Epidemiological features of hepatitis B virus infection in Malaysians

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Summary

In order to plan a strategy for control of hepatitis B virus infection in Malaysia, we determined (i) the annual rate of infection, (ii) the basic reproductive rate, Ro, of this infection, and (iii) the cost-effectiveness of HBeAg screening versus HBsAg screening of pregnant females to allow identification of neonates at risk of vertically transmitted infection. HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBc markers were tested by radioimmunoassay in sera from 1435 Malaysian subjects aged 3 months to 67 years. The mean age of infection calculated by life table analysis was 15 years (Ro = 6). The rate of infection was highest during the first 10 years of life, when infection occurred in 2% of children per year. An increased infection rate occured in males, after the age of 14 years. By the age of 50 years, 62% of males and 50% of females had been exposed to HBV. On the premise that vertical transmission, of HBV occurs from HBeAg positive mothers, then HBeAg screening would have been more cost-effective than HBsAg screening. We conclude that all Malaysian children are at high risk of infection and that the aim must be towards mass neonatal vaccination.

Key words: Hepatitis B, Epidemiological features Malaysians, HBsAg screening pregnant females.

Introduction

Approximately 5 to 10% of the Malaysian adult population are carriers of hepatitis B virus (HBV).[1] One to 2% of these carriers will develop chronic liver disease 20 to 40 years after infection.[2] Thus, the earlier the infection occurs, the more likely symptoms of liver disease will manifest during life. HBV vaccination can be used either to delay or prevent the onset of infection. Alternatively, a programme of mass vaccination could be used to eradicate HBV. The objective of this study was to provide detailed information about the epidemiology of HBV infection in a Malaysian community, to aid in the planning of a vaccination strategy.

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Subjects and methods

Sera were collected from (i) a random sample of 605 pregnant females at delivery, aged 15 to 47 years, (ii) a random sample of 472 blood donors aged, 18 to 65 years, (iii) 160 volunteers from rural areas, aged 5 to 67 years, and (iv) 198 children, aged 3 months to 12 years, referred to University Hospital, Universiti Sains Malaysia, Kelantan, but who had not been previously admitted to hospital and were not known to be suffering from liver disease. HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBc markers were determined by radioimmunoassay using kits (Abbott Laboratories, USA). The presence of HBsAg, anti-HBs or anti-HBc was taken to indicate HBV infection. Due to insufficient serum volume, HBeAg and anti-HBe testing was performed on 998 individuals only.

The influences of age and ethnic group on the presence or absence of HBV infection in males and females were determined by fitting a logistic regression model to the data.[3] Using this model, the probability of an individual being infected with HBV was shown by:

$$p\,(x_1, x_2 \ldots \ldots, x_4) = 1\,/\,(1 + \exp[-(b_0 + \sum_{i=2}^{4} b_i x_1)])$$

Where x_1 was the presence ($x_1 = 1$) or absence ($x_1 = 0$) of markers of past HBV infection, x_2 was log age in years and x_3 and x_4 were indicator variables for ethnic group (Malay, $x_3 = 1$, others $x_3 = 0$, Chinese $x_4 = 1$, others $x_4 = 0$). The intercept of the line was represented by b_0 and $b_2, \ldots, b_4$ were the logistic parameters of each variable. X^2 values for each estimated regression coefficient were derived from the likelihood ratio test. A computer programme for stepwise logistic regression using maximum likelihood estimation was run on an Apple compatible personal computer.[4] Information on socio-economic status, education and site of residence, was not collected. The mean age and rate of infection was calculated from a life table corrected for the Malaysian mortality rate.[5] This was modeled on a microcomputer spreadsheet (Visicalc, Personal Software Inc, United States of America) using the above regression equation.[6]

The basic reproductive rate, Ro, is the number of secondary cases arising from one primary, infectious case of HBV.[7] When Ro is < 1 then the infection becomes extinct. Calculation of Ro allows the proportion of the population who require vaccination to be estimated. The relevant formulae are (i) Ro = 1 + life expectancy/average age of infection, (ii) Ro = $\bar{R}o$ (1-p) + $\hat{R}o$ (p), where $\bar{R}o$ is the basic reproductive rate if there were no carriers and $\hat{R}o$ is that if all infected became carriers. p is the probability of a case becoming a high risk carrier (HBeAg + ve), (iii) proportion of children requiring immunization at or near birth = (1 - 1/Ro).

Table 1

Prevalence of HBsAg +ve and HBeAg +ve individuals stratified according to age and sex. Values in parenthesis are percentages. Gender data was missing on 9 of the original 1435 subjects.

Age (yr)	Male				Female			
	HBsAg +ve	TOTAL	HBeAg +ve	TOTAL	HBsAg +ve	TOTAL	HBeAg +ve	TOTAL
0–19	9	154 (6)	6	124 (5)	12	127 (10)	2	113 (2)
20–39	43	378 (11)	10	153 (7)	26	541 (5)	12	550 (2)
>39	12	189 (6)	0	30	0	37	0	28

The cost of preventing vertical transmission by screening for either HBsAg or HBeAg was calculated from costs prepared by the Viral Hepatitis Committee and data on the prevalence of these markers in the pregnant female group.[8]

Results

The sample was composed of Malays 91%, Chinese 8% and Indians 1%. The sex ratio was unity. Data on past HBV infection were best represented by separate equations for males and females. Ethnic group did not exert a significant effect on he outcome and the best fit logistic regression equations were, in males, $p = 1/(1+\text{expc}[-(-2.889 + 8.64 \times 10^{-4} \, 4x_2)])$, and, in females, $p = 1/(1+\exp[-(-2.400 + 6.147 \times 10^{-4} x_2)])$. The original data and the logistic regression lines are shown in figure 1. There was an increased rate of infection in males compared to females only after the age of 14 years ($p < 0.001$). The rate of infection was highest during the first 10 years of life, occurring in an average of 2% of children per year.

The proportion of HBeAg +ve and HBsAg +ve carriers are shown in table 1. Threeway contingency table analysis of this data stratified for age, sex and HBeAg status indicated that HBeAg positivity was influenced by sex ($X^2 = 8$, degrees of freedom = 1, $p = < 0.001$), but not significantly by age. If the prevalence of HBeAg shown in table 1 were to be projected onto the 1980 population of Kelantan, then approximately 55% of HBeAg carriers would be in the age group < 20 yr and 37% in the 20 − 39 yr group. Prevention of vertically transmitted infection would reduce this pool by only 2% in the first year.

Based on the predicted mean age of infection of 15 years and a life expectancy of 68 years then Ro = 6. Application of formula (iii) indicates that > 80% of children should be vaccinated at or near birth to eradicate infection.

Five percent of pregnant females were HBsAg positive and 2% HBeAg positive. None of the latter had anti-HBe. However, only 5 of the 11 HBeAg positive females had detectable HBsAg. Hence the diagnostic specificity of HBsAg screening, i.e. its ability to detect at-risk neonates, was only 0.46 (0.03 − 0.69, 95% CI). The predicted number of vertically transmitted cases that could have been prevented by using these two methods of screening in the 36,000 females who became pregnant in Kelantan in 1983, are given in table 2. The cost of preventing one case by HBeAg screening was M\$579 and by HBsAg screening M\$1385 (table 3). Thus, the marginal cost saved by HBeAg testing was M\$806 per case prevented.

Discussion

In this study it was predicted from life table analysis that 72% of Malaysians infected with HBV, acquire their infection before the age of 20 years. How were they infected? Infants born to HBeAg tve mothers have a 68 fold increased risk of HBV infection compared to those born to HBeAg -ve mothers.[9] The risk is negated if anti-HBe is present and only slightly increased in children born in HBeAg -ve/HBsAg +ve mothers.[9] However, Chan et al 1985 calculated that perinatal infection accounted for only 18% of the total number of HBsAg carriers at 1 yr of age, whilst, in our study, the first year of maternal screening/vaccination would only reduce the pre-existing HBeAg carrier pool by 2%.[9] Thus, most cases of HBV are propagated by horizontal transmission. Cvjetanovic et al (1984) computed that even after 50 yr of vaccination of at-risk neonates, the incidence of HBV is unlikely to fall by more than 30%.[10]

Table 2

Predicted numbers of at-risk children identified if 36,000 pregnant females were screened in Kelantan, assuming uniparous pregnancy

HBeAg screen	HBsAg screen	Rationale
720 at-risk	70 at-risk	2% of mothers HBeAg +ve*
720 identified	331 identified	diagnostic sensitivity of HBsAg screening only 0.46*
58 infected	27 infected	8% of identified already infected in utero[9]
662 preventable	304 preventable	identified neonates minus infected neonates
622 prevented	286 prevented	HBV vaccine efficacy 94%[18]
98 infected	434 infected	total infected, assuming 100% vertical transmission rate.

Data from this study

Sporadic, horizontal transmission probably occurs from HBeAg carriers. Individuals with acute HBV viral hepatitis give rise to few secondary cases and in one study only infected 4% of susceptible, household, contacts.[11] If our data is used in equation (ii) to calculate $\hat{R}_o$ (p = 0.04, R_o = 6 and e.g. $\bar{R}_o$ = 2), then each carrier would give rise to an average of 102 secondary cases. Although many children are probably infected by their HBeAg +ve peers, transmission can also occur between people of greatly differing ages.[12]

There was no significant sex difference for the prevalence of HBV infection until after the age of 14 years. This increased prevalence amongst males could be due to both environmental and biological factors. Males have a greater chance of exposure to HBV as they constitute 66% of persons age 10 years or over in the Malaysian workforce.[5] In addition, they may be at greater risk of infection through occupation e.g. the armed forces.[13] Evidence of a biological effect on HBV prevalence is the slower rate of HBeAg clearance amongst males compared to females.[14]

Table 3

Cost in M$ of preventing HBV infection by vertical transmission through either HBsAg or HBeAg screening of 36,000 pregnant females in Kelantan

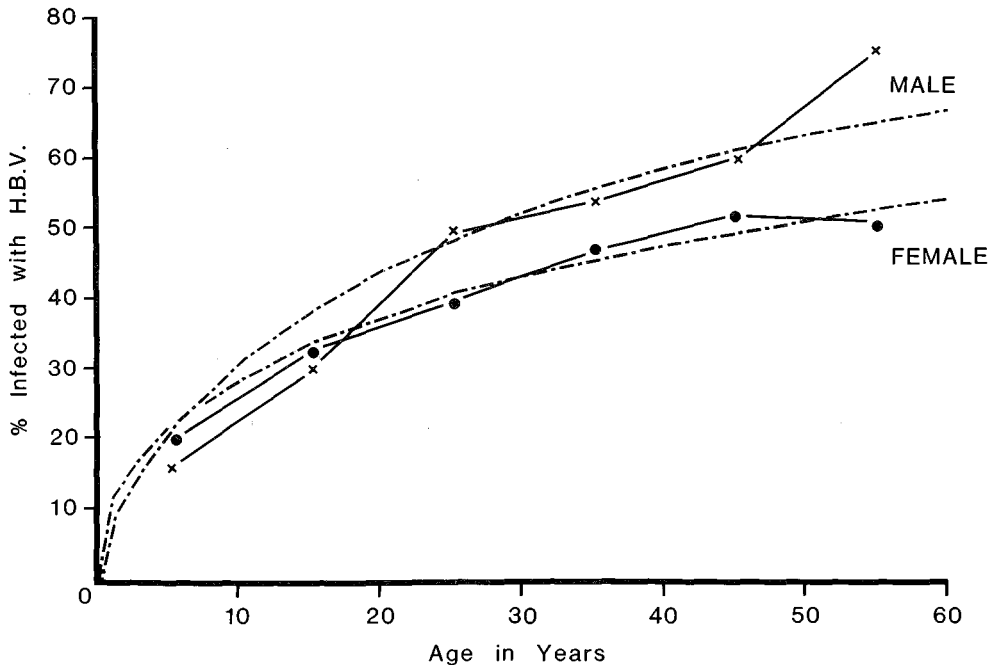| Test	Cost of screen	Cost of vaccination*	Total cost	Cases prevented	Cost to prevent one case of HBV
HbsAg	$36,000 ($1/test)	$360,000 (5% vaccinated)	$396,000	286	$ 1385
HBeAg	$216,000 ($6/test)	$144,000 (2% vaccinated)	$360,000	622	$579

Vaccine costs $200 per child.[8]

FIGURE 1

The probability of past HBV infection according to age and sex is shown by logistic regression lines. The original data is signified by x—x for males and ●—● for females.

To eradicate HBV would require mass vaccination every 5 to 10 years for more than 50 years.[10] Financial constraints limit most programmes to maternal screening and vaccination. However, neither of the two screening methods studied here are infallible, because of the occurrence of HBsAg -ve/HBeAg — ve/DNA polymerase +ve individuals.[15] The latter marker indicates active HBV replication. The occurrence of such individuals and our own HBsAg-ve/HBeAg+ve pregnant women, may be due to serological windows.[16] Finally, the costing does not take into account the additional manpower required to effectively screen and vaccinate the 85% of pregnant females who have a domicilliary delivery in Kelantan. Based on the costing in table 3, mass neonatal immunization could be introduced, when the vaccine cost falls to M$10 per child. Such a price might be achieved by use of a low dose vaccination schedule.[17]

We conclude that mass vaccination of children at birth and a booster at 5 years of age would be the preferred immunization strategy.

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