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Review

Status and progress of hepatitis B control through vaccination in the South-East Asia Region, 1992–2015

Lana Childs [a,b,*], Sigrun Roesel [c], Rania A. Tohme [a]

[a] Global Immunization Division, Centers for Disease Control and Prevention, Atlanta, GA, USA
[b] Oak Ridge Institute for Science and Education, Centers for Disease Control and Prevention, Atlanta, GA, USA
[c] World Health Organization Regional Office for South-East Asia, New Delhi, India

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ABSTRACT

In 2016, the Immunization Technical Advisory Group of the South-East Asia Region (SEAR) endorsed a regional goal to achieve ≤1% prevalence of hepatitis B surface antigen (HBsAg) among 5-year-old children by 2020. Chronic hepatitis B virus (HBV) infection is largely preventable with a birth dose of hepatitis B vaccine (HepB-BD) followed by two to three additional doses. We reviewed the progress towards hepatitis B control through vaccination in SEAR during 1992–2015. We summarized hepatitis B vaccination data and reviewed the literature to determine the prevalence of chronic HBV infection pre- and post-vaccine introduction. We used a mathematical model to determine post-vaccine prevalence of HBsAg among 5 year olds in countries lacking national serosurvey data and estimated the impact of vaccination on disease burden. Regional coverage with three doses of hepatitis B vaccine (HepB3) increased from 56% in 2011 to 87% in 2015. By 2016, 7 of 11 countries had introduced universal HepB-BD. Regional HepB-BD coverage increased from 9% in 2011 to 34% in 2015. In 2015, estimated HBsAg among 5 year olds was 1.1% with variability among countries. Myanmar (3.8%), Timor-Leste (2.7%), Indonesia (1.8%), and India (1%) had the highest prevalence of HBsAg. During 1992–2015, vaccination prevented approximately 16 million chronic HBV infections and 2.6 million related deaths. In 2015, around 197,640 perinatal HBV infections occurred in SEAR with majority occurring in India (62%), Bangladesh (24%), and Myanmar (8%). Myanmar had the highest rate of perinatal chronic HBV infections at 16 per 1000 live births. Despite significant progress in the control of HBV, SEAR needs to secure political commitment for elimination and consider additional strategies, such as promoting health facility births, universal birth dose administration, developing strong coordination between health sectors, and using alternative vaccine delivery methods, to improve HepB-BD coverage and subsequently achieve HBV control and elimination.

Contents

* Corresponding author at: Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS-E-98, Atlanta, GA 30329, USA.
E-mail address: yqj9@cdc.gov (L. Childs).

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1. Introduction

Globally, approximately 257 million persons are chronically infected with hepatitis B virus (HBV), and 686,000 die every year as a result of HBV-related liver cirrhosis and hepatocellular carcinoma (HCC) [1,2]. Chronic HBV infection develops in 90% of infants infected before 1 year of age, 25–50% of children infected during 1–5 years of age, and 5–10% of persons infected after 5 years of age [3]. The World Health Organization (WHO) Strategic Advisory Groups of Experts (SAGE) recommends infants receive hepatitis B vaccine (HepB) at birth, ideally within 24 h, but administration up to 7 days after birth, followed by two or three additional doses can still be effective [3,4]. The Global Health Sector Strategy on Viral Hepatitis (GHSSVH) calls for a 30% reduction in new cases of chronic HBV infections (equivalent to 1% hepatitis B surface antigen [HBsAg] prevalence among children aged 5 years) by 2020 [5]. GHSSVH also calls for eliminating viral hepatitis by 2030 (equivalent to 0.1% HBsAg prevalence among children aged 5 years) [5].

In the WHO South-East Asia Region (SEAR), approximately 39 million persons are living with chronic HBV infection [1]. In 2016, the SEAR Immunization Technical Advisory Group (ITAG) endorsed a regional hepatitis B control goal to achieve a HBsAg prevalence of $\leq$1% among 5-year-old children by 2020 [6].

There has not been a comprehensive assessment of the current situation of hepatitis B vaccination and infection in the SEAR. We review the status of and progress towards hepatitis B control through vaccination in the SEAR, and we suggest strategies that would help the region reach the hepatitis B control goal by 2020 and HBV elimination by 2030.

2. Methods

For each country in SEAR, we compiled data on year of HepB introduction, HepB schedule, coverage with HepB-BD and with three doses of HepB (HepB3) [7,8]. HepB-BD coverage reported to WHO does not currently differentiate timely HepB-BD, defined as HepB-BD given within 24 h of birth, from birth dose given after 24 h. Therefore, we were not able to distinguish between timely and total HepB-BD coverage. We abstracted data on the proportion of women who attended at least one antenatal care visit, the institutional delivery rates, and the proportion of births attended by skilled birth attendant (SBA) [9]. We collected data on the number of live births in 2015 [10] and the number of surviving infants during 1992–2015 [11].

To evaluate the impact of HepB in SEAR, we conducted a comprehensive search of published literature and compiled available unpublished reports on prevalence of chronic HBV infection (i.e., percent of persons HBsAg positive) before and after vaccine introduction. To estimate pre-vaccine prevalence of HBsAg in each country, we included studies published from January 1995 to August 2016 with a sample size >100. We focused on studies reporting chronic HBV infection among children and young adults. However, in countries lacking these studies, adult populations were included. We excluded studies including populations with a known lower or higher prevalence of chronic HBV infection than the general population. We calculated the pre-vaccine regional prevalence of HBsAg among 5 year old children as a weighted average of HBsAg prevalence in each country adjusted by the number of surviving infants in 2000 from the World Population Prospects [11].

To estimate post-vaccine prevalence of HBsAg in each country, we included nationally representative serosurveys among children born after nationwide HepB introduction. For countries lacking nationally representative serosurveys, we used the hepatitis B mathematical model developed by Goldstein and colleagues to estimate the prevalence of HBsAg among 5-year-old children in 2015 [12], in accordance with the SEAR and GHSSVH indicators to measure cumulative incidence of chronic HBV infection at 5 years of age [5,6]. The Goldstein model requires country specific inputs, including number of surviving infants, vaccination coverage for HepB3 and HepB-BD, prevalence of HBsAg and hepatitis B e antigen (HBeAg) among women of childbearing age (WCBA), and prevalence of anti-hepatitis B core antibody (anti-HBc) at 5 years-of-age and $\geq$30 years. More details on the model are published elsewhere [12]. We determined post-vaccine regional prevalence of HBsAg among 5-year-old children in 2015 by calculating a weighted average of HBsAg prevalence in each country adjusted by the number of surviving infants in 2015 [11]. Based on vaccination coverage data during 2011–2015, reported literature findings on chronic hepatitis B prevalence in pregnant women and children, and the estimated post-vaccination hepatitis B prevalence in children, we provided recommendations and suggested strategies needed in the next 2–3 years to help each country reach the regional hepatitis B control and elimination goals.

We used the Goldstein model to estimate the total number of chronic HBV infections during the perinatal period and for all ages, and the number of chronic HBV infections averted and lives saved for each country from the year HepB was introduced to 2015. We compiled inputs of HepB-BD and HepB3 coverage [7], and the number of surviving infants [11] for each country from the year of HepB introduction to 2015. We used seroprevalence inputs from the most recent surveys and presumed they remained constant. When no data were available, we used the estimates published by Goldstein and colleagues [12]. Seroprevalence inputs used in the Goldstein model are summarized in the supplementary table. Using the Goldstein model, we calculated the number and rate of perinatal chronic HBV infections per 1000 live births in each country in 2015.

3. Results

3.1. Status of hepatitis B vaccination in the South-East Asia Region

Thailand was the first country in the region to introduce HepB in two provinces in 1988, and nationwide in 1992 (Table 1) [13]. Bhutan, Indonesia, and Maldives introduced HepB during the 1990s, while the remaining countries introduced it during the 2000s [7]. In Indonesia, HepB was introduced nationwide in 1997 following the Lombok Hepatitis B Immunization Project (1987–1991) [14]. HepB was introduced in a phased manner in Bangladesh (2003–2005) and Nepal (2002–2004) [15]. In India, the vaccine was initially introduced in 14 metropolitan cities in 2002, and nationally during 2011–2012 [16,17]. The majority of countries provide HepB as combined pentavalent vaccine (diphtheria, tetanus, pertussis, *Haemophilus influenza* type B, and hepatitis B vaccines) at 6, 10, and 14 weeks of age with one exception (Table 1) [7]. The overall regional HepB3 coverage increased from 56% in

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