RESEARCH COMMUNICATION

Risk Factors for Hepatitis B Infection in Rural Vietnam

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Abstract

Background: Hepatitis B virus (HBV) infection is a significant public health problem in Vietnam, yet few data exist about the extent of infection. Purpose: To determine seroprevalence of HBV and the risk factors for HBV infection using a population-based epidemiological study in Vietnam. Methods: A 400 person survey for seroprevalence of hepatitis B surface antigen (HBsAg) and HBV infection was carried out in five hamlets in the Linhson village of Thainguyen province from June to August 2006. HBV infection was defined as the presence of antibodies to hepatitis core antigen (HBcAb) and/or HBsAg, with or without HBsAg. Potential risk factors for HBV transmission were determined by a structured questionnaire. Results: Of the 383 respondents aged 18-70 years, 34 (8.8%) tested positive for HBsAg, of whom 21 (61.8%) were HBeAg-negative and hepatitis B e antibody (HBeAb) positive, and 22 (64.7%) had normal alanine aminotransferase (ALT) levels. The prevalence of HBV infection was 51.8% and increased significantly with age. Only 5.2% showed evidence of vaccination. On multivariate analysis, five predictors were found for HBV infection: male gender (OR 1.6; 95% CI 1.3-1.7), age greater than 40 (OR 2.1; 95% CI 1.4-3.3), Kinh ethnicity (OR 1.8; 95% CI 1.1-2.7), a low level of education (OR 1.7; 95% CI 1.0-2.7), and a history of surgery (OR 1.9; 95% CI 1.0-3.5). Conclusions: The observed high prevalence of current and past infection with HBV in rural Vietnam highlights the need for close monitoring.

Key Words: HBV - infection rates - rural Viet Nam

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Introduction

Hepatitis B virus (HBV) infection is a significant public health problem in the world. According to the most recent World Health Organization estimate, two billion people worldwide have serologic evidence of past or present infection and at least 360 million are chronically infected and at risk of HBV-related liver diseases (Shepard et al. 2006; WHO. 2009). Southeast Asia and the Western Pacific have the highest levels of endemic HBV in the world with the estimated seroprevalence range between 2% and 31% (Chen et al., 2000; Custer et al., 2004). Vietnam is one of the countries with a high prevalence. Previous studies in various parts of the country revealed about 4-18% of the population to be positive for hepatitis B virus surface antigen (HBsAg) (Kakumu et al., 1998; Nakata et al., 1994; Tran et al., 2003). However, these studies have mainly carried out in urban population or were hospital based. There are few population-based epidemiological studies on risk factors related to HBV in rural areas of Vietnam. Therefore the present study was conducted to address the extent of HBV infection and determine risk factors for HBV in a rural area in the North of Vietnam.

Materials and Methods

Study population

The survey took place in Linhson village, Thainguyen province, located about 80 kilometers northeast of Hanoi and a gateway to Vietnam's mountainous northeastern region. With the population of over 1 million people and 70% rural, Thainguyen is home to eight main ethnic groups: the majority Kinh ethnic group accounting for 81% and other minority ethnic groups (Tay, Nung, San Diu, Hmong, San Chay, Chinese and Dao) making up 19 percent of the population. Linhson village is composed of 12 separate hamlets. Spread out over 4,000 acres, the village is served by a main clinic center with a staff of two physicians, three nurses and 12 health workers. This village has a stable population of approximately 6,000 residents and is representative of rural mountainous areas in Vietnam where most of the population work as farmers, with the main agricultural products being tea and rice.

A total of 400 persons, aged 18-70 were randomly selected from this village by a two-stage, random sampling method. In the first stage, five hamlets were randomly selected from 14 hamlets in the village by the randomizing SAS program. In the second stage, a list of adults 18-70

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years of age in these five hamlets was obtained from the administrative register of the village. A systematic random sample technique (Thompson, 2002) was then applied to select 400 subjects from this list.

Data collection

Participants who gave written consent were interviewed based on a structured questionnaire by trained nurses to obtain information about demographic characteristics, vaccination history, family history, sexual history and other related risk factors, and symptoms of hepatitis B. Participants were then examined by a physician to elicit evidence of liver disease. Ten milliliters (ml) of venous blood was drawn from each subject into 10-ml tubes. Afterwards, 0.5 ml of blood was then transferred to 1% EDTA tube for hematological indicators test. Another 2 ml was transferred to anticoagulant tube containing sodium citrate for measurement of prothrombin time. Remaining serum was frozen for subsequent transport to and analysis at Thainguyen General Hospital (TGH) and National Institute of Hygiene and Epidemiology (NIHE) in Hanoi. Biochemical indicators, HBsAg and HCV were performed at TGH and HBcAb, HBsAb, HBeAg and HBeAb were performed at NIHE.

Laboratory testing

All sera were assessed by an enzyme-linked immunosorbent assay (ELISA) (Sanofi Diagnostics Pasteur, Marnes la Coquette, France) for HBsAg and HCV. All HBsAg-positive samples were reassayed in duplicate to confirm results. Samples positive for HBsAg were tested for HBV e antigen (HBeAg) and anti HBV antibody (HBeAb). Samples negative for HBsAg were tested for antibody to hepatitis B core antigen (HBcAb) and antibody to hepatitis B surface antigen (HBsAb). Alanine aminotransferase (ALT) levels were also included

HBV infection status definition

To evaluate the potential risk factors for subjects with different HBV infection outcomes, individuals were categorized into two groups, HBV positive and HBV negative groups: the HBV-positive group was composed of subjects who tested positive for any HBV marker and the HBV-negative group tested negative for all markers. Current infection was defined as HBsAg positivity.

Statistical analysis

Data were analyzed using SAS version 9.0 (SAS.). Descriptive procedures were applied to characterize the study population. Univariate analysis was applied to each risk factor. Differences of HBV in groups of each characteristic were compared by chi-square test. The characteristics with significant difference in HBV were selected for multivariate analysis. Multiple logistic regression models were used to explore the risk factors for Hepatitis B and examine possible interactions and control for possible confounding variables. Data were modeled with the backward elimination process to identify the most parsimonious model from the saturated model. Residual analysis and partial plots were used for checking regression assumptions for final fitted model. Odds ratios and significant tests were calculated. All statistical tests were 2-tailed and differences were considered significant at $P<0.05$.

Table 1. Status of the 34 HBsAg Positive Subjects

	N	Serum ALT	
		Median [IQR]	Normal* (%)
HBeAg positive	13	25.7 [22.1-31.6]	5 (38.5)
HBeAg negative	21	31.6 [26.9-48.8]	17 (80.9)
		P= 0.04**	P= 0.02

*Serum ALT normal is defined as ALT ≤ 31 for females and ≤ 37 for males; ** Wilcoxon rank test

Results

Among the 400 selected subjects, 10 refused to have blood drawn, and in other 7 people their blood sample was hemolyzed or insufficient for analysis. Three hundred and eighty three subjects are included in this analysis with the mean age of the study population being 40.4 ± 14.6 years. Sixty-one (61%) were female and 39% were male. Most of the subjects were farmers (88%). More than half of them (56%) were Kinh and the rest (44%) were from varying different minorities (36.3% San Diu, 5.7% Tay, 1.8% Nung). The mean number of years of schooling was 6.3 ± 3.1 years. More than three quarters of the males used alcohol and/or were smokers (75.7% and 80.4%, respectively).

Of the 383 people included in the study, 34 (8.8%) tested positive for HBsAg (current infection), of whom 21 (61.8%) were HBeAg negative and HBeAb positive, and 22 (64.7%) had normal ALT levels (ALT ≤ 31 for females and ≤ 37 for males). 171 subjects (44.6%) had past HBV infection (HBcAb positive ± HBsAb positive). 18 subjects (5.2%) were positive for HBsAb only, implying vaccination. 11 subjects (2.9%) were HCV positive, 9 of them in HBV positive group: 2 subjects were both HCV positive and HBsAg positive. The serologic markers and serum ALT are summarized in Table 1. The majority of HBeAg negative patients had inactive chronic hepatitis B.

Differences in the distribution of demographic characteristics were compared between those who were current HBV infection, past HBV infection and HBV negative groups in Table 2. There were no significant differences observed for occupation, marital status, crowdedness in the household or economic status. Older subjects were more likely to have past HBV infection compared to those aged <40 (58.1% vs. 36.7%, $p<0.001$).There was a higher prevalence of HBV infection in Kinh subjects than other ethnic minorities (52.0% vs. 40.6%, $p=0.03$). The HBV prevalence within other ethnic groups could not be determined due to insufficient subjects. Those with less than 6 years schooling were more likely to be HBsAg positive compared to those with higher education (14.0% vs. 6.6%, $p=0.02$).

The frequency of risk factors associated with HBV infection was assessed. Subjects who had been in a dentist office were more likely to be past HBV positive (56.8% vs. 42.3%, $p=0.009$) compared to those who did not. Those with the history of blood transfusion also had higher

Table 2. Demographic Characteristics of Subjects by Presence of HBV Markers

Characteristics		HBV infection Current	Past	HBV Negative
Total		34 (8.9)	171 (44.6)	160 (41.8)
Gender	Male (137)	16 (11.7)	69 (50.4)	52 (38.0)
	Female (228)	18 (7.9	102 (44.7)	108 (47.4)
Age	<40 (191)	20 (10.5)	70 (36.7)	101 (52.9)**
	≥ 40 (174)	14 (8.1)	101 (58.1)	59 (33.9)
Ethnicity	Kinh (200)	17 (8.5)	104 (52.0)*	79 (39.5)*
	Minority (165)	17 (10.3)	67 (40.6)	81 (49.1)
Occupation	Farmer (320)	30 (9.4)	150 (46.9)	140 (43.8)
	Other (45)	4 (8.9)	21 (46.7)	20 (44.4)
Crowdedness				
≤ 10m^2 /person (122)		12 (9.8)	51 (41.8)	59 (48.4)
> 10m^2 /person (243)		22 (9.1)	120 (49.4)	101 (41.6)
Poverty	Yes (43)	5 (11.6)	18 (41.9)	20 (46.5)
	No (322)	29 (9.0)	153 (47.5)	140 (43.4)
Marital status				
Ever married (313)		27 (8.6)	150 (47.9)	136 (43.5)
Single (52)		7 (13.5)	21 (40.4)	24 (46.2)
Education				
≤Primary school (136)		19 (14.0)*	69 (50.7)	48 (35.3)*
>Primary school (229)		15 (6.6)	102 (44.5)	112 (48.9)

*,**p<0.05, <01

frequency of past HBV infections (68.4 vs. 45.7%, p=0.05). Those with history of tattoos, surgery or injections had a higher frequency of HBV infection compared to those who did not, but the difference did not reach statistical significance. Because the number of HbsAg positive subjects was small (n=34), we compared those with any evidence of HBV (combined current and past infection) with those with no evidence in the univariate analyses. The overall prevalence of HBV infection was 51.8% and increased with age (Figure 1). This trend was significant in female (p<0.001), but not in male (p=0.13). Evidence of HBV infection was higher in men than women (OR 1.6 : 95% CI: 1.03-2.39); in those ≥40 years (OR 2.5: 95% CI: 1.64-3.77); in Kinh ethnic group (OR 1.6: 95% CI: 1.06-2.41); and in those whow received less education (OR 1.7: 95% CI: 1.11-2.61. Subjects with a history of surgery were nearly two times more likely to have evidence of HBV infection (OR 1.97; 95% CI 1.1-3.7). Surgery was reported in 17% of Kinh, and 12.6% of ethnic minorities, but the difference is not significant (p=0.23). In multivariate analysis the following five predictors were associated with evidence of HBV infection in this community: male gender (OR 1.6; 95% CI 1.02-2.5); age greater than 40 years (OR 2.1; 95% CI 1.4-3.3), Kinh ethnicity (OR 1.8; 95% CI 1.1-2.7); a lower level of education (OR 1.7; 95% CI 1.0-2.7); and a prior history of surgery (OR 1.9; 95% CI 1.0-3.5).

Discussion

To our knowledge, this is the second community-based epidemiological study that evaluated the risk factors for HBV infection in Northern rural areas of Vietnam and is the first one conducted in a mountainous area. Although this includes 5 hamlets from only one area, our results

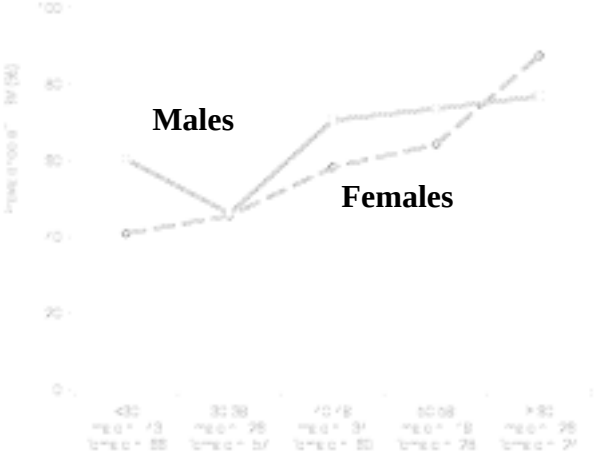

Figure 1. Prevalence (%) of HBV Infection by Age Group and Gender

differ from other published reports from other areas of Vietnam and will serve as background for future studies of HBV infection in the region and country. Compared to other studies in Asia, the prevalence of HBsAg positivity in Vietnam from this study (8.8%) is similar to the adjacent countries such as Laos (8%) (Caruana et al., 2005; Jutavijittum et al., 2007), Cambodia (9%) (Pichith et al., 1997), Thailand (6-10%) (Pichainarong et al., 2003) and China (5-18%) (Chen et al., 2000) but higher than other countries including Indonesia (4.6%), Korea (5-7%) and Japan (2-4%) (Merican et al., 2000). Asian countries remains the home for majority HBV infections in the world, accounting for 75% of chromic HBV infections worldwide (Liaw & Chu, 2009).

The sero-epidemiology of HBV infection in this rural community provides useful information for planning prevention strategies. The prevalence of HBsAg positivity in this study (8.8%) is similar to the average prevalence reported from three studies in the South of Vietnam (Kakumu et al.. 1998; Tran et al., 1993; 2003) but lower than the current rate of HBV infection in the Center of Vietnam (18.8%) (Hipgrave et al., 2003) and in the delta region of North Vietnam (19%) (Nguyen et al., 2007). This current rate of HBV infection remains high. Vaccination strategies are critical to halt spread of infection but identifying current infection is important to refer these patients for treatment and few subjects showed evidence of vaccination in our study. Although the HBV vaccine was first introduced in Viet Nam's Expanded Program on Immunization (EPI) in 1997, it was implemented in 70% of provinces only in 2004 (Mohamed et al., 2004). Findings from a recent study highlights several major factors affecting which limit optimal doses and timing of HBV vaccine, including community-based pregnancy tracking practices, relations of the immunization program with private maternity services and large urban hospitals, perceived contraindications, and family perceptions (Murakami et al. 2008).

Early age vaccination could prevent male to female intra-familial or sexual transmission which may therefore be an important factor contributing to the high prevalence of HBV in this community. Findings from a previous study in a Vietnamese refugee family showed that the risk of

HBV infection increased 11-fold for children who had an HBsAg-positive mother or siblings compared with other children (Skinhoj et al., 1983). Vaccination of families at risk should be undertaken to prevent new HBsAg carriers. As well described, more than half of our HBsAg positive-case were inactive (61.8% had HBeAg-negative, and 64.7% had normal ALT level). Analyses of HBV DNA or pre core and core promoter mutations could not be performed due to lack of resources. A more comprehensive study should be performed in this population to further delineate the natural history of chronic HBV infection in this region. The overall prevalence of current or prior HBV infection was very high (51.8%). This high prevalence remains a significant challenge for public health in Vietnam because chronic HBV is associated with high morbidity and mortality from cirrhosis and hepatocellular cancer (Liaw & Chu. 2009). A recent study in Vietnam estimated that HBV-related liver diseases such as liver cirrhosis and hepatocellular carcinoma will increase linearly from 21,900 and 9,400 in 1990 to 58,650 and 25,000 in 2025 (Nguyen et al., 2008). The age standardized incidence rate of liver cancer (per 100,000) among HBsAg (+) individuals in Hanoi City, Viet Nam from 1991-93 was 166 in males and 58 in females (Ngoan & Yoshimura., 2001).

Results from our study showed differences in HBV infection according to ethnicity. The general Vietnamese population (Kinh) has significantly higher HBV carriage rates than other minority ethnics and the reasons for this are unclear. Whether transmission occurs vertically at birth or horizontally was not determined in this study so that the possible contribution of non-vertical transmission risk factors is unknown. However, the majority of transmission in South East Asia is reportedly vertical (Merican et al., 2000), in contrast to both horizontal and vertical transmission operating in sub Saharan Africa (Botha et al., 1984). Surgery, however, was an important predictor of infection so that nosocomial transmission, especially in the older patients appears to be an important risk. Hospital hygiene has been rather poor due to the general hardship conditions of Vietnam, especially in the past. Improving hygiene in hospitals, particularly strict sterilization of sharp instruments should be performed to control cross-infections for patients.

Of particular interest, the majority of subjects who were HCV positive werea also in the HBV positive group. This may be due to similar modes of transmission of HCV and HBV. These subjects need special attention because the dual infections tend to cause severe and progressive liver disease, often resistant to therapy (Liaw, 2002). Social factors, such as lower level of education, were found to be positively correlated with risk of HBV infection. The higher prevalence of HBV infections in this group imply that health education is likely to play an important role in preventing horizontal HBV transmission in this community. Several other risk factors for HBV infections were investigated, but only surgery history were found to have significantly positive association with HBV.

In conclusion, the present study revealed a high prevalence of prior and current HBV infection in a rural area of Vietnam. The five risk factors found for acquisition of HBV infection were male gender, age greater than 40, Kinh ethnicity, a lower level of education and a prior history of surgery. These findings suggest the need for a comprehensive program for vaccination, early detection and closely monitoring of those with active HBV infection, this acting as a major cause of chronic liver disease in Vietnam.

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