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Assessment of the anti-HBs antibody response in Beninese infants following 4 doses of HBV vaccine, including administration at birth, compared to the standard 3 doses regime; a cross-sectional survey

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ABSTRACT

Hepatitis B virus (HBV) infection remains one of the major neglected health issues worldwide. In sub-Saharan Africa (SSA), HBV endemicity is high, with more than 8% of the population being chronic HBV carriers. Recently, WHO recommended that all infants should receive their first dose of the HBV vaccine as soon as possible after birth. Unfortunately, the incorporation of a birth dose of HBV in the expanded programme immunization (EPI) has not occurred in the majority of countries in SSA. From April to September 2017, a cross-sectional survey was conducted in two vaccine units located in southern Benin. We assessed the sustained 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 included (0, 6, 10, 14 weeks). Blood samples were systematically collected in the first 140 children aged 9 months and their mothers who had consented to participate for the detection of HBs antigen and the quantification of anti-HBs antibodies. The prevalence of HBV infection among infants and mothers was 2.2% and 7.1%, respectively. Infants who received 4 doses of HBV vaccine had a significantly higher level of anti-HBs antibody than those who received 3 doses of vaccine (557.9 UI/L vs. 386.9 UI/L, respectively, $P = 0.03$). We also showed that the scheme of 4 doses was associated with a significantly higher sustained protective response in comparison to the scheme of 3 doses (aOR 2.49, 95% CI 1.03–6.03, $P = 0.04$). This result provides further evidence of the importance of administering HBV vaccine at birth, but also highlights the importance for the prevention of vertical transmissions. Additional studies are needed to better establish the cost-effectiveness of such a 4 doses immunization strategy before implementing the HBV vaccination at birth in the EPI.

1. Introduction

Hepatitis B virus (HBV) infection is the most common chronic viral infection in man and remains a significant cause of morbidity and mortality worldwide [1]. An estimated one third of the world's population is infected, and more than 350 million are chronic carriers of the virus [2]. In 2017, HBV resulted in 325 400 deaths, mostly due to complications such as cirrhosis and hepatocellular carcinoma [3]. The hepatitis B surface antigen (HBsAg) seropreva-

Abbreviations: LBW, low birthweight; SGA, small birthweight for gestational age; PBO, poor birth outcome.

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lence was 3.6% worldwide with the highest endemicity observed in countries of the African region (8.8%) [1]. Benin is one of the countries with the highest rates endemicity countries of HBV across sub-Saharan Africa (SSA), with over 1.4 million people infected [4] and a prevalence of HBV infection estimated at 16% [1].

The routine expanded programme on immunization (EPI) for Beninese neonates and infants includes many vaccine preventable diseases (Table 1). The latter included measles, diphtheria, pertussis, tetanus, polio, tuberculosis, hepatitis B, haemophilus influenza type b, pneumococcus and yellow fever. Vaccines included in the EPI are provided free of charge for parents due to financial support from the Beninese government through GAVI and UNICEF sponsorships. Women of reproductive age are also receive a tetanus toxoid booster immunization to protect their babies from tetanus.

Since perinatal or early postnatal transmission, particularly during infancy, is the major source of chronic HBV infection, World Health Organization (WHO) recommends that all infants should receive their first dose of the 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 has not yet been included in the national immunization program through the EPI. Although, some health centers do apply this recommendation, however the cost associated with the vaccine are met by the child's parents and it is expensive (~8 USD per vaccine dose). In addition, little is known about the efficacy of administration of a birth vaccine dose in term of providing a sustained protection against HBV among Beninese infants, and data available on prevalence in Beninese 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 given at birth, in inducing a sustained protective response against HBV infection in comparison to the 3 doses traditionally given in the Beninese EPI to infants during the first months of life. Secondly, we determined the HBsAg prevalence among a vaccinated infant population. Lastly, we also separately evaluated the efficacy of the 4 doses scheme in infants born with a poor birth outcome such as small birthweight for gestational age (SGA), premature birth (PTB), and low birthweight (LBW).

Table 1
Immunization program for neonates, infants 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	Diphtheria, 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	Diphtheria, 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	Diphtheria, 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.

2. Methods

2.1. Study design and population

We conducted a cross-sectional study among infant aged 9 months old, from April to September 2017, to compare the humoral response induced by a scheme of 4 doses of HBV vaccination, including a birth initiation dose, to the traditional immunization schedule of 3 doses of HBV as implemented by the Beninese EPI. 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 number of 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 9 months old with registered HBV vaccination for either the 3 or 4-doses schedule and who attended health facilities for measles and yellow fever vaccination as part of the routine immunization schedule. The mothers of these infants were also included for investigations. To be recruited, an infant had to meet the following criteria: being in the 9th month of life, having completed the 3 doses of HBV vaccine according to the EPI or 4 doses of HBV vaccine (3 doses of the EPI plus the birth dose), no severe health conditions evident at the time of the survey, acceptance to donate a blood sample, and informed consent provided by the parents/guardian.

Recruitment comprised convenience sampling. The first 140 infants, for whom parents had 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 CHU-MEL health centre was chosen because it is one of the main public health facilities proposing the birth dose of HBV vaccine to the parents of newborns, depending on their financial means. The study received ethical approval from the institutional review board of CHU-MEL and by Ministry of Health.

2.2. Vaccination schedule

The HBV vaccination was administered, as part of a fixed combination (Shanta®, Sanofi, Telangana, Inde) with other vaccines that included inactivated polio, diphtheria-tetanus-pertussis (DTP) and haemophilus influenza type b. Two different schemes of HBV vaccination were given to children: (i) 3-dose schedule at

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6, 10, and 14 weeks, respectively; and (ii) 4-dose schedule, where a monovalent birth dose was followed by the routine 3 doses at 6, 10, and 14 weeks, respectively. The birth dose comprised of administration of 10 μg of recombinant HBV vaccine (Euvax B®, LG Life Sciences, Korea) intramuscularly in the deltoid muscle within 24 h of life.

2.3. Study procedures

After obtaining parents' informed consent, sociodemographic and economic characteristics of the infant's family (infant gender, mother's age, gravidity, education and parent's profession) were collected, as well as pregnancy history (adverse pregnancy outcomes: LBW, PTB, SGA). Anthropometric data such as weight and height were recorded in the mother and infant in order to assess their nutritional status. Information regarding the timing of exclusive breast feeding, as well as the mother and infant HBV status were also collected.

Venous blood samples (5 mL in a dry tube) were obtained from children for both anti-HBs antibody quantification and HBs serology. The mother's blood was also collected for HBs serology. Serological testing was performed with the commercial test kits Monolisa® Anti-HBs Plus (Bio-Rad laboratory). The concentrations of antibody with specificity for the surface antigen (anti-HBs) were detected by a quantitative and qualitative enzyme-linked immunoassay (ELISA) from Bio-Rad Diagnostic System ELISA test system. Anti-HBs concentrations were measured and reported in UI/L using the 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 which bound to any antigen-antibody complexes present. 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 to turn blue. The blue color then turned 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.

2.4. Definition

Three classes of subjects were identified according to the magnitude of their anti-HBs concentrations: (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 sustained 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 < 10th percentile for gestational age using INTERGROWTH-21st charts [7].

2.5. 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 pairs 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 or Mann Whitney test whereas proportions were compared using a Chi-square test or Fisher exact test, as appropriate.

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

3. 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 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 giving exclusive breastfeeding to their infant for more than 6 months. The proportions of infants born with LBW, PTB or SGA were 22.4%, 13.8%, 23.9%, respectively. Less than 3% of infants presented with HBV infection. Children of HBV infected mothers were more frequently infected than those of non-infected mothers (10% vs. 1.6%, $P = 0.08$). The prevalence of HBsAg was higher among infants who received a birth dose, although not statistically significant so, when compared to those who did not (2.8% vs. 1.5%, $P = 0.58$). However, the prevalence of HBsAg was lower among mothers of infants receiving the birth dose compared to those who did not (5.6% vs. 8.8%, $P = 0.45$). 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). Fig. 1 presents the distribution of the mean concentrations of anti-HBs' antibodies 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 infants with a sustained protective response was significantly higher among those given the 4 doses of vaccination in comparison to infants with 3 doses of vaccination (80.6% vs. 65.6%, respectively, $P = 0.03$; Fig. 2). However, as far as HBsAg infected mothers were concerned, there was no significant difference in either anti-HBs antibody levels or sustained protective responses between children who had received the birth dose and those who had not (Table S1).

Univariate linear and logistic regressions (Table 3) showed that scheme of 4 doses was associated with a significantly higher mean concentration of anti-HBs' antibody (coefficient 170.9, 95% CI 14.9–327.1, $P = 0.03$) and with a sustained protective response against HBV (odds ratio 2.37, 95% CI 1.08–5.25, $P = 0.03$). Restricting the analysis to infants born from non-infected and non-vaccinated mothers, we observed the same trend in the results (Table S2). After considering the potential confounding factors, the scheme of 4 doses of vaccine was still associated with a significantly higher sustained protective response (adjusted odds ratio 2.49, 95% CI 1.03–6.03, $P = 0.04$).

Regarding the distribution of protective responses among infant with a poor birth outcomes (Fig. 3), we observed that the propor-

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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) Mean[b] (±SD) or %	4 doses of vaccination (n = 72) Mean[b] (±SD) or %	*P* value[a]
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 (greater than6 months)	Yes	81.7%	79.3%	83.8%	0.51
Low birthweight (birthweight < 2500 g)	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/m^2	<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.

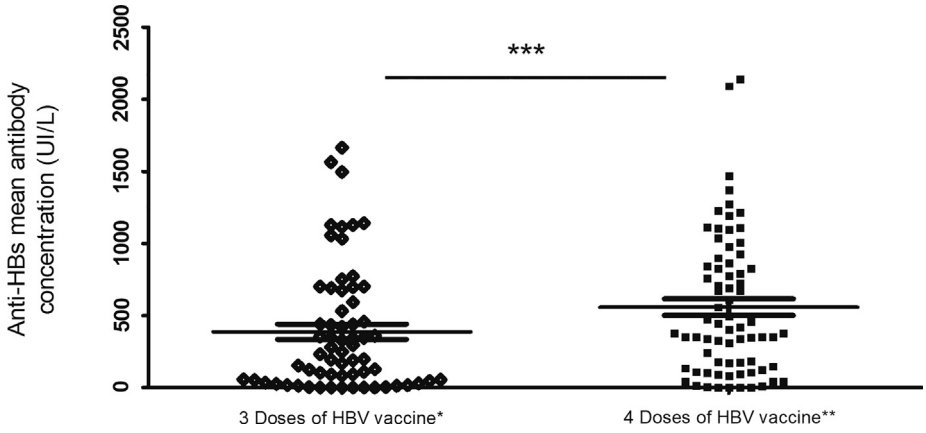

Fig. 1. Distribution of anti-HBs concentrations according to the scheme of vaccination. *Scheme of 3 doses of HBV vaccination (6, 10, 14 weeks); **Scheme of 4 doses of HBV vaccination (0, 6, 10, 14 weeks); ***P value < 0.05.

tion of those with sustained response was higher among infants 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.

4. Discussion

The present study is the first to assessed the efficacy of the 4 doses of HBV vaccine scheme, including administration at birth, in inducing a sustained protective response, in Beninese infants. 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 maternal/child HBV transmission is approximatively 20% [10]. This is a worrying health issue, particularly given 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 of the efficacy of the number and schedule of doses of HBV vaccine administered 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 significantly higher chance of sustained protective response than the traditional scheme of 3 doses given 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

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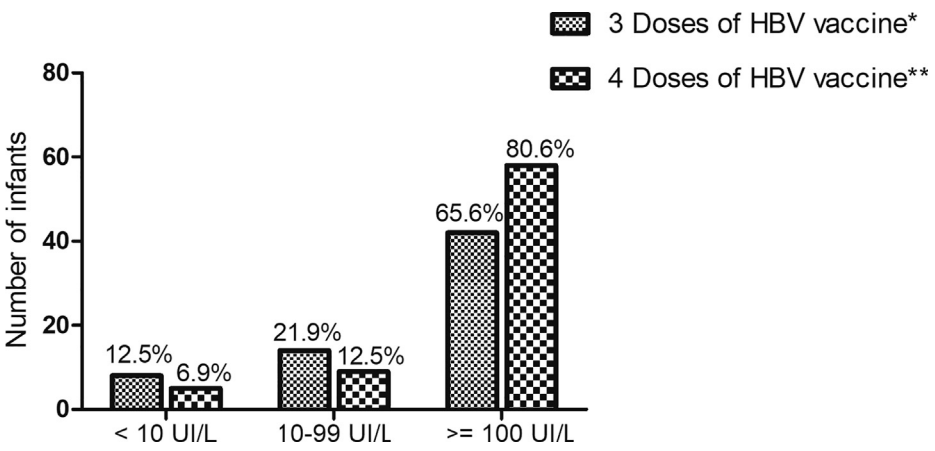

Fig. 2. Distribution of infants included in the study according to the magnitude of the anti-HBs levels (non-responders: <10 UI/L; responders: 10–100 UI/L; high responders or sustainable response: ≥100 UI/L). * Scheme of 3 doses of HBV vaccination (6, 10, 14 weeks); **Scheme of 4 doses of HBV vaccination (0, 6, 10, 14 weeks).

Table 3
Effect of scheme of 4 doses vs. 3 doses of vaccination on the Sustained Protective Response against Hepatitis B Virus among infants of 9 months old, Southern Benin, 2017 (N = 136).

Scheme of vaccination		Univariate analysis			Multivariate analysis		
	% of infant with anti-HBV sustained protective response	OR	95% CI	*P* value	aOR[†]	95% CI	*P* value
3 doses (n = 64)	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 = 64)	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.

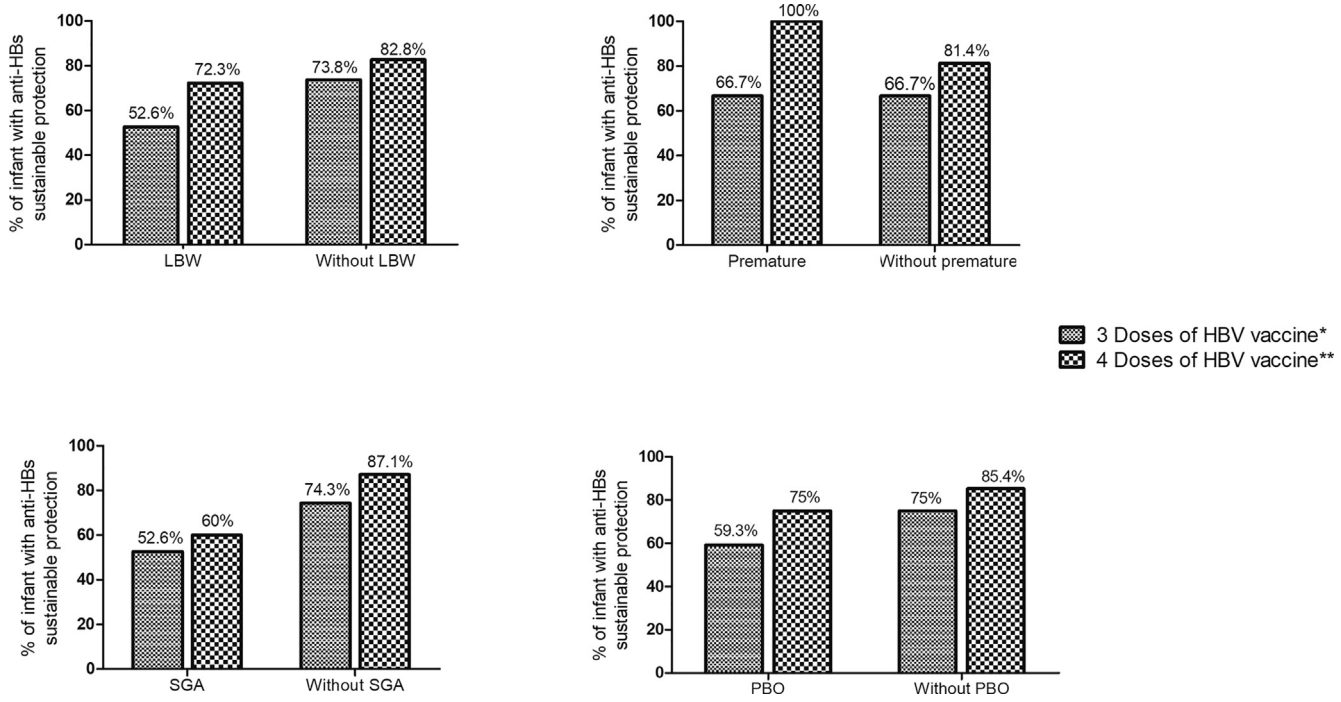

Fig. 3. Distribution of infants with a sustained protective response born with a poor birth outcome. * Scheme of 3 doses of HBV vaccination (6, 10, 14 weeks); ** Scheme of 4 doses of HBV vaccination (0, 6, 10, 14 weeks).

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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 reported that delaying the birth dose resulted in an increased risk of HBV infection [15]. In addition, several studies have also documented the short-term efficacy of HBV vaccine in neonates for reducing vertical transmission [16–18]. However, our results contrast with some studies. Das et al., did not find any difference between standard routine HBV vaccination and the schedule of vaccination including a 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). A sustained protective response resulting 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 date of initiation of the primary vaccine regime (birth or later in infancy), the vaccine dosage, the number of vaccine doses given, the interval 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 have also shown that children from infected mothers did not have a significantly different anti-HBs antibody levels or sustained protective responses, suggesting that sizeable proportion of infants were probably infected before receiving the birth dose. Indeed, the prevalence of HBsAg was higher among children who received the birth dose even though statistically not significant, suggesting a high risk of vertical transmission in spite of the birth dose.

Moreover, among children born with poor birth outcomes (LBW, PTB, SGA) who received 4-doses of HBV vaccine with a birth administration, there was a higher proportion of sustained protective responses than among those who received 3-doses through routine EPI at 9 months', although this result was of borderline statistical significance for the group with PTB. Early immunization of preterm newborns remains a much debated topic. Some authors argue for the early immunization of preterm newborns as soon as is clinically possible [5,22], but on the other hand, others have shown a short-term advantage of delayed vaccination of preterm babies [23,24]. However, as most of these studies were conducted in high-income countries, caution should be taken when generalising the results to the context of developing countries, meriting further studies in the latter.

This study has some limitations that should be considered. Most importantly, it was not a randomized clinical trial, meaning there could be confounding factors that have affected the study results, despite the adjustments included in multivariate analyses. 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 the validity of comparisons with other studies.

Several points argue in favour of implementing HBV vaccination at birth in the EPI in low-income countries, as recommended by WHO. Firstly, 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 few 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. Furthermore, 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 the HBV vaccine to newborns by a health professional.

Our study has highlighted the importance of early immunization during the neonatal period in conferring a sustained protective response again HBV infection throughout the first months of life when the risk of infection is considerably higher. However, it is important to keep in mind that neonatal immunization will not completely eradicate mother-to-infant HBV transmission [30], as also highlighted in this study. 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 to incorporate the HBV birth vaccine dose into the EPI. Nevertheless, ensuring that all infants receive a dose of HBV vaccine within 24 h of birth requires implementing specific measures such as increasing the number of infants born in health facilities or attended by trained health staff. As well, a comprehensive intervention program that includes improved access to hepatitis B screening and appropriate management of HBV infection during pregnancy, in addition to the introduction of a hepatitis B vaccine birth dose, would be beneficial for reducing the burden of HBV infection in SSA countries.

5. Financial support

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.12.031.

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