective response in comparison to the scheme of 3 doses (aOR 2.49, 95% CI 1.03-6.03, *P*=0.04). This result brings additional evidence of the importance of the birth HBV vaccine dose. This highlights the need for additional studies to well-established the cost-effectiveness of such a strategy before implementing the birth HBV vaccine in the EPI.

Key words: Hepatitis B virus; vaccination scheme; sustainable protective response; Benin

Introduction

Hepatitis B virus (HBV) infection is the most common chronic viral infection and remains a significant cause of morbidity and mortality worldwide [1]. An estimated one third of the world's population has been infected, and more than 350 million are chronic carriers of the virus [2]. In the 2017, HBV resulted in 325 400 deaths, mostly due to complications such as cirrhosis and hepatocellular carcinoma [3]. The hepatitis B surface antigen (HBsAg) seroprevalence was 3.6% worldwide with highest endemicity in countries of African region (8.8%) [1]. Benin is one of the highest endemicity countries of HBV in sub-Saharan Africa (SSA) with over 1.4 million infected people [4] and a prevalence of HBV infection estimated to 16% [1].

In Benin, the routine immunization program for neonates and infants include many vaccine preventable diseases (Table 1). However, the EPI is mainly focused on measles, diphtheria, pertussis, tetanus, polio, tuberculosis, hepatitis B, haemophilus influenza type b, pneumococcus and yellow fever. Only vaccines included in the EPI are provided free of charge for parents as they are supported by the Beninese government through GAVI and UNICEF sponsorships. Women of reproductive age are given tetanus toxoid vaccine to protect their babies from tetanus.

Since perinatal or early postnatal transmission, particularly during infancy, is the major source of chronic HBV infection, WHO recommends that all infants should receive their first dose of vaccine as soon as possible after birth, ideally within 24 h [5]. In most of SSA countries including Benin, the initiation of the HBV birth vaccine dose is not yet included in the national immunization program through the expanded program on immunization (EPI). However, some health centers apply this recommendation but the fees are in charge of child's parents and are expensive (~ 8 USD per vaccine dose). In addition, little is known about the

efficacy of a birth vaccine dose administration to provide a sustainable protection against HBV among Beninese infants. Moreover, data available on prevalence in infants and young children are particularly sparse.

The aim of the present study was to assess the efficacy of the scheme of 4 doses of HBV vaccine with a first dose initiation at birth to induce a sustainable protective response against HBV infection in comparison to 3 doses traditionally used in the Beninese EPI among infants during the first months of life. Secondly, we determined the HBsAg prevalence among a vaccinated infant population. As well, we have also evaluated the efficacy of the 4 doses scheme in infant born with a poor birth outcome such as small birthweight for gestational age (SGA), premature birth (PTB), and low birthweight (LBW).

Methods

Study design and population

We conducted a cross-sectional study, from April to September 2017, to compare the humoral response induced by a scheme of 4 doses of HBV vaccination with a birth initiation dose to a traditional 3 doses of HBV immunization schedule applied by Beninese EPI among infants aged to 9 months' old. The HBV vaccine schedule was retrospectively assessed using the vaccination card. During the study period, all parents of eligible infants from the two study sites, whatever the HBV vaccine doses received (either 3 or 4 doses), were systematically approached to participate in the survey.

The study population was composed of children aged to 9 months with updated HBV vaccination for 3 or 4-doses schedule and who attended health facilities for measles and yellow fever vaccination as part of routine immunization schedule. The mothers of these infants have also been investigated. To be recruited, infant had meet the following criteria:

being in the 9th month of life, completed the 3 doses of HBV vaccine according to the EPI or 4 doses of HBV vaccines (3 doses of the EPI plus the birth dose), no severe health conditions at the time of the survey, acceptance of blood sample, and given informed consent by the parents/guardian.

We used convenience sampling recruitment. The first one hundred and forty infants, in which parents have given their consent, were enrolled, between April and September 2017, in two health centers, "Centre de Santé de Cotonou I" and "Centre Hospitalier Universitaire de la Mère et de l'Enfant-Lagune" (CHU-MEL), both located in Southern Benin. The study was approved by the institutional review board from CHU-MEL and the departmental direction of Ministry of Health.

Vaccination schedule

The HBV vaccination was administrated, as part of a fixed combination (Shanta®, Sanofi, Telangana, Inde) with other vaccines including inactivated polio, diphtheria-tetanus-pertussis (DTP), haemophilus influenza type b. Two different schemes of HBV vaccination were given to children: (i) 3-doses schedule at 6, 10, and 14 weeks, respectively; and (ii) 4-doses schedule, where a monovalent birth dose is followed by 3 doses at 6, 10, and 14 weeks, respectively. The birth dose consisted of administering 10 µg of recombinant HBV vaccine (Euvax B®, LG Life Sciences, Korea) intramuscularly in the deltoid muscle within 24 hours of life.

Study procedures

After obtaining parent's informed consent, we collected sociodemographic and economic characteristics of infant's family (infant gender, mother's age, gravidity, education and parent's profession), the pregnancy history (adverse pregnancy outcomes: LBW, PTB, SGA). Anthropometric data such as weight and height were recorded in the couple mother-infant in

order to assess their nutritional status. Information about timing of exclusive breast feeding, as well as the mother and infant HBV status have been also collected.

Blood specimens (5 mL, dry tube) were obtained in children for anti-HBS antibody quantification and for serology. Testing of the serological specimens was performed with test kits marketed by the Monolisa® Anti-HBs Plus (Bio-Rad laboratory). Antibody concentrations against the surface antigen (anti-HBs) were detected by a quantitative and qualitative enzyme-linked immunoassay (ELISA) also marketed by the Bio-Rad Diagnostic System ELISA test system. Anti-HBs concentrations were measured and reported in UI/L using WHO international reference standard [6].

In the assay procedure, participant serum and controls were incubated with the antigen-coated microwells. If antibodies to HBs were present in a specimen or control, they bound to the antigen. Excess sample was removed by a wash step. The conjugate was then added to the microwells. The conjugate bound to any antigen-antibody complexes present in the microwells. Excess conjugate was removed by a second wash step, and a chromogen/substrate solution was added to the microwells and allowed to incubate. If a sample contained anti-HBs, the bound enzyme (HRP) caused the coloration of tetramethyl-benzidine in the chromogen solution which turned into blue. The blue color turned into yellow after the addition of a stopping solution. If a sample did not contain anti-HBs, the chromogen/substrate solution in the well remained colorless during the substrate incubation, and after addition of the stopping solution. The color intensity, measured spectrophotometrically, was proportional to the amount of anti-HBs present in the serum. Absorbance value readings for participant serum were compared to a cutoff value determined by the 10 UI/L calibrator.

Definition

According to the magnitude of the anti-HBs concentrations, three classes of subjects were identified: (i) “non-responders” with anti-HBs levels < 10 UI/L; (ii) “responders” with anti-HBs levels between 10 and 100 UI/L; (iii) “high responders or sustainable response” with anti-HBs levels ≥ 100 UI/L. LBW and PTB were defined as a birthweight <2500 g and a gestational age <37 weeks, respectively. SGA was defined as a birth weight < 10^{th} percentile for gestational age using INTERGROWTH-21^{st} charts [7].

Data management and statistical analysis

Data were entered into Microsoft Access database and analyzed with Stata 13.0 Software (Stata Corp, College Station, TX). We first described the baseline characteristics of mother-infant pair according to the vaccination scheme. Anti-HBs concentrations were log-transformed prior to calculating geometric mean concentration. Means were compared using Student’s *t*-test whereas proportions were compared using a Chi-square test or Fisher exact test, as appropriate.

The relationship between anti-HBs concentration, sustainable protective response and different vaccination schemes were studied by using univariate linear and logistic regressions. In order to take into account potential confounding factor, a multivariate regression model was performed using *P* values < 0.20 in univariate analysis. Manuel backward selection procedure was performed and a *P*-value below 0.05 was considered statistically significant.

Results

A total of one hundred and forty (140) mother-infant pairs were enrolled in this study. Table 2 presents the general characteristics of the study population. Mothers had an average age of 28.7 years and 36.4% of them were primigravidae. More than three-quarters of women (89.2%) were literate and 75.5% had a profession with income. A high proportion of women

had an abnormal body mass index (71%). The prevalence of HBV infection among women was 7.1% and only 11% had an updated HBV vaccination during the pregnancy. All children were aged to 9 months at the time of the survey and 47.9% were female. The prevalence of underweight, stunting and wasting were 9.5%, 8.2%, 10.4%, respectively. Most mothers (82%) declared to give exclusive breastfeeding to their infant for more than 6 months. The proportion of infants born with LBW, PTB and SGA were 22.4%, 13.8%, 23.9%, respectively. Less than 3% of infant presented HBV infection. Maternal and infant sociodemographic, nutritional characteristics and HBV status were similar between infants who received 4 doses (n=72) and those with 3 doses (n=68) of vaccination (Table 2).

The geometric mean anti-HBs' antibody level was of 174.1 UI/L (95% confidence interval [CI]: 121.2-250.2). Figure 1 presents the distribution of the mean concentration of anti-HBs' antibody according to the vaccination scheme. Infants with 4 doses of HBV vaccine had an anti-HBs antibody level significantly higher than those with 3 doses of vaccine (557.9 UI/L vs. 386.9 UI/L, respectively, *P*=0.03). The proportion of infant with a sustainable protective response among infant with 4 doses of vaccination was significantly higher in comparison to infants with 3 doses of vaccination (80.6% vs. 65.6%, respectively, *P*=0.03; Figure 2).

The univariate linear and logistic regressions (Table 3) showed that scheme of 4 doses was significantly associated with a higher mean concentration of anti-HBs' antibody (coefficient 170.9, 95% CI 14.9-327.1, *P*=0.03) and with a sustainable protective response against HBV (odds ratio 2.37, 95% CI 1.08-5.25, *P*=0.03). Even restricting the analysis on infants born from non-infected and non-vaccinated mothers, we observed the same trend in the results (Table S1). After considering the potential confounding factors, the scheme of 4 doses of vaccine remains significantly associated with a sustainable protective response (adjusted odds ratio 2.49, 95% CI 1.03-6.03, *P*=0.04). Regarding the distribution of protective response among infant with a poor birth outcome (Figure 3), we observed that the proportion of

sustainable response was higher among infant with LBW, PTB, SGA who received 4 doses of vaccine than those who received 3 doses of vaccine (72.3% vs. 52.6%; 100% vs. 66.7%; 60% vs 52.6%, respectively) with a borderline significant association for PTB.

Discussion

It is the first time that the efficacy of 4 doses of HBV vaccines with a birth administration, for obtaining a sustainable protective response, is assessed in Benin. In SSA countries, HBV vaccine coverage remains low or incomplete (< 70% of vaccine coverage for whole Africa) and HBV birth-dose vaccination has not yet been implemented in the WHO-sponsored EPI [8]. In Benin, the percentage of infants under 1 year who have completed 3-doses of HBV vaccination is less than 75% [9] and the prevalence of HBV maternal/child transmission is around to 20% [10]. This is a worrying health issue as it is well-known that over 90% of children infected in early life become chronic carriers of HBV, with a high risk of liver cancer [11,12]. Immunogenicity studies for efficacy of scheduled and number administered doses of HBV vaccination are particularly uncommon in West Africa.

In the present study, we have shown that the scheme of 4 doses with a birth administration was significantly associated with a sustainable protective response than the traditional scheme of 3 doses to infants during the first year of life. A meta-analysis of randomized controlled trials of HBV vaccine administered at birth had previously shown that immunized infants born to mothers infected with HBV were 3.5 times less likely to become infected [13]. Ekra *et al.*, have shown, through a non-randomized vaccine effectiveness trial in Côte d'Ivoire, that children born of HBsAg positive women who received a birth dose of vaccine had a modest decrease in risk of becoming HBsAg positive [14]. One British study has previously reported that delaying the birth dose resulted in an increased risk of HBV infection [15]. In addition, several studies have also supported the short-term efficacy of HBV vaccine in neonates for

reducing vertical transmission [16–18]. However, our result contrasts with some studies. Das *et al.*, did not find any difference between standard routine HBV vaccination and the schedule vaccination including birth dose [19]. This difference could be partially explained by the number of administered doses of HBV vaccine. Indeed, in our study, the birth dose was followed by 3 additional doses of HBV vaccine (4 doses vs. 3 doses in Das *et al.*, study). The sustainable protective response from HBV vaccination is related to the induction of anti-HBs antibodies, but also involves the induction of memory T-cells [20]. Apart from the beginning of the primary vaccine regime (birth or later in infancy), the vaccine dosage, the number of vaccine doses given, the gap time between last and preceding dose, and the use of plasma-derived or recombinant vaccines are the main determinants of long-term protection after HBV vaccination in infancy [21].

We also found that infants born with poor birth outcomes (LBW, PTB, SGA) who received 4-doses of HBV vaccine with a birth administration had a highest proportion of sustainable protective response than those who received 3-doses through routine EPI by 9 months age, although this result did reach borderline statistical significance for PTB. Early immunization of preterm newborns still remains much debated. Some authors agree with the early immunization of preterm newborns as soon as possible clinically [5,22], and on the other hand, others showed the short-term advantage of delayed vaccination of preterm babies [23,24]. But, as most of these studies were conducted in high-income countries, the results should be interpreted with caution as part of developing countries context, and hence deserve further studies.

This study has some limitations that should be considered. Most importantly, it was not a randomized clinical trial, and there could be confounding factors that may have affected the study' results despite the multivariate adjustments. We also did not measure the anti-HBs antibody concentration of mothers during pregnancy and at the time of the survey. That could

have allowed taking into account the mother-to-foetus antibody transfer during pregnancy. Finally, we measured antibody levels at age 9 months, while optimal antibody concentrations likely occur earlier at 1–2 months' post-vaccine dose. This may limit comparisons with other studies.

Several points argue in favour to implement HBV vaccine dose in the EPI in low-income countries, as recommended by WHO. First, HBV is most commonly spread from mother to child at birth, or from person to person in early childhood in highly endemic-areas [25–29]. Secondly, infection in adulthood leads to chronic hepatitis in less than 5% of cases, whereas infection in infancy and early childhood leads to chronic hepatitis in about 95% of cases [29]. Finally, as the HBV status during pregnancy remains often unknown in Benin because only a low proportion of pregnant women complete the prenatal biological check-up due to lack of financial resources, vaccinating all children with a birth HBV dose, could be decisive for controlling HBV infection. Also, more than four in five live births (84%) occurred in a health facility and 15% at home. In addition, 78% of births were performed by a qualified personnel [9]. There is, therefore, a good opportunity, to provide the birth dose of HBV vaccine to newborns by a health professional.

Our study has highlighted the importance of early immunization during the neonatal period for conferring a sustainable protective response again HBV infection throughout the first months of life where the risk of infection is higher. However, it's important to keep in mind that neonatal immunization has not yet completely eradicated mother-to-infant HBV transmission [30]. These findings emphasize a need for further evaluations on HBV vaccine in SSA settings to determine if a birth dose is cost-effective for African children and if our local governments and medical authorities should invest additional financial and logistical resources for implementing the HBV birth vaccine dose into the EPI. Nevertheless, ensuring that all infants receive a dose of HBV vaccine within 24 hours of birth requires implementing

specific measures such as increasing the number of infants born in facilities or attended by trained health staff.

Conflict of interest.

None declared

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Authors contributions.

M.A., C.V.A., and E.L. conceived and designed the study. M.A., E.A., and Y.D. analysed the data. C.V.A., S.B., A.Y., M.A. and E.L. contributed reagents, materials, and analysis tools. M.A., C.V.A., E.L., A.Y., S.K.A., S.I. drafted and finalized the manuscript. The final manuscript was read and approved by all authors.

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Figure legends

Figure 1. Distribution of anti-HBs concentrations according to the scheme of vaccination.

* Scheme of 3 doses of HBV vaccination (6, 10, 14 weeks); ** Scheme of 4 doses of HBV vaccination (0, 6, 10, 14 weeks); *** P value <0.05

Figure 2. Distribution of infants included in the study according to the magnitude of the anti-HBs levels (non-responders: <10 UI/L; responders: 10-100 UI/L; high responders or sustainable response: ≥100 UI/L).

* Scheme of 3 doses of HBV vaccination (6, 10, 14 weeks); ** Scheme of 4 doses of HBV vaccination (0, 6, 10, 14 weeks)

Figure 3. Distribution of infant with a sustainable protective response born with a poor birth outcome.

Abbreviations: LBW, Low birthweight; SGA, Small birthweight for gestational age; PBO, Poor birth outcome.

* Scheme of 3 doses of HBV vaccination (6, 10, 14 weeks); ** Scheme of 4 doses of HBV vaccination (0, 6, 10, 14 weeks)

Tables

Table 1. Immunization program for neonates, infant and pregnant women recommended in Benin

Vaccine, Year[$]	Description	Schedule	Comments
Infant vaccination schedule included in the EPI*			
BCG, 1982	Bacille Calmette-Guérin vaccine	Birth	Free of charge
OPV, 1982	Oral polio vaccine	Birth; 6, 10, 14 weeks	Free of charge
DTP-Hib-HepB, 2005	Diphteria, Tetanus, Pertussis, Haemophilus influenza, and Hepatitis B vaccine	6, 10, 14 weeks	Free of charge
PCV 13, 2011	Pneumococcal conjugate vaccine	6, 10, 14 weeks	Free of charge
IPV, 2015	Inactivated polio vaccine	14 weeks	Free of charge
Measles, 1982	Measles vaccine	9 months	Free of charge
YF, 2002	Yellow fever vaccine	9 months	Free of charge
Infant vaccination schedule not included in the EPI			
HepB	Hepatits B vaccine	Birth	Charged
RV	Rotavirus vaccine	10, 14 weeks	Charged
MenA	Meningococcal A vaccine	9 months	Charged
MCV	Meningococcal conjugate vaccine ACYW135	12 months	Charged
PCV	Pneumococcal conjugate vaccine	18 months	Charged
DTPHibHepB	Diphteria, Tetanus, Pertussis, Haemophilus influenza, and Hepatitis B vaccine	18 months	Charged
IPV	Inactivated polio vaccine	18 months; 6, 11-15 years	Charged
MMR	Measles, mumps, and rubella vaccine	18 months	Charged
TCV	Typhoid conjugate vaccine	24 months, booster every 3 years	Charged
DTaP	Diphteria, Tetanus, acellular pertussis vaccine	6, 11-15 years	Charged
HPV	Human papillomavirus vaccine (females)	9-13 years	Charged, 2nd dose 6 months after 1st dose
Pregnant women or non-pregnant women of childbearing age vaccination schedule			
TT	Tetanus toxoid vaccine	1st contact pregnancy; +1, +6 months; +1, +1year	5 doses

*National Agency of the Expanded Program on Immunization and Primary Health Care; $ Year of introduction in the EPI
EPI: Expanded program on immunization

Tables

Table 2. General characteristics of mothers and infants at 9 months of life included in the study, Southern Benin, 2017 (N=140)

Characteristics		All participants	3 doses of vaccination (n=68)	4 doses of vaccination (n=72)	*P* value[a]
			Mean[b] (± SD) or %	Mean[b] (± SD) or %	
Infants characteristics					
Gender	Female	47.9%	50.7%	49.3%	0.62
Weight (g)		8368.9 (± 1408.1)	8275.3 (± 1351.5)	8450.1 (± 1460.6)	0.49
Height (cm)		72.4 (± 6.0)	71.4 (± 5.1)	73.2 (± 6.6)	0.09
Underweight [c]	Yes	9.5%	13.6%	5.9%	0.15
Stunting [d]	Yes	8.2%	8.6%	7.8%	0.87
Wasting [e]	Yes	10.4%	12.1%	8.9%	0.57
Exclusive breastfeeding (> 6 months)	Yes	81.7%	79.3%	83.8%	0.51
Low birthweight (birthweight < 2500g)	Yes	22.4%	29.2%	15.9%	0.07
Premature birth (gestational age < 37 weeks)	Yes	13.8%	17.5%	10.6%	0.27
Small birthweight for gestational age [f]	Yes	23.9%	33.3%	15.6%	0.02
HBV status	Positive	2.2%	1.5%	2.8%	0.58
Maternal characteristics					
Age, years		28.7 (± 4.8)	28.8 (± 4.7)	28.6 (± 4.9)	0.84
Primigravidae	Yes	36.4%	38.2%	34.7%	0.67
Body mass index, kg/m²	< 18.5	3.8%	6.3%	1.5%	
	18.5-24.9	29.0%	26.9%	30.9%	0.41
	25.0-29.9	29.0%	31.7%	26.5%	
	≥ 30	38.2%	34.9%	41.2%	
Education	Literate	89.2%	88.1%	90.3%	0.67
Profession with income	Yes	75.5%	77.6%	73.6%	0.58
HBV status	Positive	7.1%	8.8%	5.6%	0.45
Updated vaccination during pregnancy	Yes	11.0%	10.8%	11.3%	0.92

Abbreviations: SD, standard deviation; HBV, Hepatitis B virus

[a] The student's *t*-test and χ^2 test were used for comparing continuous and categorical variables, respectively.

[b] Arithmetic mean

[c] Underweight was defined as a weight-for-age z-score < -2 standard deviation

[d] Stunting was defined as a weight-for-age z-score < -2 standard deviation

[e] Wasting was defined as a weight-for-length z-score < -2 standard deviation

[f] Small birthweight for gestational age was defined as being at 10th percentile of birthweight for gestational age using INTERGROWTH-21st charts

Tables

Table 3. Effect of scheme of 4 doses vs. 3 doses of vaccination on the Sustainable Protective Response against Hepatitis B Virus among infants of 9 months old, Southern Benin, 2017 (N=140)

Scheme of vaccination	% of infant with anti-HBV sustainable protective response	Univariate analysis			Multivariate analysis		
		OR	95% CI	*P* value	aOR[†]	95% CI	*P* value
3 doses (n=68)	65.6	1			1		
4 doses (n=72)	80.6	2.37	(1.08, 5.25)	0.03	2.49	(1.03, 6.03)	0.04
Scheme of vaccination	Anti-HBV mean*antibody concentration (UI/L)	Mean difference	95% CI	*P* value	Mean difference [‡]	95% CI	*P* value
3 doses (n=68)	116.4	1			1		
4 doses (n=72)	249.1	170.9	(14.9, 327.1)	0.03	126.6	(-36.4, 289.7)	0.12

Abbreviations: HBV, Hepatitis B Virus; OR, Odds ratio; aOR, Adjusted odds ratio; CI, Confidence interval.

* Geometric mean

† Adjusted for infant wasting and maternal education.

‡ Adjusted for infant wasting, maternal age, maternal profession and household density.

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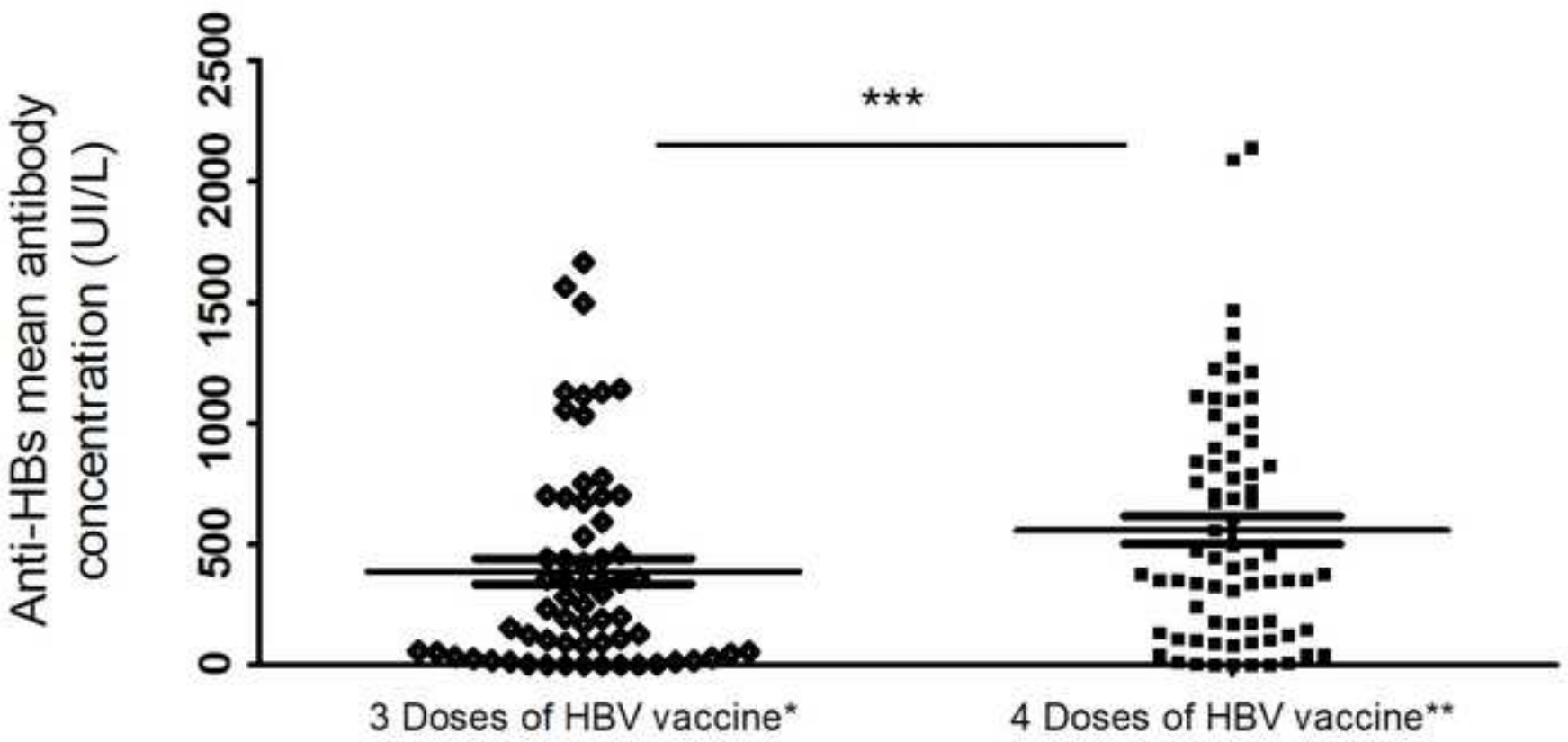

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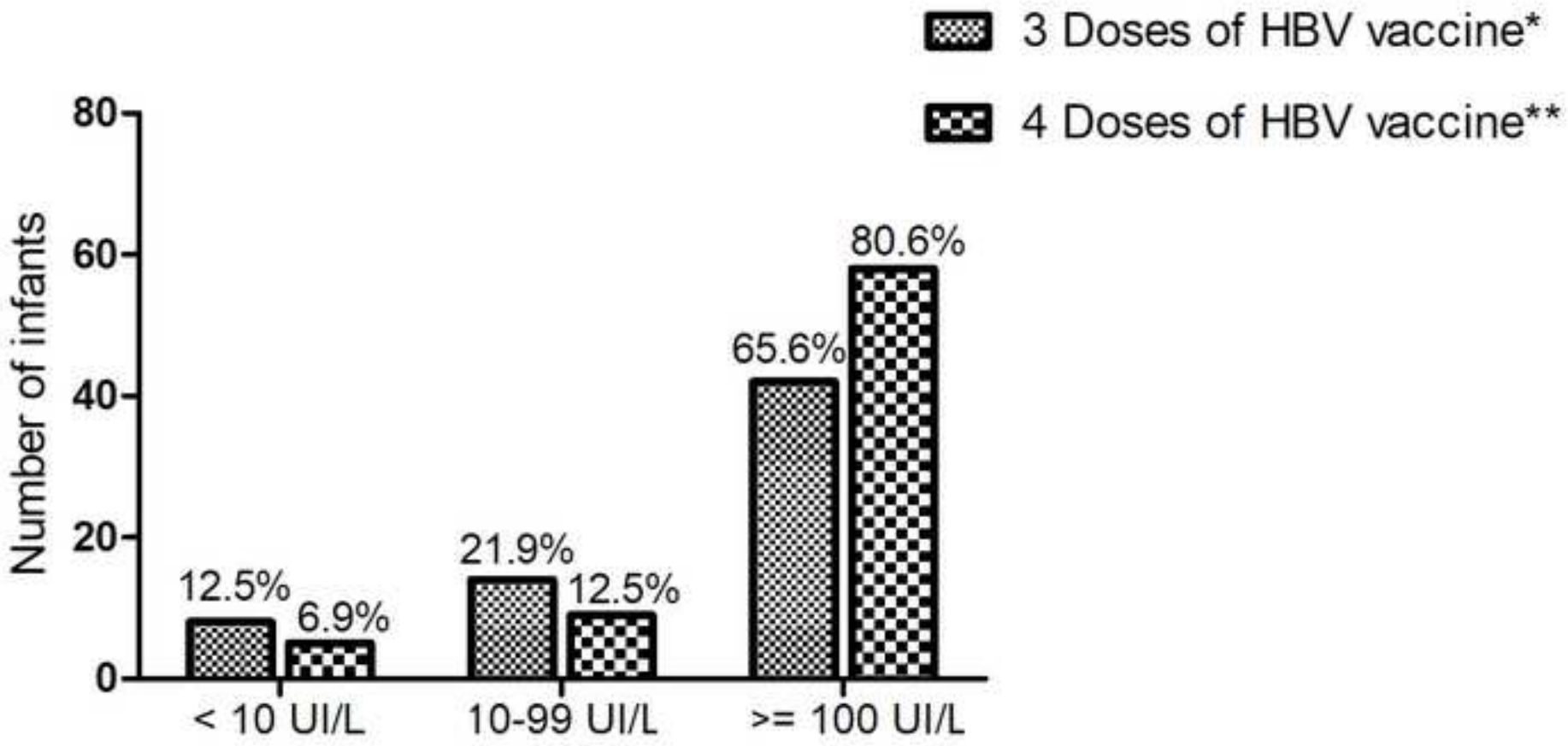

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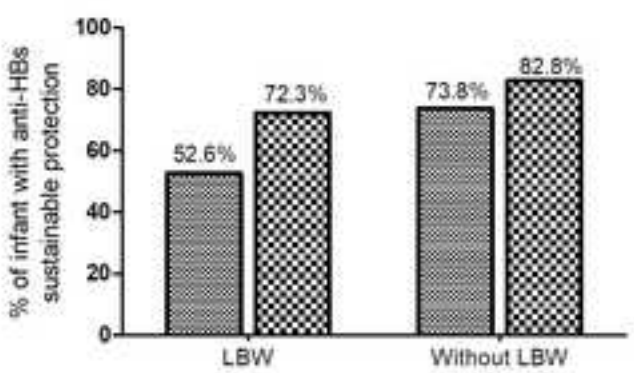

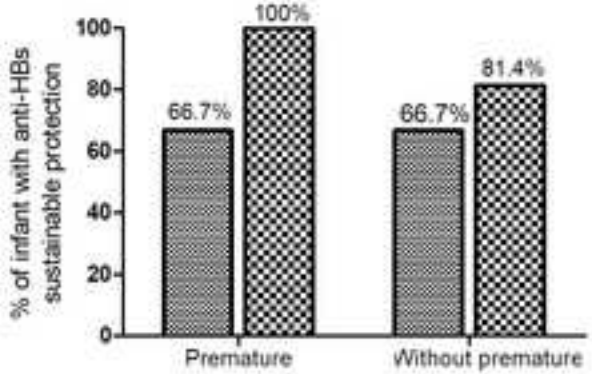

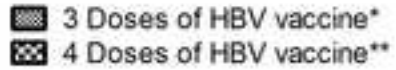

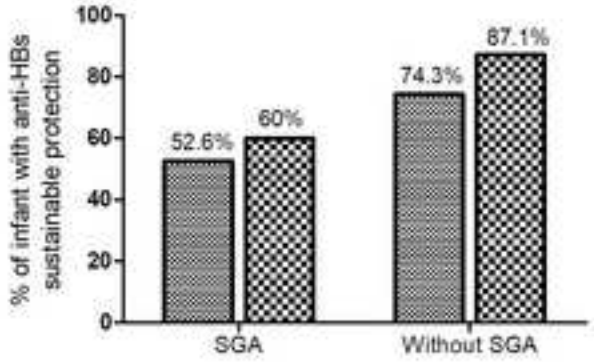

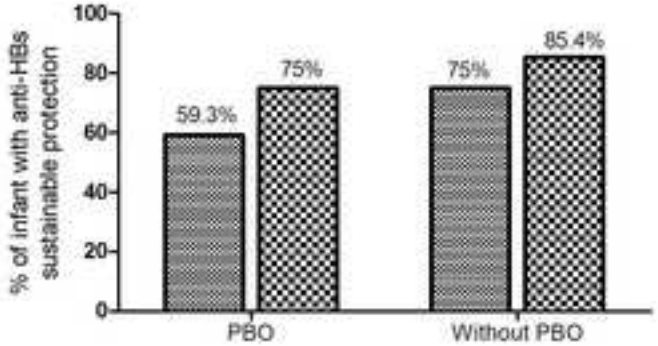

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