



Antibody levels in children after 10 years of vaccination against hepatitis B: a Brazilian community-based study

Níveis de anticorpos em crianças 10 anos após a vacinação contra hepatite B: um estudo brasileiro de base comunitária

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ABSTRACT

Introduction: It is known that the hepatitis B (HB) vaccine is effective, but it is alarming that sudden drops of antibody levels may coincide with the onset of adolescence. **Methods:** Antibody levels against HB vaccine surface antigen (anti-HBs) and HB vaccine core antigen (anti-HBc) were measured on the blood samples of children with a mean age of 11.4 years. **Results:** About 54.8% had protective levels of anti-HBs. Of those who were anti-HBc-positive (4.4%), an average of 218.4 anti-HBs mIU/mL was found. **Conclusions:** Immunological protection was found in the majority of children. However, more studies are needed to elucidate the heritability of nonresponders and establish strategies against such events.

Keywords: Hepatitis B virus. Vaccination. Anti-HBs. Anti-HBc. HBsAg.

RESUMO

Introdução: Sabe-se que a vacina contra a hepatite B é eficaz, mas é preocupante que quedas bruscas nos níveis de anticorpos possam coincidir com o início da adolescência. **Métodos:** Níveis de anticorpos anti-HBs e anti-HBc foram medidos nas amostras de sangue de crianças com idade média de 11,4 anos. **Resultados:** Cerca de 54,8% apresentaram níveis protetores de anti-HBs. Dos que apresentaram anti-HBc positivo (4,4%), uma média de anti-HBs de 218,4mUI/mL foi encontrada. **Conclusões:** Proteção imunológica foi encontrada na maioria das crianças. No entanto, mais estudos são necessários para elucidar a herança de não-respondedores e estabelecer estratégias contra tais acontecimentos.

Palavras-chaves: Vírus da hepatite B. Vacinação. Anti-HBs. Anti-HBc. HBsAg.

The vaccine against hepatitis B (HB) is included in the routine immunization schedule for children in most countries and has been proven effective in long-term reduction of chronic HB virus (HBV) infections¹. It is known that the duration of immune protection of the vaccine in various populations ranges from 5 to 10 years²⁻⁴. More recent studies of longer follow-ups show that there is still sufficient anamnestic response up to 20 years after vaccination¹. However, it is alarming that the levels of antibody against HBV surface antigen (anti-HBs) is decreasing over time²⁻⁴, and sudden drops coincide with the beginning of adolescence, the age group that historically has an increased risk for the development of HB⁵.

Brazil has a variable distribution of endemicity for HBV. Most regions have a low degree of endemicity⁶. However, the southern region of Brazil includes areas of intermediate to high endemicity and has the highest incidence of Brazilian HB. The State of Santa Catarina is a component of this region, and the City of Criciúma is located in the southern part of Santa Catarina, which showed the highest number of cases for HBV infection in the state⁷. These findings may reflect a higher relative number of diagnoses, but the endemicity is still significant and worrisome.

There are few long-term, large-scale population studies and community case studies to monitor the immunogenicity of the vaccination that stemmed from universal programs against HB in childhood. From a demographic standpoint, the analysis of a universal vaccination program is important to guide collective or individual conduct to rise above its failures. This study aimed at verifying different types of antibodies in children who received vaccination against HB in accordance with the standard method in the City of Criciúma in 1994 and 1995.

The classic method of vaccination for HB was implemented in Santa Catarina in 1994, with the first dose administered soon after birth and the second and third doses one month and six months later, respectively. Since then, newborns of Criciúma have received 10µg of Engerix B (GlaxoSmithKline Beecham), which is the dose currently recommended for children and adolescents who have not reached the age of 20 years.

The study population consisted of children from Criciúma who were vaccinated against HB in 1994 and 1995. According to the data available through the National Program of Immunization/Evaluation of the Program of Immunization (NPI/EPI), 1,177 children were vaccinated in Criciúma in 1994 and 3,423 in 1995. Based on the total number of 4,600 vaccinated children, a representative sample for this population was calculated with a 95% confidence interval, which resulted in a sample size of 385 children.

To gather a representative sample of subjects, sixteen basic health centers (BHCs) were chosen in an equitable geographical representation of the city regions. In each BHC, between 20 and 50 children with a record of three doses of HB vaccine were selected.

Parents or guardians were contacted, and those who agreed to participate signed a consent form to attend the meetings scheduled for information collection, accompanied by their children. The questionnaire completed by parents or guardians had questions about the child's general data, such as family history of contact with HB and knowledge about the possibility for the child to have any immunosuppressive disease, such as HIV⁺, type 1 diabetes mellitus, or chronic renal failure.

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Received in 26/12/2010

Accepted in 28/07/2011

Male and female healthy adolescents who had received all three doses of HB vaccine soon after birth, with the last dose in 1994 or 1995, were eligible for the study. Exclusion criteria were as follows: the lack of a complete schedule of HB vaccination doses, the absence of official data on HB vaccination, and the finding of a known immune deficiency.

A blood sample of 5-10mL was collected from each participant to perform the quantification of anti-HBs, as well as antibody levels against HBV core antigen (anti-HBc). An additional dosage of HBV surface antigen (HBsAg) was administered in subjects with positive anti-HBc to ascertain whether any of the children was a carrier of chronic HB. According to the manufacturer, Liaison® anti-HBs testing uses chemiluminescence immunoassay for the quantitative determination of directed antibodies in human blood or plasma. Qualitative analysis using ELISA kits was performed with DiaSorin®.

Levels of anti-HBs equal to or greater than 10mIU/mL are considered protective against HBV infection³⁻⁴. Therefore, participants with such levels of anti-HBs were classified as protected, and those with evidence of anti-HBs below 10mIU/mL were classified as potentially unprotected.

The data were compiled in Microsoft Office Excel computerized database and analyzed using the GraphPad InStat 3.0. Results were expressed as relative and medium values. Student's t-test was used for statistical analysis to compare the means between the two groups. Chi-square test was used to compare proportions between groups. P values less than 0.05 were considered significant.

This study was approved by the ethics committee of the *Universidade do Extremo Sul Catarinense* (UNESC) under protocol number 229/2005.

A total of 405 children participated in this study, with a mean age of 11.4 (± 0.9) years; 53.6% were female subjects. Of the total number of participants, 222 (54.8%) had protective levels of anti-HBs above 10mIU/mL. The average level of anti-HBs in the female group was 89.3mIU/mL (± 201.6), and that in the male group was 106mIU/mL (± 238.3), with no statistically significant difference between them ($p=0.445$).

The majority (73.1%) of vaccinated children had anti-HBs level below 50mIU/mL. **Figure 1** shows the distribution of the results of anti-HBs levels among the 405 children studied.

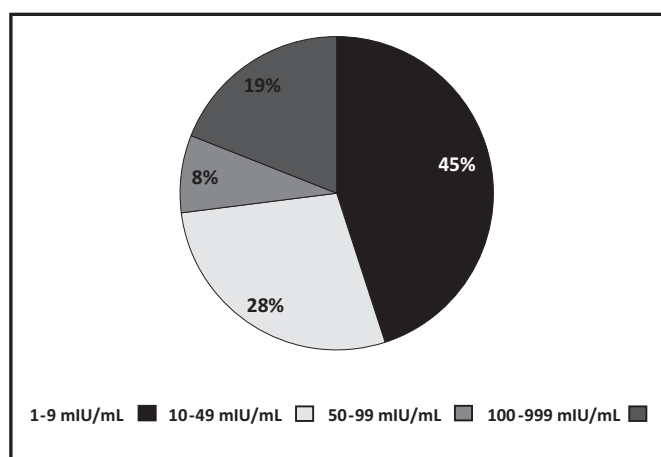


Figure 1 - Distribution of anti-HBs levels approximately 10 years after the last immunization.

Among those who had contact with HBV, detection of anti-HBc positive was found in 18 (4.4%) of 405 children. These 18 subjects with positive anti-HBc showed mean anti-HBs level of 218.4mIU/mL (± 334.65), being significantly higher than those with negative anti-HBc, which showed a mean anti-HBs level of 91.4mIU/mL (± 211.4) ($p < 0.05$). **Figure 2** illustrates this information.

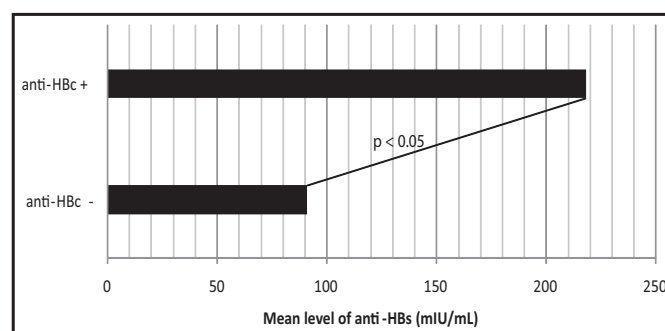


Figure 2 - Comparison of mean anti-HBs levels between positive and negative anti-HBc children.

All children with positive anti-HBc were negative for HBsAg, which excluded anyone with chronic HB.

Studies that monitored children and adolescents in countries highly endemic for HBV have shown that more than 50% of the participants who received HB vaccine during childhood retained protective levels of anti-HBs 4-10 years after vaccination⁸. In this study, 54.8% of children vaccinated 10-11 years ago had anti-HBs levels above 10mIU/mL. This result was similar to that found by Berlioz-Arthaud et al.⁹, in which 52% of children were protected until 10 years after the last immunization. Higher values were found in a multicenter study in Italy by Zanetti et al.¹⁰, who observed that 89% of children vaccinated 10 years ago were still protected.

It is estimated that 5% to 10% of healthy and immunocompetent adults, who receive the standard vaccination against HB, fail to produce satisfactory immune response, with protective levels of anti-HBs¹¹. This phenomenon has been observed in all the research on effectiveness of HB vaccine, and its cause remains largely unknown¹². However, it is known that the phenotypes of specific human leukocyte antigens are currently considered the most important genetic markers for nonresponders¹³.

Decreased levels of anti-HBs after vaccination are important risk factors for the development of breakthrough infections and chronicity of HB, especially in adolescent male participants¹⁴. The lack of response to vaccination, although inadvertent, increases the risk alarmingly. Teenagers are constantly exposed to HBV when they adopt the natural lifestyle of this period. In that age, many physical and psychological changes occur parallel to maturation and constant striving for social acceptance. Thus, the scenario of exposure and sexual maturation, along with experimenting with injectable drugs, plays a major role in the development of HBV infection⁵.

The 18 (4.4%) individuals found positive for anti-HBc in this study may have developed this serology because of a lack of responsiveness to primary vaccination. As the response to the vaccine is not routinely checked throughout the country, we do not have enough data to determine whether the positivity for anti-HBc is the result of the lack of response or whether it reflects some breakthrough infection. Anyway, the early identification of nonresponders would be useful because, as recommended by Sjogren¹⁵, strategies can be adopted such as the administration of HB hyperimmune gamma

globulin or revaccination. Moreover, appropriate conduct would prevent its immunologically unprotected arrival during the period of high risk in youth.

The development of HBsAg positivity in individuals who responded to the primary schedule of vaccination against HB is a rare and transient event², even in those whose serology of anti-HBs has fallen to very low or undetectable levels¹.

The vaccination program has been proven effective in Criciúma for what it was proposed, and immunological protection against HBV infection was found in the majority of children 10 years after being vaccinated at birth. However, it is alarming that most children can enter adolescence with nonprotective levels of anti-HBs, and some may not have responded adequately to vaccination. Further studies are required to elucidate the heritability of nonresponders and to establish individual- and population-based strategies against such events.

ACKNOWLEDGMENTS

We would like to thank Solomon Kweku Sagoe Amoah for his contribution in correcting this text to the English language.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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