Vaccine (2008) **26**, 1032—1037

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/vaccine

Effects of vertical HIV infection on the persistence of anti-HBs after a schedule of three doses of recombinant hepatitis B vaccine

Sérgio Júlio Fernandes[a,*], **Natasha Slhessarenko**[b], **Francisco José Dutra Souto**[b]

[a] *Secretaria de Saúde do Estado de Mato Grosso, Rua Thogo da Silva Pereira, 53 Centro, Cuiabá, MT 78020-500, Brazil*
[b] *Faculdade de Ciências Médicas, Universidade Federal de Mato Grosso, Avenida Fernando Corrêa, S/N Coxipo, Cuiabá, MT 78060-900, Brazil*

Received 22 October 2007; received in revised form 15 December 2007; accepted 16 December 2007
Available online 7 January 2008

KEYWORDS
Perinatal HIV transmission;
Hepatitis B vaccine;
Children

Summary Anti-HBs persistence following HBV vaccination among HIV-positive children has never been systematically studied in central Brazil. An historical cohort study was performed aiming to evaluate persistence of anti-HBs in HIV-positive children in comparison with an HIV-negative child group. Fifty-eight HIV-positive and 116 HIV-negative individuals were enrolled. Birth weight, breast-feeding duration, and the time elapsed since the last hepatitis B vaccine doses were similar between the groups. Fourteen (24%) out of 58 HIV-positive participants were anti-HBs positive and 101 (87%) out of 116 were HIV-negative ($p < 0.001$). Among anti-HBs-positive individuals, the geometric mean titres were 118 and 298 mIU/mL, respectively to HIV-positive and HIV-negative groups ($p = 0.04$). These results disclose a worrying picture regarding the failure of standard HBV vaccination among Brazilian HIV-infected children.

Introduction

Hepatitis B virus (HBV) infection is a major public health problem worldwide, especially in developing countries with moderate-to-high endemicity [1]. Since the 1980s immunogenic, safe and effective recombinant vaccines against the surface antigen of HBV (HBsAg) have been available [2—5]. Vaccination programmes against HBV aimed at newborns and children have succeeded remarkably in reducing HBV endemicity in several countries [6—8].

In Brazil HBV vaccine was included in the nationwide public programme of child vaccination in 1998. Although the Brazilian National Health Service has prioritized vaccination of newborns, there has been an attempt to extend it to teenagers in recent years.

Despite the effectiveness of the HBV vaccine, it is recognized that the standard immunization schedule with three

* Corresponding author at: Avenida Presidente Marques, 1219 Apartamento 402, Santa Helena, Cuiabá, MT 78045-100, Brazil. Tel.: +55 65 30528820; fax: +55 65 36158863.
E-mail address: sergiojuliofernandes@yahoo.com.br (S.J. Fernandes).

0264-410X/$ — see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2007.12.020

doses generates a lower seroconversion rate in some groups such as the elderly, obese, and immunodeficient patients, including HIV-infected children [3,9].

The Brazilian STD/AIDS public programme has made available virological tests, highly active antiretroviral therapy (HAART) and drugs against opportunistic agents to HIV-infected people since the 1990s. This improvement in medical assistance for HIV-positive patients has prolonged survival. However, a concern about long-term persistence of anti-HBs following HBV vaccination has arisen, since some reports have shown a significant decline of anti-HBs titres in HIV-infected children when compared to the HIV-negative population [10]. As a consequence, re-immunization or additional booster doses might be an alternative to improve protection against HBV [11,12].

Although there are studies on HBV vaccinal response in healthy children in Brazil [13,14], there is no report addressing anti-HBs persistence or HBV infection incidence in Brazilian previously vaccinated HIV-infected children so far. The aim of this study was to investigate the persistence and the level of anti-HBs in HIV-perinatally infected children vaccinated against HBV by the National Health Service in a state of Central Brazil.

Patients and methods

The present study involved assessing anti-HBs persistence in a group of HIV-vertically infected children formerly vaccinated against HBV in public health units in the Mato Grosso state capital, Cuiabá. In order to evaluate the importance of HIV-vertical infection on that outcome, a comparison group of healthy children (children who had not been exposed to HIV) was created, allowing data to be analyzed as though in a retrospective cohort study. In addition, another goal was to compare levels of anti-HBs titres between the groups.

Vertical transmission was confirmed by the diagnosis of HIV infection in children as early as the 1st years of life, lack of other possible routes of HIV exposure and confirmation of the mothers' infection.

The HIV-positive participants were recruited from the only two public outpatient services that function as a reference for paediatric infectious diseases in the region. Eligibility was limited to the range of 18 months to 12 years.

The comparison group comprised HIV-negative children from a public primary care outpatient unit of the same city. Two HIV-negative children matched by age and gender functioned as controls for each HIV-positive child.

All children of both groups had received at least three doses of recombinant hepatitis B vaccine in the past and none of them had had their anti-HBs status assessed before. Between 1995 and 2002, the participants received recombinant vaccines manufactured by the laboratories SmithKline Beecham (Belgium) or LG Chemical Ltd. (South Korea). In 2002, a Brazilian hepatitis B recombinant vaccine (Butang®, Butantan Institute, Sao Paulo) was released to use in children and teenagers, after that high immunogenicity was demonstrated in an equivalence trial [13]. Since 2003, it was included in the Brazilian National Health Service. So, the participants who were vaccinated from 2003 to 2006 received one of these three vaccine labels in a non-controlled way.

In spite of their HIV status, children were excluded if he or she had (1) a history of corticosteroid use or immunosuppressive therapy, (2) a history of any hereditary or acquired immunodeficiency condition, except for HIV infection for case participants, (3) an incomplete HBV vaccination history as documented by his or her vaccine record card as provided by the National Health System. Information about the children was obtained from parents, or the person responsible, regarding the weight at birth and time of breast-feeding. Number and date of HBV vaccine doses were verified using the personal vaccine record cards. History of blood productions transfusion, use of ARVT, how long ARVT had been used, results of CD4+ T lymphocyte counts and HIV viral load were verified using the medical records of HIV-infected children.

All participants had blood collected and tested for HBsAg and anti-HBc antibodies by electrochemical-luminescence (Elecsys® system, Roche, Mannheim, Germany). These tests were performed in order to ensure that HBV natural infection had not taken place. Children with positive tests were excluded since the natural infection is a stronger stimulus to anti-HBs than vaccine. Participants of the HIV-negative group were tested for anti-HIV antibodies (HIV combi®, Roche, Mannheim, Germany) to ensure their HIV-negative status. Anti-HBs antibodies were searched for using Elecsys® (Roche, Mannheim, Germany) and quantified according to the manufacturer's recommendations. Values greater than or equal to 10 mIU/mL were considered reactive. T-lymphocyte subsets were determined using the flow cytometry technique (FACSCount®, Becton-Dickinson, NJ, USA). HIV1-RNA detection and measurement was carried out using NASBA (Biomèrieux, Marcy-I'Etoile, France). These tests were carried out at the Public Health Central Laboratory in Cuiabá in the state of Mato Grosso.

The study protocol was approved by the ethics research board of the Federal University of Mato Grosso. Written consent was obtained from each parent or person responsible for the child prior to participation.

The outcome of greatest interest was from the anti-HBs results. Analysis of categorical variables was based on χ^2 test results with Yates' correction and Fisher's exact test. Where appropriate, relative risk (RR) or odds ratios (OR) with their respective 95% confidence interval, were calculated to determine the strength of association. A conditional logistic regression model was constructed by non-automatic methods to assess the independent effect of variables on the outcome (Stata 8.2, Statacorp, College Station, TX, EUA, 2005). Student's *t*- and Mann—Whitney *U*-tests were performed in order to analyze continuous variables. Linear regression models were performed to assess possible associations between anti-HBs titres and other continuous variables. Significance was determined at the 0.05 probability level in all analyses.

Results

Seventy-six HIV-positive children participated in the research in 2006, when the study was performed. All of them were interviewed and 58 satisfied the inclusion criteria. One hundred and sixteen HIV-negative children who met the criteria were enrolled, and comprised the comparison group. Age varied from 18 months to 12 years, with the median