

# Immune response in infants after universal hepatitis B vaccination: a community-based study in Malaysia

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**INTRODUCTION** This study aimed to assess the immune response in infants who received the three-shot hepatitis B vaccine in Malaysia.

**METHODS** Consecutive infants born between March 2002 and April 2010 who received three doses of hepatitis B vaccine at a community clinic in Malaysia were enrolled in the study. Screening for hepatitis B surface antigen (HBsAg) and antibody against HBsAg (anti-HBs) was performed after the completion of primary immunisation, at approximately one year of age.

**RESULTS** A total of 572 infants (median age  $9.3 \pm 2.7$  months; range 6.3–48 months) were screened for immune response to hepatitis B vaccination – 553 (96.7%) infants had adequate levels of anti-HBs ( $\geq 10$  IU/L). Of the 440 mothers whose HBsAg status was known, 14 (3.2%) were positive for HBsAg. None of the 14 infants who were born to HBsAg-positive mothers were positive for HBsAg, and all but one infant had anti-HBs level  $\geq 10$  IU/L. Gender, gestational age and maternal HBsAg status were not found to significantly affect the subsequent immune response in infants following vaccination.

**CONCLUSION** The proportion of Malaysian mothers who are positive for HBsAg remains high. The three-shot hepatitis B vaccine, given as part of universal vaccination against hepatitis B, provides adequate anti-HBs in the vast majority of infants in a community setting in Malaysia.

Keywords: community, hepatitis B vaccination, immune response

## INTRODUCTION

Hepatitis B virus (HBV) infection remains a global health problem, with more than 350 million people chronically infected with the virus worldwide.<sup>(1)</sup> Hepatitis B vaccines are effective in preventing HBV infection. In 2009, the World Health Organization (WHO) reported that up to 177 countries had included hepatitis B vaccination into their national infant immunisation programmes.<sup>(2)</sup> Various studies have shown that immunisation in infancy provides adequate protection against HBV infection, which lasts even till school-going age.<sup>(3)</sup> However, studies have also found that not every recipient of the vaccine produces adequate protective levels of the antibody after completion of primary immunisation.<sup>(4)</sup>

In Malaysia, universal hepatitis B vaccination of all newborn infants has been implemented since 1989. However, to the authors' knowledge, only one industry-sponsored study has ever assessed the seroprotective anti-hepatitis B antibody (anti-HBs) levels in a setting where hepatitis B vaccines were given in combination with other childhood vaccines.<sup>(5)</sup> The efficacy of the universal hepatitis B vaccination programme has never been assessed in a community setting in Malaysia. The aim of the present study was to assess the immune response of newborns who received the three-shot hepatitis B vaccine at community child health clinics in Malaysia, by measuring their anti-HBs levels after immunisation at approximately one year of age.

## METHODS

The present study was conducted among infants who attended the child health clinic at Lam Wah Ee Hospital (LWEH), a charitable hospital that caters mainly to the lower-to-middle income population in Penang, Malaysia. The study was approved by the institutional ethics review committee.

Consecutive newborn infants delivered at LWEH between March 2002 and April 2010 (study period, 8 years 2 months), who were managed by a single clinician, were screened for anti-HBs levels after the completion of their primary immunisation, at approximately one year of age. All newborn infants were given the three-shot hepatitis B vaccine at birth, one month and six months of age. Prior to 2002, the hepatitis B vaccine given at LWEH was Hepavax-Gene (Crucell, Leiden, The Netherlands), while that given after 2002 was Engerix-B® (GlaxoSmithKline Biologicals, Rixensart, Belgium). Infants delivered to mothers who were positive for hepatitis B surface antigen (HBsAg) were additionally given anti-hepatitis B immunoglobulin (Hepabig®; VHB Life Sciences, Mumbai, India) within 24 hours of birth.

Screening for anti-HBs levels was performed at approximately one year of age. Adequate protective level of anti-HBs was defined as antibody level  $\geq 10$  IU/L.<sup>(6)</sup> Screenings for HBsAg and anti-HBs were performed using chemiluminescent microparticle immunoassay techniques (Abbott Architect ci8200 Analyser; Abbott Diagnostics, Abbott Park, IL, USA).

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**Table 1. Immune response to hepatitis B vaccination in Malaysian infants (n = 572).**

Variable	No. of infants (%)		p-value
	Antibody level $\geq 10$ IU/L (n = 553)	Antibody level $< 10$ IU/L (n = 19)	
<b>Gender</b>			0.15
Male	290 (52.4)	14 (73.7)	
Female	263 (47.6)	5 (26.3)	
<b>Gestational age</b>			0.26
Term	485 (87.7)	18 (94.7)	
Preterm	58 (10.5)	1 (5.3)	
Unknown	10 (1.8)	0 (0)	
<b>Maternal HBsAg status</b>			0.50
Positive	13 (2.4)	1 (5.3)	
Negative	412 (74.5)	14 (73.7)	
Unknown	128 (23.1)	4 (21.1)	

HBsAg: hepatitis B surface antigen

## RESULTS

A total of 572 consecutive infants, delivered between March 2002 and April 2010 at LWEH, who received the three-shot hepatitis B vaccine, were screened for immune response to hepatitis B vaccination (Table 1). Of these, 304 (53.1%) infants were male. The ethnicities of the infants were: 283 (49.5%) Chinese, 143 (25.0%) Malay, 140 (24.5%) Indian, and 6 (1.0%) minor ethnicities. A majority of infants (n = 503, 88.0%) were delivered at term (gestational age  $\geq 37$  completed weeks). A total of 426 (74.5%) mothers were HBsAg negative, while 14 (2.4%) were HBsAg positive. Among women with known HBsAg status (n = 440), 14 (3.2%) were HBsAg-positive. The HBV status of 132 (23.0%) women was unknown. All 572 infants received the first dose of hepatitis B vaccine at birth. However, only 506 (88.5%) and 551 (96.3%) infants had a record of receiving the second and third dose of the vaccine, respectively, at LWEH. Screening for anti-HBs was performed at a median age of  $9.3 \pm 2.7$  (range 6.3–48) months.

Among the 572 infants, 19 (3.3%) had inadequate antibody response – anti-HBs antibody was not detected in 3 (0.5%) infants, while antibody levels were  $< 10$  IU/L for another 16 (2.8%) infants. Among the remaining 553 (96.7%) infants who had antibody levels  $\geq 10$  IU/L, 310 (54.2%) had antibody levels  $> 1,000$  IU/L. Factors such as gender, gestational age and maternal HBsAg status were not found to significantly affect the subsequent anti-HBs antibody levels in infants receiving hepatitis B vaccination (Table 1). The majority of infants (13/14) delivered to HBsAg-positive mothers had adequate antibody levels. None of the infants in our group was found to be HBsAg-positive.

## DISCUSSION

Universal hepatitis B vaccination is known to bring enormous benefits to communities where HBV infection is endemic.<sup>(1)</sup> Hepatitis B vaccination has been associated with the elimination or reduction of childhood hepatocellular carcinoma,<sup>(7)</sup> acute liver failure<sup>(8)</sup> and, more recently, virus-associated membranous

nephropathy.<sup>(9)</sup> Universal hepatitis B immunisation of newborns has been implemented in Malaysia since 1989.<sup>(10)</sup> Since then, there has been a steady decline in the seroprevalence of HBsAg – from 2.5% for children born in 1985 (four years before universal immunisation) to 0.4% among school children born in 1996.<sup>(10)</sup>

The results of the present study show that universal hepatitis B vaccination of newborns in Malaysia is highly successful. 96.7% of the 572 infants immunised in our study were found to have adequate levels of anti-HBs at approximately one year of age. Furthermore, none of the 14 infants who were born to HBsAg-positive mothers were found to be HBsAg-positive. Among these 14 infants, 13 were found to have adequate levels of protective anti-HBs following immunisation. Failure to produce detectable antibody levels even after three doses of hepatitis B vaccines has been reported in a small minority of patients.<sup>(11)</sup> Researchers have adopted various methods to overcome this problem, including administering a fourth dose of vaccine<sup>(11)</sup> or a booster dose at a later age.<sup>(3)</sup> However, it should be noted that the risk of acquiring HBV infection among non-responders has been found to be similar to that among those given booster vaccines.<sup>(3)</sup>

The present study also found that chronic HBV infection remains high among Malaysian mothers, with 3.2% of women whose HBsAg status was known testing positive for HBsAg. This underscores the importance of universal hepatitis B vaccination. We expect that the proportion of HBsAg-positive women will dramatically decrease as the cohort of Malaysian women who received universal hepatitis B vaccination (introduced in 1989) enters reproductive age. However, for women who had not been immunised, screening at antenatal clinics for HBsAg remains an important strategy for reducing vertical transmissions.<sup>(12)</sup>

One of the potential drawbacks of the present study was the lack of information on the status of hepatitis B e antigen (HBeAg) among women who were HBsAg positive, as it is well known that vertical transmission is more likely to occur among infants born to women who are positive for both HBeAg and HBsAg.<sup>(12)</sup>

In conclusion, the proportion of Malaysian mothers who are positive for HBsAg remains high. Our results suggest that universal vaccination of newborns with three doses of hepatitis B vaccine in a community clinic setting in Malaysia has proven highly successful in preventing the perinatal transmission of HBV infection, as well as achieving adequate protective levels of anti-HBs in a vast majority of infants.

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