ORIGINAL ARTICLE

Hepatitis B seroprevalence among University of Malaya Students in the Post-universal Infant Vaccination Era

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SUMMARY
Aim: A nationwide HBV vaccination for neonates in the Expanded Programme on Immunization (EPI) was implemented in Malaysia in 1989. The objective of this study was to investigate the prevalence of HBsAg, anti-HBs and anti-HBc among the new student intakes in the Faculties of Medicine and Dentistry, University of Malaya from 2005 to 2011.

Materials and Methods: All new students enrolled for undergraduate and postgraduate courses were screened for HBV infection. Serum samples collected were tested for the presence of HBsAg, anti-HBs and anti-HBc with the use of fully automated analysers. Statistical analyses were done using Open Epi version 2.3.1

Results: The overall HBsAg prevalence among the 2923 new intakes was 0.62%. The HBsAg prevalence rate was 1.08% (15/1390) for those born before 1989 and only 0.20% (3/1533) among those born in or after 1989. By year of testing, HBsAg prevalence declined steadily from 1.27% (5/394) in 2005 to 1.20% (5/418) in 2006, 0.95% (4/421) in 2007, 0.49% (2/410) in 2008, 0.49% (2/407) in 2009 and finally 0% in both 2010 (0/445) and 2011 (0/428). Although 66.14% of those vaccinated during infancy had no demonstrable immunity at the time of screening, only 6 (0.39%) students were found to have anti-HBc, including the 3 who were HBsAg positive.

Conclusion: These findings suggested effective prevention of HBV transmission with the universal and voluntary vaccination programs in Malaysia.

KEY WORDS:
Hepatitis B virus, EPI, HBsAg, Anti-HBs, Students

INTRODUCTION
Hepatitis B virus (HBV) infection is a major cause of liver pathology presenting as acute hepatitis and chronic complications such as cirrhosis and hepatocellular carcinoma. Individuals infected perinatally or in early childhood are at a greater risk of progression from acute to chronic infection than those infected later in life. Asia and the Western Pacific region share about 75% of chronic HBV infections in the world. In public health surveillance, persisting HBV infection is detected by the presence of hepatitis B surface antigen (HBsAg) in the blood. Countries with HBsAg prevalence of at least 8% are classified as high endemicity countries.

Since the introduction of HBV vaccination in the early 1980s, the prevalence of HBsAg positivity has declined, particularly in hyperendemic areas where transmission is mostly perinatal or during early childhood. The World Health Organization (WHO) through its Global Advisory Group of the Expanded Program on Immunization (EPI), recommended hepatitis B vaccination to be integrated into national immunization programmes in countries with HBsAg prevalence of 8% or more. In the early stages of this extended immunization programme, the global infant HBV vaccine coverage was low and varied, but by 2007 the coverage rate had reached 65% in most countries and data from hyperendemic regions have shown the effectiveness of the programme for the prevention of HBV transmission. In Taiwan, for instance, within ten years of HBV vaccine introduction, the HBsAg prevalence declined from 9.3% to 1.3% in children younger than 12 years and from 9.8% to 0.7% among those younger than 15 years of age. Similarly, in Thailand, HBsAg prevalence among 1 to 18-year-olds fell from 3.4% to 0.7% ten years after the implementation of EPI with HBV vaccination.

Malaysia was an intermediate endemicity country with HBsAg prevalence of 5-7% before nationwide HBV vaccination for neonates was introduced in 1989. Under this EPI, all newborns are given three doses of HBV vaccine to prevent mother-to-infant transmission. The first dose is given in the hospital soon after birth, the second at the one month post-partum follow up visit, and the third, at the fifth month, either in the hospital or at a rural health centre. The impact of this programme on the prevalence of chronic HBV infection in the Malaysian population has been assessed by Ng et al. for school children aged 7-12 years. The HBsAg detection rate in these children declined from 2.5% among those born in 1985 (before the implementation of universal infant vaccination) to 0.4% among those born in 1996.

Many universities screen applicants for medical, dental and nursing courses, as healthcare workers are at risk for infection through exposure to patients’ body fluids but conversely, if infected, can potentially transmit their HBV to patients under their care. In 1994, the Britain’s Committee of Vice-Chancellors and Principals issued guidance to universities on medical and dental students’ fitness to practise in relation to...
hepatitis B. Universities that have adopted this committee’s guidance have barred HBV-infected individuals from entry into medical and dental courses and from post-graduate specialist training. In regions with high HBV endemcity, however, there has been no consensus on the suitability of students with good academic achievement but infected with HBV, for medical and dental training.

The objective of this study was to investigate the prevalence of HBsAg and anti-HBs among the new student intakes in the Faculties of Medicine and Dentistry, University of Malaya. The anti-HBc, a serological marker of HBV infection, was analyzed among new intakes vaccinated under the EPI, to study the level of post-vaccination exposure to HBV infection.

MATERIALS AND METHODS
This is a prospective cross-sectional study from 2005 to 2011. All new students enrolled for undergraduate and postgraduate courses in the Faculty of Medicine and Faculty of Dentistry were screened for HBV infection. Demographic data and history of HBV vaccination, including the number and timing of vaccine doses given, were obtained from each student, using a standard questionnaire. All students born in and after 1989 were considered as being vaccinated under the EPI. As HBV screening of students is a routine procedure at the University and only anonymous HBV data was used for analysis, ethics committee review for the study was waived in accordance with the standard operating procedure of the university’s Medical Ethics Review Committee.

Detection of HBsAg and anti-HBs
Serum samples collected from 2005 to 2007 were tested for the presence of HBsAg and anti-HBs by a fully automated analyser, AxSym Abbott Plus (Abbott Laboratories, Diagnostics Division, Abbott Park, IL USA). Assay procedures were conducted according to the manufacturer’s instructions. All samples found to be HBsAg reactive in the first screen were re-tested in the same analyser and only repeatedly reactive samples were considered HBsAg positive. Anti-HBs was reported as >/= 10 mIU/ml.

Detection of Anti-HBc IgG
Anti-HBc IgG was assayed using the Architect Anti-HBc II (Abbott Laboratories, Diagnostics Division, Abbott Park, IL USA) and conducted according to the manufacturer’s instructions. This test was only performed for new intakes born in or after 1989 i.e. those who had received HBV vaccination from EPI.

Statistical analyses
Statistical analyses were done using Open Epi version 2.3.1. Descriptive analyses were used for the baseline demographic and clinical data. Bivariate analyses (i.e Student independent-test and Chi-square) were conducted to test the association between demographic and clinical data. P value of <0.05 was used to test the significance level. Odds ratio and its associated 95% confidence interval were used for categorical data analysis to estimate risk.
DISCUSSION

The EPI was established in 1974 through a World Health Assembly resolution to ensure that all children in all countries benefited from life-saving vaccines. Following the introduction of universal infant HBV immunization in 1992, the WHO Western Pacific Region (WPR) adopted in 2005, a regional goal of hepatitis B control to reduce the prevalence of chronic HBV infection as indicated by the seroprevalence of HBsAg to less than 2% by 2012 and ultimately to less than 1% in children 5 years of age and below. In many countries in the WPR, the seroprevalence of HBsAg is still over 8% but the importance of universal vaccination is evidenced by the dramatic reduction in HBsAg seroprevalence among children in countries that have implemented nationwide infant vaccination programmes.

In this study on new students entering a Malaysian university for medical and paramedical studies, the HBsAg seroprevalence declined from 1.27% in 2005 to 0% in 2011, in line with increasing proportions of students vaccinated under the EPI. This trend attested to the efficacy of the universal infant HBV vaccination programme for protection against chronic HBV infection, for at least 18-19 years, without a booster vaccination. This protection, however, was not complete as there was still a 0.20% risk of infection among those vaccinated from birth. These break-through infections might be caused by high maternal viral load, inadequate immune response to the first course of vaccination, diminished immunity afterwards, or infection with vaccination escape mutants (VEMs). It has been reported that VEMs selected out by anti-viral treatment have been transmitted to individuals immunized with the HBV vaccine and that HBV immunization for infants might not prevent transmission of VEMs from mothers. As the use of antivirals for the treatment of HBV infection increases, VEM-related infections and consequently vaccine breakthrough infections would become increasingly common.

Anti-HBs was not detected in 66.14% of those vaccinated at birth compared to only 13.12% of those vaccinated voluntarily at an older age (Table III). This difference is most likely to be due to the longer time interval between vaccination and testing in the first group. The duration of effective protection after infant vaccination and the need as well as timing for a booster vaccination has been long debated. North American and European authorities do not recommend booster vaccinations for immunocompetent individuals who have responded to a primary course of vaccination. This advice is based on the observation that immunological memory seems to last for at least 15 - 18 years, in adequately vaccinated immunocompetent individuals, in the form of persisting anti-HBs and/or in vitro B-cell stimulation or an anamnestic response to a vaccine challenge. Nevertheless, researchers have found that the geometric titres of vaccine-induced anti-HBs decline with time with the persistence of protective antibody strongly.
predicted by the extent of the maximal antibody response to vaccination and the long-term risk of HBV infection inversely related to the maximal antibody response to vaccination. In Malaysia, as in many other countries, the adequacy of this antibody response is mostly assumed as there is no routine testing for seroconversion following vaccination. In Taiwan, Lin et al. reported 37.4% anti-HBs prevalence among children 12 years after full primary neonatal vaccination, and Lu et al. found HBV infection in 1/3 of children 15 years after initial vaccination. In the Netherlands, del Canho et al. reported a child with an adequate antibody response (about 60 mIU/mL of anti-HBs at the age of one year) becoming HBsAg reactive in the fifth year of follow-up. Among children in Alaska, Peterson et al. found that 88% of those vaccinated at birth had no detectable anti-HBs at the age of 5 years and one third failed to demonstrate an anamnestic response to a booster dose. These reports indicated a decline of protective antibody to undetectable levels in a substantial proportion of children less than 15 years after primary vaccination in infancy and, more importantly, a not infrequent failure of immunological memory on revaccination. Hence, some countries currently still have a policy of administering booster doses to certain risk groups, to provide reassurance of protective immunity against breakthrough infection. One of these risk groups consists of healthcare workers for whom HBV infection is an important occupational hazard. Tan et al. reported an infection rate of 25% in about 2500 health employees in the state of Negri Sembilan, Malaysia, among whom the HBsAg was positive in 2.1% and anti-HBs in 22.8%, with increased relative risks among medical assistants and laboratory staff. It is a common practice, in most parts of Malaysia, to give a booster vaccination to those entering a medical or other healthcare profession. There is evidence that the anamnestic response elicited by a booster vaccination might not be able to re-establish protective memory within a week. This delayed response might cause infection in some of those exposed to highly infectious patients. Hence, there may still be a place for regular boosters and follow-up monitoring for at-risk healthcare workers.

CONCLUSION

Overall, there is serological evidence that the universal infant HBV immunization program in Malaysia has been effective in reducing the rate of chronic HBV infection in children up to about 19 years of age. However, further investigations are necessary to evaluate the adequacy of the current vaccination program for special at-risk groups, as well as the need for booster doses and long-term monitoring, for early detection of clinically significant breakthrough infection or the carrier state. A catch-up HBV vaccination program is needed to vaccinate the students born before the implementation of EPI who have no immunity to HBV infection.

ACKNOWLEDGEMENT

This study is supported by a University Malaya grant UM H-0000-30410-H72412 (8122113). K.P. Ng, Y.F. Ngeow, K. Rozainah and Rosmawati bt Mohamed were involved in the acquisition, analysis, and interpretation of data. All authors contributed to the drafting and revising of the manuscript. The final version of the manuscript has been approved by all authors.

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