Vaccine 32 (2014) 4304–4309

Contents lists available at ScienceDirect

Vaccine

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

Prevalence of chronic hepatitis B virus infection before and after implementation of a hepatitis B vaccination program among children in Nepal

Shyam Raj Upreti[a], Santosh Gurung[b], Minal Patel[c,*], Sameer M. Dixit[d], L. Kendall Krause[b], Geeta Shakya[e], Kathleen Wannemuehler[c], Rajesh Rajbhandari[d], Rajendra Bohara[b], W. William Schluter[b]

[a] Child Health Division, Department of Health Services, Ministry of Health and Population, Kathmandu, Nepal
[b] Expanded Programme on Immunization, World Health Organization, PO Box 108, United Nations House, Kathmandu, Nepal
[c] Global Immunization Division, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30329, United States
[d] Center for Molecular Dynamics Nepal, GPO Box 21409, Kathmandu, Nepal
[e] National Public Health Laboratory, Department of Health Services, Ministry of Health and Population, Kathmandu, Nepal

ARTICLE INFO

Article history:
Received 25 February 2014
Received in revised form 28 May 2014
Accepted 6 June 2014
Available online 18 June 2014

Keywords:
Hepatitis B virus
Nepal
Seroprevalence
Vaccine

ABSTRACT

Background: In Nepal, an estimated 2–4% of the population has chronic hepatitis B virus (HBV) infection. To combat this problem, from 2002 to 2004, a national three dose hepatitis B vaccination program was implemented to decrease infection rates among children. The program does not currently include a birth dose to prevent perinatal HBV transmission. In 2012, to assess the impact of the program, we conducted a serosurvey among children born before and after vaccine introduction.
Methods: In 2012, a cross-sectional nationally representative stratified cluster survey was conducted to estimate hepatitis B surface antigen (HBsAg) prevalence among children born from 2006 to 2007 (post-vaccine cohort) and among children born from 2000 to 2002 (pre-vaccine cohort). Demographic data, as well as written and oral vaccination history were collected. All children were tested for HBsAg; mothers of HBsAg positive children were also tested. Furthermore, we evaluated the field sensitivity and specificity of the SD Bioline HBsAg rapid diagnostic test by comparing results with an enzyme immunoassay.
Results: Among 2181 post-vaccination cohort children with vaccination data by either card or recall, 86% (95% confidence interval [CI] 77–95%) received ≥3 hepatitis B vaccine doses. Of 1200 children born in the pre-vaccination cohort, 0.28% (95% CI 0.09–0.85%) were positive for HBsAg; of 2187 children born in the post-vaccination cohort, 0.13% (95% CI 0.04–0.39%) were positive for HBsAg ($p = 0.39$). Of the six children who tested positive for HBsAg, two had mothers who were positive for HBsAg. Finally, we found the SD Bioline HBsAg rapid diagnostic test to have a sensitivity of 100% and a specificity of 100%.
Conclusions: This is the first nationally representative hepatitis B serosurvey conducted in Nepal. Overall, a low burden of chronic HBV infection was found in children born in both the pre and post-vaccination cohorts. Current vaccination strategies should be continued.

1. Introduction

Worldwide, more than 2 billion people have been infected with hepatitis B virus (HBV); approximately 240 million have chronic HBV infection, 20–25% of whom will eventually die from HBV-related liver disease, including cirrhosis and hepatocellular carcinoma [1,2]. The prevalence of chronic HBV infection, defined by the presence of hepatitis B surface antigen (HBsAg), varies markedly, from <1% in the United States and Australia to >7% in countries like China [3–5]. Regardless of country-specific prevalence, the World Health Organization has recommended at least

Abbreviations: Anti-HBc, antibody to hepatitis B core antigen; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HepB3, 3-dose hepatitis B vaccination coverage; HepB-BD, hepatitis B birth dose vaccine; SBA, skilled birth attendant; WHO, World Health Organization.

* Corresponding author. Tel.: +1 404 639 8907; fax: +1 404 315 2497.
E-mail addresses: drshyam@hotmail.com (S.R. Upreti), gurungs@searo.who.int (S. Gurung), hgo9@cdc.gov (M. Patel), s.dixit@cmdn.org (S.M. Dixit), kendallkrause@gmail.com (L.K. Krause), geeta.nphl@gmail.com (G. Shakya), kpw9@cdc.gov (K. Wannemuehler), r.rajbhandari@cmdn.org (R. Rajbhandari), boharar@SEARO.WHO.INT (R. Bohara), schluterw@wpro.who.int (W.W. Schluter).

http://dx.doi.org/10.1016/j.vaccine.2014.06.027
0264-410X/

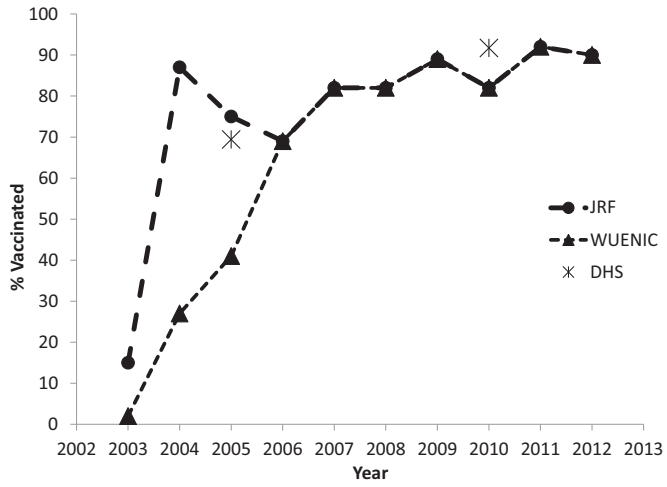

Fig. 1. Hepatitis B3 vaccination coverage, Nepal, 2003–2012. JRF = joint reporting form [15], WUENIC = WHO/UNICEF estimates for national immunization coverage [15]; DHS = Demographic and Health Survey [19,32].

three doses of hepatitis B vaccine for all infants, including a first dose within 24 h of birth [6].

Nepal is considered to have low to intermediate endemicity of chronic HBV infection, with an estimated HBsAg population seroprevalence of 2–4% [1]. However, no nationally representative serosurvey has been conducted so the population prevalence is unknown. In blood donors, the prevalence ranged from 0.35% to 1.2% [7–10]; small convenience surveys of healthy Nepalese adult males found a seroprevalence of 0.93–4%, with variations across different regions [11–14].

To protect future generations of Nepalese children, Nepal introduced a single antigen hepatitis B vaccine in a phased manner from 2002 to 2004 for infants. Shortly thereafter, the single antigen vaccine was phased out and replaced with a combination tetravalent vaccine containing diphtheria, tetanus, pertussis, and hepatitis B antigens (DTP-HepB). Beginning in 2009, hepatitis B vaccine has been administered as a pentavalent DTP-HepB-Hib combination vaccine to infants at 6, 10, and 14 weeks of age. Coverage has steadily improved, starting at 27% in 2004 and rising to 82% in 2010 (Fig. 1) [15]. Mothers are not routinely screened for HBsAg, and neither hepatitis B immunoglobulin nor a hepatitis B birth dose vaccine (HepB-BD) is routinely administered to newborns to prevent perinatal HBV transmission.

To determine the impact of the vaccination program and the burden of HBV perinatal transmission, Nepal undertook a serosurvey of children born prior to and following vaccine introduction.

2. Methods

In April 2012, we conducted a nationally representative cross-sectional three-stage cluster survey among children born from April 2000 to April 2002 (10–12 year olds, pre-vaccine cohort) and children born from April 2006 to April 2007 (5–6 year olds, vaccine era cohort). To assess the contribution of perinatal transmission, mothers of children testing positive for HBsAg were tested for HBsAg.

2.1. Sample size and sampling

The sample size of 2144 for the post-vaccine era children was calculated based on an expected HBsAg seroprevalence of 0.5%, a one-sided precision of +0.5% (Wilson-Score method), a 95% probability of achieving that precision, and a design effect of 2. The sample size for the pre-vaccine cohort was based on the objective of comparing seroprevalence in the two groups. A sample size of 1186 was calculated for the pre-vaccine cohort based on a Fisher's exact test assuming pre-vaccination seroprevalence of 2% and post-vaccination seroprevalence of 0.5%, $\alpha = 0.05$, and 80% power.

To ensure adequate representation of Nepal's diverse geographic, economic, and social characteristics, the country was stratified into distinct strata that factored in the population density (urban/rural), the three ecological zones that divide the country north to south (mountains, hills, and Terai) and the Kathmandu metropolitan area. The mountain zone consists of rural areas only, and Kathmandu is completely urban. Thus, a total of six strata were created: Kathmandu metropolitan, mountain rural, hill urban, hill rural, terai urban, and terai rural (see Supplemental map).

The primary sampling units (PSUs) for the first stage were village development committees (VDCs) in the rural areas and municipalities in the urban/metropolitan areas. Fifty PSUs were proportionally allocated based on the estimated proportion of the total population residing in each stratum. PSUs were selected based on probability proportion to estimated size (PPES) within each stratum: 3 in terai-urban, 21 in terai-rural, 2 in hill-urban, 18 in hill-rural, 4 in mountain-rural, and 2 in Kathmandu (see Supplemental map). Within each selected PSU, four wards were randomly selected using PPES. Within each selected ward, eleven 5–6 year olds and six 10–12 year olds were chosen by randomly visiting households until the desired number were enrolled. Only one child was selected in each household in each age cohort. In the few instances where a selected ward did not have enough children to meet the required sample size, the remainder were selected from a neighboring ward.

2.2. Eligibility

Children were eligible for participation if they were born in the aforementioned time frames. Children were excluded if they were unable to give blood because of severe illness or hemophilia. For each eligible child, informed consent was obtained from a parent and assent was obtained from the child. If consent or assent was not provided, the child was not enrolled in the survey.

2.3. Data collection

If consent was obtained, a brief questionnaire was administered to the caregiver. The questionnaire collected demographic data, potential risk factors for infection, and vaccination history. If written vaccination history was not available, vaccination history based on caregiver recall was obtained.

2.4. Specimen collection and laboratory testing

Approximately 5 mL of blood was collected by venipuncture. In the field, the sample was centrifuged, and the serum was tested using the SD BioLine HBsAg rapid test (Standard Diagnostics, Inc., Korea, sensitivity 100% (95% CI 96.3–100%), specificity 100% (95% CI 97.9–100%)) [16]. Mothers of children with positive field-based tests, and who provided consent, had a venipuncture sample of blood taken, and were also tested using the rapid test. Samples from all children who tested positive, a random selection of 10% of those who tested negative, and all samples from mothers of all positive children were tested by enzyme-linked immunosorbent assay (ELISA) for HBsAg (Anti-Surase B96 (TMB), General Biological Corp., Taiwan, 100% sensitivity, 99.6% specificity [17]) and total antibody to hepatitis B core antigen (anti-HBc) (Anti-Corase B96 (TMB), General Biological Corp., Taiwan, 100% sensitivity, 99.6% specificity [18]) at the Nepal National Public Health Laboratory following the standard kit protocols.