Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Immunogenicity and safety of two doses of catch-up immunization with *Haemophilus influenzae* type b conjugate vaccine in Indian children living with HIV

Bikas K. Arya [a], Sangeeta Das Bhattacharya [a,*], Catherine G. Sutcliffe [b], Malay K. Saha [c], Subhasish Bhattacharyya [f], Swapan Kumar Niyogi [d], William J. Moss [b], Samiran Panda [e], Ranjan Saurav Das [a], Mausom Mallick [c], Sutapa Mandal [d]

[a] *School of Medical Science and Technology, Indian Institute of Technology (IIT) – Kharagpur, India*
[b] *International Vaccine Access Center and Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA*
[c] *National HIV Reference Laboratory/Division of Virology, National Institute of Cholera and Enteric Diseases (NICED)/Indian Council of Medical Research (ICMR)-Kolkata, India*
[d] *Division of Bacteriology, National Institute of Cholera and Enteric Diseases (NICED)/Indian Council of Medical Research (ICMR)-Kolkata, India*
[e] *Division of Epidemiology, National Institute of Cholera and Enteric Diseases (NICED)/Indian Council of Medical Research (ICMR)-Kolkata, India*
[f] *Department of Pediatrics, Midnapore Medical College and Hospital-Midnapore, India*

ARTICLE INFO

Article history:
Received 6 October 2015
Received in revised form 1 February 2016
Accepted 4 March 2016
Available online xxx

Keywords:
HIV
Haemophilus influenzae type b
Conjugate vaccines
Anti-Hib PRP IgG
Immune response
Nasopharyngeal carriage

ABSTRACT

Background: Children living with HIV are at increased risk of disease from *Haemophilus influenzae* type b (*Hib*). Data are limited on the immunogenicity of a two-dose, catch-up schedule for Hib conjugate vaccine (HibCV) among HIV-infected children accessing antiretroviral therapy (ART) late.
Objectives: The objectives of the study were to: (1) evaluate baseline immunity to Hib and the immunogenicity and safety of two doses of HibCV among HIV-infected Indian children; and (2) document the threshold antibody level required to prevent Hib colonization among HIV-infected children following immunization.
Methods: We conducted a prospective cohort study among HIV-infected children 2–15 years of age and HIV-uninfected children 2–5 years of age. HIV-infected children received two doses of HibCV and uninfected children received one. Serum anti-Hib PRP IgG antibodies were measured at baseline and two months after immunization in the HIV-infected children. Nasopharyngeal (NP) swabs were collected at baseline and follow-up.
Results: 125 HIV-infected and 44 uninfected children participated. 40% of HIV-infected children were receiving ART and 26% had a viral load >100,000 copies/mL. The geometric mean concentration of serum anti-Hib PRP antibody increased from 0.25 μg/mL at baseline to 2.65 μg/mL after two doses of HibCV, representing a 10.6-fold increase ($p < 0.0001$). 76% percent of HIV-infected children mounted an immune response. Moderate or severe immune suppression, trimethoprim/sulfamethoxazole prophylaxis, and lower baseline antibody levels were associated with lower post-vaccine serum anti-Hib PRP IgG antibodies. A serum anti-Hib PRP IgG antibody level ≥3.3 μg/mL was protective against Hib NP colonization. There were no differences in adverse events between HIV-infected and uninfected children.
Conclusion: Including a catch-up immunization schedule for older HIV infected children in countries introducing Hib vaccines is important. Older HIV-infected children with delayed access to ART and without suppressed viral loads mounted an adequate immune response following two doses of HibCV.

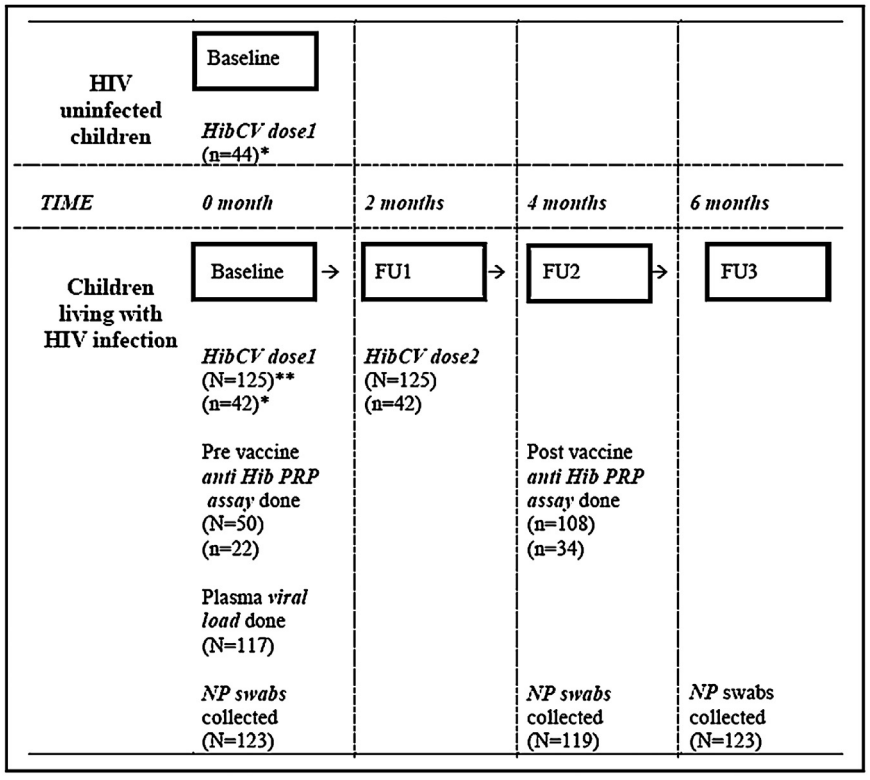
1. Introduction

HIV-infected infants and children are at increased risk of disease from *Haemophilus influenzae* type b (Hib), particularly bacteremic and non-bacteremic pneumonia [1]. Hib conjugate vaccines (HibCV) protect HIV-infected children [2,3]. Over the past twenty years, 190 countries have introduced HibCV, including many countries with a high burden of pediatric HIV infection [4].

India has an estimated 105,000 HIV-infected children and one of the highest numbers of HIV-infected pregnant women in the world [5,6]. Hib vaccines were recently introduced as a primary series of three doses of pentavalent vaccine (DTP, hepatitis B and

* Corresponding author. Tel.: +91 3222 283576; fax: +91 3222 282221.
E-mail address: sangeeta@smst.iitkgp.ernet.in (S.D. Bhattacharya).

http://dx.doi.org/10.1016/j.vaccine.2016.03.012
0264-410X/



** N = number of children in age group 2-15 years
*n = Number of children in age group 2-5 years
HIV uninfected cohort were followed for adverse events only and not immune response

Fig. 1. Timeline of immunization and follow-up in children living with HIV 2–15 years of age.

Hib) [4,7]. However, there are no specific recommendations for Hib vaccination in HIV-infected children and HibCV is not included in the Indian government program for HIV-infected children [8].

Information is lacking on baseline immunity to Hib among HIV-infected children living in settings where HibCV has not been introduced as part of the universal immunization program [9]. Hib transmission occurs through respiratory droplets and family members are at increased risk of being colonized and developing disease [10]. HibCV decreases carriage and thus indirectly protects unvaccinated individuals [11,12]. HIV-infected children live in families where multiple members may be living with HIV and at increased risk for Hib disease. The threshold level of serum anti-Hib polyribosyl-ribitol-phosphate (PRP) IgG antibody for protection from nasopharyngeal colonization with Hib in HIV-infected children has not been established.

We conducted a prospective cohort study to measure the impact of two doses of monovalent HibCV on nasopharyngeal carriage of Hib among HIV-infected and uninfected children and their parents, in West Bengal. We report the immune response at baseline and after two doses of HibCV and the threshold of serum anti-Hib PRP IgG antibodies most likely to prevent Hib colonization in a cohort of HIV-infected children.

2. Methods

2.1. Ethical clearance

The Institutional Review Boards of all participating institutions approved this study. Additional approvals were obtained from the District Chief Medical Officer of Health, the Government of West Bengal Health and Family Welfare Department, and the Drug Controller General of India. Written informed consent was obtained from all guardians prior to enrolment.

2.2. Study design

We conducted a prospective cohort study from March 2012 to October 2014 in East and West Midnapore, two primarily rural districts of West Bengal. At the time of the study, West Bengal had not introduced HibCV and penetration of HibCV in the private market was only 0.8% [13]. Two cohorts were enrolled: (1) families of children living with HIV; and (2) families of healthy HIV-uninfected children. The primary objective was to determine the impact of HibCV on carriage in vaccinated children and their unvaccinated parents. The results of the primary outcome are reported elsewhere [14]. This analysis describes the immunogenicity of two doses of HibCV among HIV-infected children and the safety of the vaccine among both HIV-infected and uninfected children.

HIV-infected children 2–15 years of age presenting for routine care who had not previously received HibCV were recruited at the Antiretroviral Treatment (ART) Center at Midnapore Medical College. The Center had 293 registered children and did not perform virological assays to confirm HIV status in children <18 months. ART was started when the CD4 count decreased below 350 cells/mm^3 and all children were recommended to receive trimethoprim/sulfamethoxazole (TMP/SMX) [15,16]. HIV-uninfected children 2–5 years of age who had not received the primary Hib series were recruited from the Hijli Rural Hospital, a primary health center in West Midnapore. All mothers in this cohort were tested and were found to be HIV negative.

HIV-infected children were given two doses of HibCV (0.5 mL each) two months apart, at baseline and the first follow-up visit

Please cite this article in press as: Arya BK, et al. Immunogenicity and safety of two doses of catch-up immunization with *Haemophilus influenzae* type b conjugate vaccine in Indian children living with HIV. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.03.012