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Impact of Adverse Events Following Immunization in Viet Nam in 2013 on chronic hepatitis B infection

Xi Li [a], Eric Wiesen [b,*], Sergey Diorditsa [b], Kohei Toda [c], Thi Hong Duong [d], Lien Huong Nguyen [d], Van Cuong Nguyen [d], Tran Hien Nguyen [d]

[a] Johns Hopkins University, Candidate for Master of Science in Public Health, 615 N. Wolfe St., Baltimore, MD 21205, United States
[b] Expanded Programme on Immunization Unit, World Health Organization, Western Pacific Regional Office, PO Box 2932, Manila, Philippines
[c] Expanded Programme on Immunization Unit, World Health Organization Country Office, 63 Tran Hung Dao Street, Hoan Kiem District, Ha Noi, Viet Nam
[d] National Institute of Hygiene and Epidemiology, 1 Yersin Street, Hai Ba Trung, Ha Noi 10000, Viet Nam

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ABSTRACT

Adverse Events Following Immunization in Viet Nam in 2013 led to substantial reductions in hepatitis B vaccination coverage (both the birth dose and the three-dose series). In order to estimate the impact of the reduction in vaccination coverage on hepatitis B transmission and future mortality, a widely-used mathematical model was applied to the data from Viet Nam. Using the model, we estimated the number of chronic infections and deaths that are expected to occur in the birth cohort in 2013 and the number of excessive infections and deaths attributable to the drop in immunization coverage in 2013. An excess of 90,137 chronic infections and 17,456 future deaths were estimated to occur in the 2013 birth cohort due to the drop in vaccination coverage. This analysis highlights the importance of maintaining high vaccination coverage and swiftly responding to reported Adverse Events Following Immunization in order to regain consumer confidence in the hepatitis B vaccine.

1. Introduction

Hepatitis B virus (HBV) infection is a major public health concern in Viet Nam. In adults born before the hepatitis B vaccine was introduced, 7–24% were chronically infected according to several studies conducted across the country [1–3]. Perinatal transmission from infected mothers to infants is common, and more than half of the population has been exposed to HBV [2–4]. People who are infected in infancy usually don't have symptoms, but 80–90% will develop chronic infection that lasts into adulthood [5]. It is estimated that 20–30% of adults who are chronically infected will develop liver cancer or liver cirrhosis [5]. Viet Nam has one of the highest liver cancer incidence rates in the world, with an annual rate of 37.9 per 100,000 population in males [6]. Liver cancer is the most common cause of cancer deaths in Viet Nam, causing over 20,000 deaths each year [7].

Despite the heavy burden of HBV-related death, new infections can be effectively prevented through hepatitis B vaccination. If given within 24 h of birth, the vaccine is highly effective in preventing mother-to-child transmission [8,9]. The complete series of 3 doses can provide long term protection [10]. In Viet Nam, hepatitis B vaccine was introduced in 1997, and was expanded nationwide in 2002 [11]. A birth dose was added to the immunization schedule in 2003 [11]. A dramatic reduction in prevalence of chronic hepatitis B has been observed in children after the introduction of hepatitis B vaccine. A national survey conducted in Viet Nam in 2011 estimated that children born in 2000–2003 have significantly higher prevalence of chronic HBV infection than children born in 2007 to 2008 (3.64% vs. 1.64%) [11]. The same study found that hepatitis B vaccination coverage increased from 46.1% to 84.0% for the 3 dose series and from 22.0% to 30.4% for the birth dose during the same time period [11]. Hence it is evident that the prevalence of chronic HBV infection can be reduced by achieving high vaccination coverage. The reduction in hepatitis B transmission is expected to result in a corresponding reduction in liver cancer and liver cirrhosis as the new birth cohorts enter adulthood.

Achieving high vaccination coverage requires both a strong system to deliver the vaccine and high demand for the vaccine. Public demand for vaccine is often influenced by media reports on illness or deaths after vaccination. Adverse Events Following Immunization (AEFIs) denotes "any untoward medical occurrence" that follows immunization, which does not necessarily indicate causal

* Corresponding author. Tel.: +63 2 528 9034.
E-mail address: wiesene@wpro.who.int (E. Wiesen).

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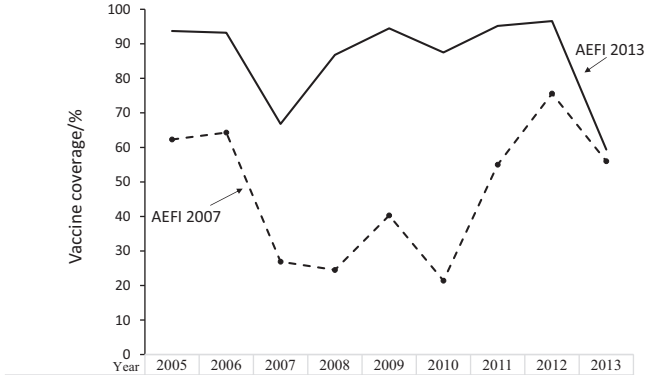
relationship with vaccination [12]. The events can be purely coincidental, but can lead to widespread fears over vaccine safety and major reductions in vaccine demand.

Despite strong efforts to increase hepatitis B vaccination coverage in Viet Nam, publicized news of Adverse Events Following Immunization (AEFIs) have led to fluctuations in hepatitis B vaccination coverage in recent years (Fig. 1). In 2007, the birth dose coverage of hepatitis B vaccine dropped from 64.3% in the previous year to 26.9%, partially attributable to media reports of AEFIs. In 2013, several AEFIs occurred involving both the hepatitis B monovalent vaccine used for the birth dose and the pentavalent vaccine used for the 3-dose series. Following these AEFIs, the pentavalent vaccine, Quinvaxem (DTwP-HepB-Hib) was suspended from May to October 2013 [13]. The monovalent hepatitis B vaccine was not suspended. While investigations of the AEFIs did not identify problems with the vaccine safety, the widespread media coverage of these events led to a major reduction in consumer confidence in the hepatitis B vaccine. As the public concern over vaccine safety became pervasive, the hepatitis B birth dose coverage decreased from 75.6% in 2012 to 56.0% in 2013. This paper estimates the impact of the reduction in vaccination coverage in 2013 on the number of new infections and future deaths related to hepatitis B.

2. Methods

2.1. Model overview

A published model developed by Goldstein et al. in 2005 was used to estimate the expected number of HBV infections and deaths in children born in 2013 under the reported vaccination coverage [14]. Since the risk of infection and outcome of infection is dependent on age, the model assumes all infections occur in three age periods: (1) perinatal infection in infancy, (2) transmission in early childhood (<5 years old), and (3) transmission later in life (>5 years old). The number of perinatal infections was calculated from the number of infants exposed to HBV at birth and the probability of transmission. The prevalences reported in studies conducted before vaccine introduction were used to estimate annual rate of infection without vaccination. The number of early childhood infections was calculated based on the prevalence of anti-HBc at 5 years of age, a marker that reflects both past and current infection, after excluding the number of children infected at birth. For infection among individuals aged five years and above, a constant proportion of infections occurring each year before the age of 30 was assumed, after accounting for age-specific all-cause mortality. The rate of loss of chronic infection (HBsAg) was set to 0.5% each year beginning at the age of 20, and we assumed these people who lost HBsAg are no longer at risk of HBV-related complications. The probabilities of progressing to acute or chronic infection was assumed to be only dependent on age and children have much higher probability of developing chronic infection than adults. Age specific-mortality rate of liver cirrhosis and liver cancer was applied to calculate number of deaths related to chronic hepatitis B. Vaccine efficacy was set to 95% for both birth dose and the 3-dose series in the base analysis. The description of the model and parameters can be found in this paper by Goldstein et al. [14].



Year	2005	2006	2007	2008	2009	2010	2011	2012	2013
HepB Birth Dose	62.3	64.3	26.9	24.5	40.3	21.4	55.0	75.6	56.0
HepB3	93.7	93.2	66.8	86.8	94.5	87.5	95.2	96.6	59.4

Fig. 1. Administrative coverage of Hepatitis B Vaccine (%) in Viet Nam.

2.2. Model input

A literature review was conducted to determine the seroprevalence of HBV infection in children, pregnant women and adults before the introduction of vaccine using the key words of the sero-markers and the country's name. A total of 207 articles were retrieved from Pubmed, and data from 41 articles that reported prevalence of the sero-markers were extracted. In the 41 studies, 26 were conducted among Vietnamese immigrants and 15 were conducted in Viet Nam. Of those conducted in Viet Nam, 7 out of 15 were conducted among repeated blood donors or liver disease patients. The remaining 8 studies were among people who are not expected to be at substantially increased or decreased risk of hepatitis B infection including 5 community-based studies, 1 study among potential blood donors, 1 study among non-liver disease patients and 1 among women who attend antenatal care (Table 1) [1–4,15–18]. None of the studies that reflect baseline prevalences were nationally representative. Only one study conducted in 1999 reported all the data required for the model and this study was from a community-based random sample consisting of both children and adults [16]. In this study, 228 children aged 4 to 6 years and 596 adults aged 25 to 40 years, including 114 females, were randomly selected from two districts of Thanh Hoa province [16]. We used the results of this study as model inputs for base analysis. As reported in this study, the prevalence of HBsAg in women of reproductive age was 15.8%, the prevalence of HBeAg in HBsAg positive women was 27.8%, the prevalence of anti-HBc at the age of 5 was 36.4%, and the prevalence of anti-HBc at the age of 30 was 79.2% [16]. Reported prevalence from the other studies in Table 1 were used for sensitivity analysis.

The numbers of surviving infants and vaccination coverage were extracted from WHO/UNICEF Joint Reporting Form (JRF) from Viet Nam of 2013 [19]. According to the JRF reported to WHO and UNICEF by Viet Nam Ministry of Health, the total number of surviving infants in 2013 was 1782,720. The hepatitis B vaccination coverage for the birth dose was 56.0% and that for the complete series of at least three doses (HepB3) was 59.4% [19].

General mortality rate was derived from World Population Prospects 2012 Revision, published by United Nations Population Division. The estimated age-specific death rates in Viet Nam in 2005–2010 were used [20].

2.3. Sensitivity analysis

A univariate sensitivity analysis was performed to examine the impact of uncertainty in the model inputs and vaccine efficacy: HBsAg prevalence in pregnant women, HBeAg prevalence in HBsAg positive women, anti-HBc prevalence at the age of 5 years and at the age of 30 years, birth dose vaccine efficacy and efficacy of the complete series. Each parameter was changed one at a time, while others remained constant. The highest and lowest reported prevalence in the studies presented in the supplementary table were used to calculate the high and low estimates of chronic HBV infection and deaths caused by HBV infection. When the prevalence estimates in the base analysis are the highest among all reported values, in the case of anti-HBc prevalence at 5 years of age and

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