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Brief communication

Response to the complete hepatitis B vaccine regimen in infants under 12 months of age: a case series

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ABSTRACT

Objectives: Describing rates of seroconversion and its associated factors in a series of Brazilian infants following the final dose of the vaccine at 6 months of age.
Methods: Peripheral blood samples were collected after the third dose of the vaccine for the detection of anti-hepatitis B surface antibodies among infants of 7–12 months of age. We measured the association between seroconversion and birthweight, gestational age, time since administration of the vaccine in the maternity hospital and whether or not testing for hepatitis B surface antigen had been performed during pregnancy.
Results: We examined 40 infants. The mean birthweight was 2787 g (standard deviation = 853 g) and mean gestational age was 37.5 (standard deviation = 3.08) weeks. The proportion that seroconverted was non-significantly higher in infants who weighed ≥2000 g at birth (96.7%) than in those with birthweights <2000 g (80%, $p = 0.149$). There was no difference between the infants who were born at <37 weeks of gestational age and those born at ≥37 weeks ($p < 0.178$) neither between seroconversion and the time of application of the first dose of the vaccine after delivery ($p = 0.202$).
Conclusion: The proportion of infants who seroconverted was similar to that found in other Brazilian studies. There were no differences in the proportion seroconverting by age at first immunization.

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Introduction

One of the characteristics of hepatitis B virus (HBV) infection is a greater risk for chronic infection when the virus is acquired early in life,[1,2] ranging from 80% to 90% for those acquired in the neonatal period and from 30% to 50% for those acquired during later childhood.[2,3] The risk of progression to chronic hepatitis decreases to 5–10% when the infection is acquired in adolescence or adulthood.[1,3]

Although distribution of HBV is global, its endemic profile differs substantially.[1] In Brazil, around 1% of the population are chronic carriers of hepatitis B.[4,5] The Amazon region has been classified as an area of high endemicity, with a prevalence of HBsAg that reaches as high as 8%.[5] In the state of Amazonas, the prevalence of HBsAg positivity in pregnant women varies from 4% to 8% in the regions of the Juruá and Purus rivers.[6]

Vaccination of full-term newborn infants has been shown to achieve seroconversion rates of over 95% after completion of the three-dose vaccination regimen when the first dose is administered on the first day of life (preferably in the first 12 h), irrespective of dose and/or the strain used in the production of the vaccine.[3,7,8] Questions remain with respect to seroconversion in preterm newborn infants who complete the full vaccine regimen, even when immunization is initiated in the first few days of life and particularly in those weighing <2000 g at birth. Studies published after 1991 report a variation in the proportion of preterm infants weighing <2000 g at birth who seroconvert, which range from 55% to 100%.[8–11] HBV vaccination at birth was officially instituted in the childhood immunization schedule in Brazil in 1997, coverage being based on the fact that transmission in early infancy occurs most frequently in populations in which HBV infection is highly or moderately endemic.[12]

The objective of the present study was to describe immunological response to the complete 3-dose hepatitis B vaccine regimen and to assess factors associated with seroconversion in a series of infants up to 12 months of age receiving outpatient care at a public maternity hospital in Manaus.

Material and methods

This study was conducted in the city of Manaus, Amazonas, Brazil, between July 2009, and May 2010. The sample was selected at the outpatient clinic of the *Balbina Mestrinho* Maternity Hospital, which is considered a referral center for high-complexity neonatal and obstetric care for residents of Amazonas. The study was approved by the Internal Review Board of the Amazonas Foundation of Tropical Medicine under approval 3573-08/FMT-AM.

Infants who participating in the study were selected from the medical records of outpatients who fulfilled the following inclusion criteria: child of an HBsAg-negative mother (when serological status was known) or of unknown HBsAg status; between 7 and 12 months of age irrespective of gestational age and/or birthweight; and had completed the entire vaccine regimen (Buthang® recombinant DNA vaccine) prior to their 6-month birthday, as registered in the child's healthcare card in accordance with the Ministry of Health's National Immunization Program.[12]

After the mothers or guardians had signed the informed consent form, a questionnaire was completed with data on their pregnancy, delivery and immediate postpartum, as well as their medical history prior to the time of consultation. Gestational age at birth was recorded from the mother's hospital chart and the child's healthcare card, using the curve established by Alexander et al.[13] to determine the adequacy of birthweight for gestational age. After the interview, a 1,5 mL sample of peripheral blood was taken from the infant and sent to the Amazonas Foundation of Hematology and Hemotherapy for serological testing to detect antibodies against the hepatitis B surface antigen (HBsAb) using ELISA (Abbott Murex, UK). We defined seroconversion as having an HBsAb titer of ≥10 mIU/mL.

The database was analyzed using the SPSS statistical software program, version 17.0. A descriptive statistical analysis was performed, and possible associations between low birthweight and the independent variables were tested using the Fisher exact test, with p-values < 0.05 being considered statistically significant.

Results

A total of 40 infants between 7 and 12 months of age seen at the outpatient department during the study period were enrolled. Parents of 13 infants declined to participate. Mean gestational age was 37.5 (standard deviation [SD] = 3.08) weeks. Mean birthweight was 2787 (SD = 853) g; 18 (45%) were male and 22 (55%) female. Ten (25%) of the infants weighed <2000 g at birth, while the remaining 30 (75%) weighed ≥2000 g. Twenty-four (60%) mothers had been tested prenatally for HBsAg, and all were negative

Overall 36 (90%) infants seroconverted. Twenty-eight (97%) infants with birthweight ≥2000 g seroconverted compared to 8 (80%) of those weighing <2000 g at birth ($p = 0.149$) (Table 1). There was no significant difference in the proportion seroconverting between the infants who were born at <37 weeks of gestational age and those born at ≥37 weeks ($p < 0.178$), Twenty-three (58%) infants received their first dose of the vaccine in the maternity hospital (≤48 h of life); 73% of these weighed ≥2000 g at birth. Of the children who received the first dose of the vaccine prior to 24 h of life, only 1 (10%) weighed <2000 g at birth. There were no differences in the proportion seroconverting by age at first immunization ($p = 0.116$).

Discussion

This is the first study to be carried out in the Amazon region that evaluates serological response to hepatitis B vaccine in which premature newborn (<37 weeks) and low birthweight infants were included. We found no significant difference in seroconversion between those who weighed <2000 g at birth and those weighing ≥2000 g following three doses of the Buthang® vaccine. Chawareewong et al.[14] studied 25 premature infants of HBsAg-negative mothers in Thailand and reported overall seroconversion rates of around 88% after completion of the 3-dose regimen of the recombinant DNA vaccine

Table 1 – Factors associated with seroconversion to HBsAg among infants, *Balbina Mestrinho* Maternity Hospital, Manaus, Amazonas.

Variables	Anti-HBs ≥10 mUI/mL		Anti-HBs <10 mUI/mL		*p*-value*
	n	%	*n*	%	
Birthweight					
≥2000 g	29	96.7	1	3.3	0.149
<2000 g	8	80.0	2	20.0	
Maternal serology during prenatal care or at the maternity hospital					
HBsAg performed (tested negative)	22	91.7	8	8.3	0.625
HBsAg not performed	15	93.2	1	6.3	
Gestational age					
<37 weeks	9	24.3	2	18.2	0.178
≥37 weeks	28	75.7	1	3.4	
Infant gender					
Male	17	94.4	1	5.6	0.577
Female	20	90.9	2	9.1	
Administration of the first dose of the vaccine					
<12 h after birth	1	100.0	0	0	0.116
12–23 h after birth	21	95.5	1	4.5	
24–47 h after birth	0	0	0	0	
≥48 h after birth	15	88.2	2	11.8	

* $p < 0.05$ (Fisher exact test).

when the first dose was applied up to the tenth day of life. Our finding of an 80% seroconversion rate in infants weighing <2000 g at birth was similar to that found in Thailand (88%).

Of the studies conducted in Brazil that evaluated seroconversion following the complete vaccination regimen against hepatitis B and that also included the sample premature infants (<37 weeks) and low birthweight infants, two are noteworthy. Freitas da Motta evaluated 110 newborn infants (57 full term infants and 53 premature infants) and reported that 77% of the premature infants with birthweight <1800 g seroconverted after use of the Engerix B® vaccine (Smith Kline Beecham).[9] Sadeck reported that 75% of infants weighing <1500 g at birth seroconverted following use of the Recombivax® vaccine (Merck Sharp & Dohme).[10] The two studies were conducted in the southeast of Brazil with vaccines produced from the same strain of fungi (*Saccharomyces cerevisiae*); however, the doses were different (RecombivaxHB®: 5 μg/dose of 0.5 mL; Engerix B®: 10 μg/dose of 0.5 mL).

Golebiowska reported that 98.4% of vaccinated preterm infants had levels >10 mIU/mL following a 4-dose vaccine regimen (at 0, 1, 2 and 12 months) and that administration of the vaccine after the first day of life was correlated with low anti-HBs levels when birthweight was <2000 g compared to infants with birthweight ≥2000 g.[15] In our study, there were no differences between the time of application and seroconversion after completion of the vaccine regimen, since the majority of the infants who responded to the vaccine weighed ≥2000 g. The Ministry of Health routinely recommends application of the first dose of the vaccine in the maternity hospital and preferably within the first 12 h following delivery, irrespective of whether the mother's serological status is known or not.[12]

Our study was primarily limited by its small sample size. Additionally we were unable to recruit many infants with birthweight <2000 g. It is difficult on a outpatient basis in view of the high rate of child mortality in the city of Manaus, which was around 15.93 per 1000 liveborn infants for the year 2008 (unpublished data, State Health Department, Manaus), and because of the loss-to-follow-up that occurred during outpatient evaluation of child development, which resulted in difficulties in selecting infants between 7 and 12 months of age with a low birthweight.

Further studies aimed at identifying factors that could determine the absence of seroconversion or a delay in achieving seroconversion following completion of an anti-hepatitis B vaccine regimen, particularly in infants whose birthweight was <2000 g. These studies may provide information on the best way to ensure the immunization of children against HBV infection in the Amazon region, which could lead to control of transmission of the disease. Currently, the state of Amazonas struggles to increase immunization coverage, with the goal of achieving 95% vaccine coverage for all age groups, particularly for those under 12 months of age.

Conflict of interest

The authors of this manuscript declare no conflicts of interest of any kind that would interfere with the development of this study.

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