Hepatitis B virus exposure, vaccination status and susceptibility in Healthcare Workers from Lao People's Democratic Republic: Cross-Sectional Study

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Abstract

Background: Despite high prevalence of chronic hepatitis B virus (HBV) infection in adults in Lao People's Democratic Republic (PDR), Lao healthcare workers (HCWs) were previously been shown to have low levels of protection against infection. Furthermore, the prevalence of hepatitis D virus (HDV; which increases disease severity in HBV infected individuals) is not known in Lao PDR.

Objective: To investigate the exposure, vaccination status and seroprotection against HBV as well as exposure to HDV in Lao healthcare workers from five provinces

Methods: In 2020, 666 HCWs aged 20-65 years old from five provinces of the Lao PDR were recruited and sera were tested by Enzyme-linked immunosorbent assay (ELISA) to determine their HBV and HDV co-infection status.

Results: HBV exposure, as indicated by the presence of anti-HB core (anti-HBc) antibodies, was 40% overall and significantly higher for HCWs from Oudomxay province (67.7%, P=.001). The seroprevalence of HBsAg was 5.4% overall and increased with age from 3.6% in those aged ? 30 years to 6.8% in those aged ? 50 years. Only 28.7% of participants had serological indication of immunization. We could find no evidence for HDV exposure in the current study.

Conclusions: We recommend strengthening the national vaccination program for HCWs and implementing pre-employment testing.

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Conclusion: We recommend strengthening the national vaccination program for HCWs and implementing pre-employment testing.
Keywords: Hepatitis B; Hepatitis D; Healthcare workers; Laos

Introduction
Hepatitis B virus (HBV) is a major global public health concern that can cause chronic infection, cirrhosis, liver cancer and death. HBV is transmitted by exposure to infected blood or other body fluids such as semen and vaginal fluid during sexual intercourse, tattooing, unsafe medical practices and mother-to-child routes during pregnancy or shortly after birth [1, 2]. Most people infected with HBV are asymptomatic and may be unaware of being infected and of the risk to transmit the virus to others. Hepatitis D virus (HDV) requires HBV presence for its replication in hepatocytes. HBV-HDV co-infection greatly increases the risk of liver cirrhosis and hepatocellular carcinoma development [3, 4].
The World Health Organization (WHO) estimated that in 2019 about 296 million people were living with chronic HBV infection with 820,000 deaths [5]. The highest prevalence of infection occurs in

the WHO Western Pacific Region, with more than one-third of the HBV infections worldwide [5, 6]. Within this region, Lao People's Democratic Republic (PDR) is considered to have intermediate to high endemicity of HBV infection, with hepatitis B surface antigen (HBsAg) prevalence ranges from 5-10% and the rate of exposure (anti-HB core (anti-HBc) antibody positive) reaching up to 50% in blood donors and the general population [7-13].
HDV co-infects approximately 5-10% of HBV infected individuals worldwide, although prevalence varies by geographic region [3, 4]. Currently, epidemiological data for HDV are unavailable in Lao PDR.

The HBV vaccine was first introduced in Lao PDR in 2001 at 6, 10 and 14 weeks of age (currently in the form of the pentavalent vaccine; diphtheria-tetanus-pertussis-hepatitis B-Haemophilus influenzae). The birth dose within 24 hours was introduced to all new-borns in Lao PDR in 2004 [12]. However, most adults, including healthcare workers (HCWs) were born before vaccine introduction.

HCWs are exposed to blood and body fluids due to their occupational activities and are therefore a risk group for HBV infection, with an infection rate up to 10 times higher than in the general population [14]. Needle-stick injuries are the most frequently reported unsafe medical practice events [15]. Other transmission routes are possible, such as from contaminated surfaces, as HBV also persists in dry blood for up to one week [14, 16-18]. The HBV transmission risk from HCWs to patients varies depending on the setting. Most published cases are reported in developed countries, while evidence is often lacking for developing countries [18, 19]. HBV screening and vaccination before starting clinical practices are recommended to reduce the associated risk of disease transmission from and to patients [20].

A previous study in 2013 found that Lao HCWs had low levels of seroprotection to HBV and low evidence of vaccination [8]. A similar serological profile was found for Lao dentists, who also had low knowledge and inadequate safety practices [10]. In 2019, the Lao Ministry of Health developed a strategic plan on combatting the transmission of viral hepatitis by agreeing to provide health education and hepatitis B vaccination to susceptible groups including HCWs [21]. Despite this agreement and international recommendations [2], HBV vaccination in HCWs in Lao PDR is not routine yet. In the current study, we aimed to investigate the exposure, vaccination status and seroprotection against HBV as well as exposure to HDV in Lao healthcare workers from five provinces, to provide guidance to key stakeholders such as the Lao Ministry of Health (MOH) for HBV control decision-making.

Methods

Study population

For this study, we utilized HCWs serum samples collected in 2020 in the context of an investigation of COVID-19 serology. The sample collection was detailed previously [22]. In brief, HCWs were recruited from central, provincial and district hospitals in Vientiane capital, Oudomxay, Luangprabang, Savannakhet and Champasak provinces. Participants were randomly selected in each department and included clinicians, nurses and laboratory technicians. We also included other non-clinician workers (administrative HCWs) in order to see if there was a trend in HBV exposure according to patient contact. After individual informed consent was obtained, a structured questionnaire was used to collect information on demographics and 5mL of whole blood was collected. Serum was separated by centrifugation and stored at 4°C for a maximum of seven days and at -80°C for long-term.

Ethics approval and consent to participate

Ethics approval was obtained from the Lao National Ethics Committee for Health Research (NECHR) (Ref #052/2020). Informed consent was obtained from all subjects involved in the study.

Serology testing

Anti-HBc and anti-HBs were measured by commercial ELISA according to the manufacturers' instructions (Diasorin, Italy and Biorad, United States). All anti-HBc positive/anti-HBs negative samples were tested for HBsAg (Biorad) [7]. HBsAg positive samples were defined as "acute or chronic infection", anti-HBc positives as "previously exposed" and anti-HBc negative, but anti-HBs positive participants as "vaccinated". All HBsAg-positives were tested for anti-HDV antibodies by ELISA (DIA.PRO, Italy).

Data analysis

Descriptive data, bivariate analysis and multivariable analysis were done with STATA version 14. Categorical variables and continuous variables were calculated for descriptive data. In order to determine the association between independent variables (HBV serostatus) and dependent variables (sociodemographics, work status), bivariate analysis was employed. Multivariable analysis was performed on all variables with a p value of ≤ 0.2 in a bivariate model. Crude odds ratios (crude ORs) and adjusted odds ratios (aOR) are reported.

Results

Population characteristics

The total number of participants was 666. The median age was 34 years (range 20 to 65), 77.8% were female and 96.5% were of Lao-Tai ethnicity. Most participants were living in Vientiane capital (61.6%) and 53.6% had ≤10 years work experience. The majority of the participants had direct contact with patients (93.1%) (Table 1).

Table 1. Socio-demographic characteristics of participants.

Characteristic	N	%
Total	666	100
Sex		
male	148	22.2
female	518	77.8
Age group (years)		
≤ 30	248	37.2
31-49	300	45.1
≥ 50	118	17.7
Ethnicity		
Lao-Tai	643	96.5
Mone-Khmae	11	1.7
Hmong-Mien	12	1.8
Province		
Vientiane	410	61.6
Oudomxay	31	4.6
Luangprabang	47	7.1
Savannakhet	72	10.8
Champasak	106	15.9
Years of work		
≤10y	357	53.6
11-30y	235	35.3
≥31y	74	11.1
Contact status with patients		
Indirect contact	46	6.9
Direct contact	620	93.1

Hepatitis B and D serology

Overall, 267/666 (40.1%) HCWs were seropositive for anti-HBc antibodies (exposure), with no significant difference between males and females. HBV exposure in those aged ≤ 30 years was 81/248 (32.7%) and was significantly higher in those aged ≥ 50 years old (66/118, 55.9%; aOR 2.78 [1.76-4.38], *P*<.001). HCWs from Oudomxay had higher anti-HBc seroprevalence than those from Vientiane (67.7% and 39.0%; aOR 3.75 [1.71-8.23] *P*=.001) (Table 2, Figure 1-2).

Overall, 36 (5.4% when extrapolated to the total study population) were HBsAg positive (currently infected). The HBsAg prevalence was higher among men than women although not significantly different (8.1% and 4.6%, respectively; aOR 0.48 [0.23-1.01], *P*=.06). HBsAg seroprevalence increased with age from 3.6% in those aged ≤30 years to 6.8% in those aged ≥50, although this also did not reach statistical significance (Table 2, Figure 1).

The overall prevalence of the serological profile for vaccination - anti-HBs positive and anti-HBc negative - was 191/666 (28.7%). After multivariable analysis, vaccination serology in those aged ≤30 years (58/248, 23.4%) was lower than in age group 31-49 years (34.7%, aOR 1.70 [1.16-2.49], *P*=.006) (Table 3, Figure 1).

All 36 HBsAg positive samples were tested negative for anti-HDV antibodies.

	Anti-HBc positives					HBsAg positives				
	n/N (%)	**Crude OR [95%]**	***P-value***	**Adjusted OR [95% CI]**	***P-value***	**n/N (%)**	**Crude OR [95%]**	***P-value***	**Adjusted OR [95% CI]**	***P-value***
Total	267/666 (40.1%)					36/666 (5.4)				
Sex										
male	65/148 (43.9)	1.0				12/148 (8.1)	1.0			
female	202/518 (39)	0.81 [0.56-1.18]	0.2	a	a	24/518 (4.6)	0.55 [0.26-1.12]	0.1	a	a
Age group (years)										
≤ 30	81/248 (32.7)	1.0				9/248 (3.6)	1.0			
31-49	120/300 (40)	1.37 [0.96-1.95]	0.07	a	a	19/300 (6.3)	1.79 [0.79-4.04]	0.1	a	a
≥ 50	66/118 (55.9)	2.61 [1.66-4.10]	<0.001	2.78 [1.76-4.38]	<0.001	8/118 (6.8)	1.93 [0.72-5.13]	0.1	a	a
Ethnic										
Lao-Tai	254/643 (39.5)	1.0				36/643 (5.6)	1.0			
Mone-Khmae	8/11 (72.7)	4.08 [1.07-15.53]	0.03	a	a	0/11 (0)	a	a	b	b
Hmong-Mien	5/12 (41.7)	1.09 [0.34-3.48]	a	a	a	0/12 (0)	a	a	b	b
Province										
Vientiane	160/410 (39)	1				26/410 (6.3)	1.0			
Oudomxay	21/31 (67.7)	3.28 [1.50-7.14]	0.003	3.75 [1.71-8.23]	0.001	0/31 (0)	a	a	a	a
Luangprabang	19/47 (40.4)	1.06 [0.57-1.96]	a	a	a	1/47 (2.1)	0.32 [0.04-2.42]	0.2	a	a
Savannakhet	21/72 (29.2)	0.64 [0.37-1.11]	0.1	a	a	3/72 (4.2)	0.64 [0.18-2.17]	a	a	a
Champasak	46/106 (43.4)	1.19 [0.77-1.84]	a	a	a	6/106 (5.7)	0.88 [0.35-2.21]	a	a	a
Year of service										
≤10	123/357 (34.5)	1				17/357 (4.8)	1.0			
11-30	104/235 (44.3)	1.51 [1.07-2.11]	0.01	NS	NS	14/235 (5.9)	1.26 [0.61-2.62]	a	b	b
≥31	40/75 (54.1)	2.23 [1.34-3.71]	0.002	NS	NS	5/74 (6.8)	1.44 [0.51-4.06]	a	b	b
Contact status with patients										
Indirect contact	23/46 (50.0)	1				4/46 (8.7)	1.0			
Direct contact	244/620 (39.3)	0.64 [0.35-1.18]	0.1	NS	NS	32/620 (5.2)	0.57 [0.19-1.69]	a	b	b

Table 2. Factors associated with anti-HBc and HBsAg positivity

Categories were included in multivariable analysis when p≤0.2 for one of the variables.

[a]Non-significant, [b]Not appropriate/not included in multivariable analysis

Table 3. Factors associated with serological profile suggestive of previous vaccination (anti-HBs positive/anti-HBc negative).

	Anti-HBs+/Anti-HBc-				
	n/N (%)	**Crude OR [95%]**	***p-value***	**Adjusted OR [95% CI]**	***p-value***

Total	191/666 (28.7)				
Sex					
male	37/148 (25)	1.0			
female	158/518 (29.7)	1.26 [0.83-1.92]	0.2	a	a
Age group (years)					
≤ 30	58/248 (23.4)	1.0			
31-49	104/300 (34.7)	1.73 [1.19-2.53]	0.004	1.70 [1.16-2.49]	0.006
≥ 50	29/118 (24.6)	1.06 [0.63-1.78]	a	a	a
Ethnic					
Lao-Tai	186/643 (28.9)	1			
Mone-Khmae	1/11 (9.1)	0.24 [0.03-1.93]	0.1	a	a
Hmong-Mien	4/12 (33.3)	1.22 [0.36-4.12]	a	a	a
Province					
Vientiane	125/410 (30.5)	1.0			
Oudomxay	5/31 (16.1)	0.43 [0.16-1.16]	0.09	a	a
Luangprabang	19/47 (40.4)	1.54 [0.83-2.87]	0.1	a	a
Savannakhet	19/72 (26.4)	0.81 [0.46-1.43]	a	a	a
Champasak	23/23 (21.7)	0.63 [0.38-1.04]	0.07	a	a
Years of service					
≤10	97/357 (27.2)	1.0			
11-30	72/235 (30.6)	1.18 [0.82-1.70]	a	a	a
≥31	22/74 (29.7)	1.13 [0.65-1.96]	a	a	a
Contact status with patients					
Indirect contact	12/46 (26.1)	1.0			
Direct contact	179/620 (28.9)	1.25 [0.68-2.28]	a	a	a

Categories were included in multivariable analysis when p≤0.2 for one of the variables.
[a]Non-significant

Figure 1. Hepatitis B serology by age group. ***P*≤.01, ****P*≤.001

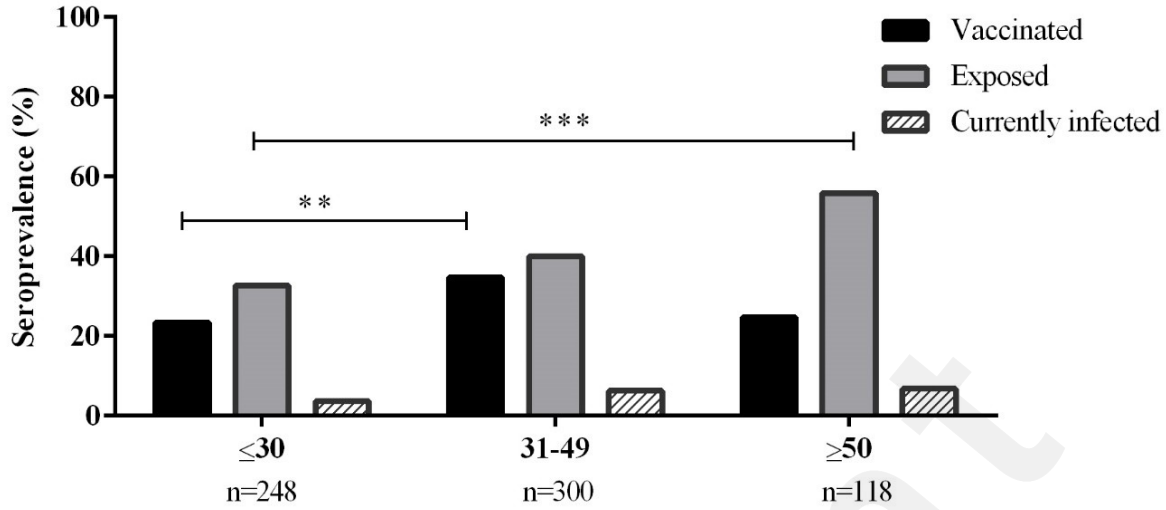
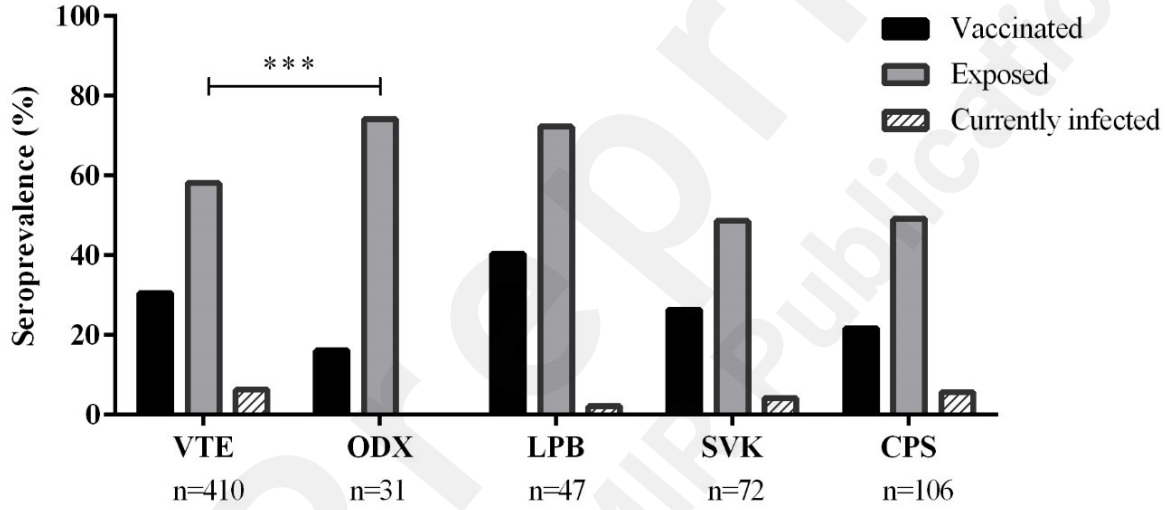


Figure 2. Hepatitis B serology by province. Abbreviations: VTE-Vientiane, ODX-Oudomxay, LPB-Luangprabang, SVK-Savannakhet, CPS-Champasak. ****P*≤.001



Discussion

This study reported a moderate prevalence of 5.4% HBsAg positivity among HCWs. This is similar to previous studies of Lao healthcare workers ranging from 3-12% [8, 10]. However, it is lower than the prevalence in the adult general population (8-10%) [7, 12], perhaps due to the fact that two thirds of the participants were females, who have lower exposure and HBsAg prevalence as compared to males [10, 13, 23, 24]. Indeed, in the current study, male HCWs had higher prevalence of HBsAg than female HCWs, although this did not reach significance (8.1% versus 4.6%, p = 0.1). This difference could be due to differential immune response, hormones or risks practices [25, 26]. Also, we found that HBsAg positivity increased with age. This is similar to what we reported previously in HCWs and the general population [8, 23]. Our data show that a substantial proportion of Lao HCWs are chronically infected with HBV and therefore appropriate precautions are needed to reduce the risk of onward transmission to patients. In addition, HBsAg positive HCWs should get access to counselling and treatment.

None of the HBsAg positive carriers had anti-HDV antibodies in the current study, suggesting that

HDV prevalence might be low in Lao PDR. However, since HDV prevalence varies with geographical regions and study cohorts (e.g. in neighbouring Vietnam, the prevalence ranged from 0 to 43% among HBsAg positive carriers [27-30], and in Thailand from 0 to 65% [31-33]), further studies are needed to determine whether there are any subpopulations with HDV exposure in Laos.

Anti-HBc seroprevalence, indicating exposure, was 40.1%. This high level is similar to other studies in Lao PDR [7, 9, 12]. As expected, HBV exposure increased with age, being 32.7% among those aged ≤30 years, and 40% and 55.9% in those 31-49 and ≥50 years of age. This was in accordance with previous published studies in the Lao general population [7, 11, 12, 24, 34] and HCWs [8, 10] and may reflect exposure in the workplace or elsewhere. There was no correlation of exposure with the length of time in the job or type of job as in a previous study of Lao HCWs [8]. However, the distinction between staff with and without contact with patients was not always clear as some administration staff may have previously worked in a clinical setting. HBV exposure was higher in those living in the northern provinces. In particular, HCWs from Oudomxay had significantly higher exposure than HCWs from other provinces. The data agreed with studies of HBV in Lao blood donors where significantly higher exposure was found in the northern provinces [13, 34]. The reason for this geographical variation is not clear. The rate of HBsAg positivity was not significantly higher in the northern provinces in the current study. This may be due to the lower proportion of participants from the northern provinces in the current study and the overall lower numbers of HBsAg positives, and/or because HBV infection is happening during adulthood, when chronic infection is less likely to occur. This study found a low percentage of HCWs who had the serological profile of vaccination (28.7%). This profile was more common in those 31-49 years of age (34.7%) suggesting that this age group has been vaccinated against HBV during their adult age or perhaps during an *ad hoc* HBV vaccination campaign in their hospitals. Although the rate of participants with serological profile of vaccination in the current study is higher than other studies conducted in HCWs in Laos (13.6% [10] and 21% [8]) and Indonesia (11.6%) [35], it remains inadequate and reveals a large number of HCWs without protective anti-HBs antibodies (31.2%) (Table S1). Importantly, many of the participants with anti-HBc antibodies and anti-HBs antibodies may also have been vaccinated, but there is no way to distinguish these from the HBV exposed individuals without vaccination based on the laboratory results.

Conclusions

According to the findings of this study, HBsAg prevalence is intermediate with no evidence of HDV coinfection in HCWs in Lao PDR. Importantly, a high proportion of HCWs remains susceptible to infection. Therefore, there is a need to strengthen the national vaccination program for HCWs and to implement mandatory pre-employment hepatitis B testing. This would reduce the risk of HBV infection for both HCWs and patients.

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Data Availability

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Conflict of interests

The authors declare no conflict of interests.

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Authors' contributions
Conceptualization, S.V., K.P. and A.P.B; methodology, S.V., K.P., V.K. and A.P.B.; formal analysis, S.V., K.P., V.K., and A.P.B.; investigation, S.V., K.P., and V.K.; writing-original draft preparation, S.V., J.M.H. and A.P.B.; writing-review and editing, S.V., J.M.H., and A.P.B.; supervision, M.M., S.K., S.S., S.V., J.M.H. and A.P.B.; funding acquisition, J.M.H., A.P.B., S.K. and S.S.; All authors have read and agreed to the published version of the manuscript.

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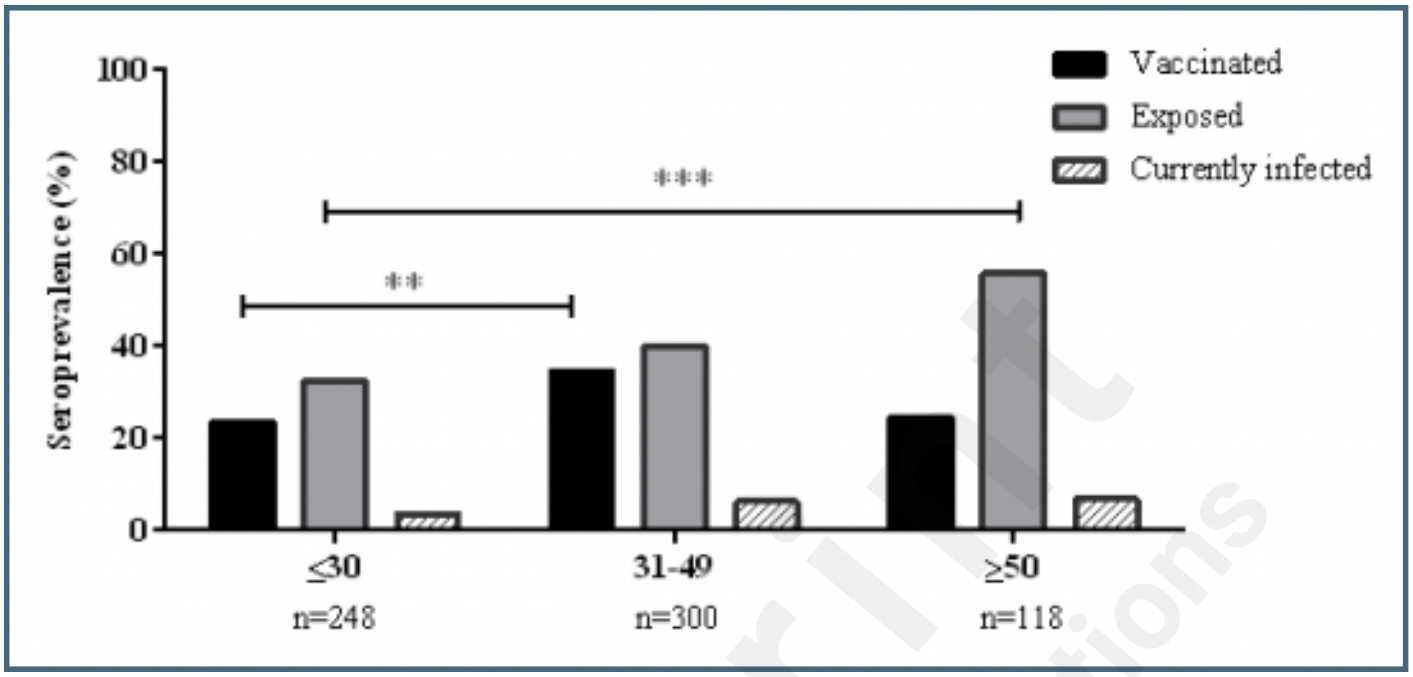
Abbreviations

Anti-HBc: Anti-HB core
Anti-HBs: Anti-HB surface
aORs: Adjusted odd ratios
cORs: Crude odd ratios
CPS: Champasak
ELISA: Enzyme-linked immunosorbent assay
HBsAg: Hepatitis B surface antigen
HBV: Hepatitis B virus
HCWs: Healthcare workers
HDV: hepatitis D virus
LPB: Luangprabang
Lao PDR: Lao People’s Democratic Republic
NA: Not appropriate/not included in multivariable analysis
NS: Non Significant
ODX: Oudomxay
SVK: Savannakhet
VTE: Vientiane
WHO: World Health Organization

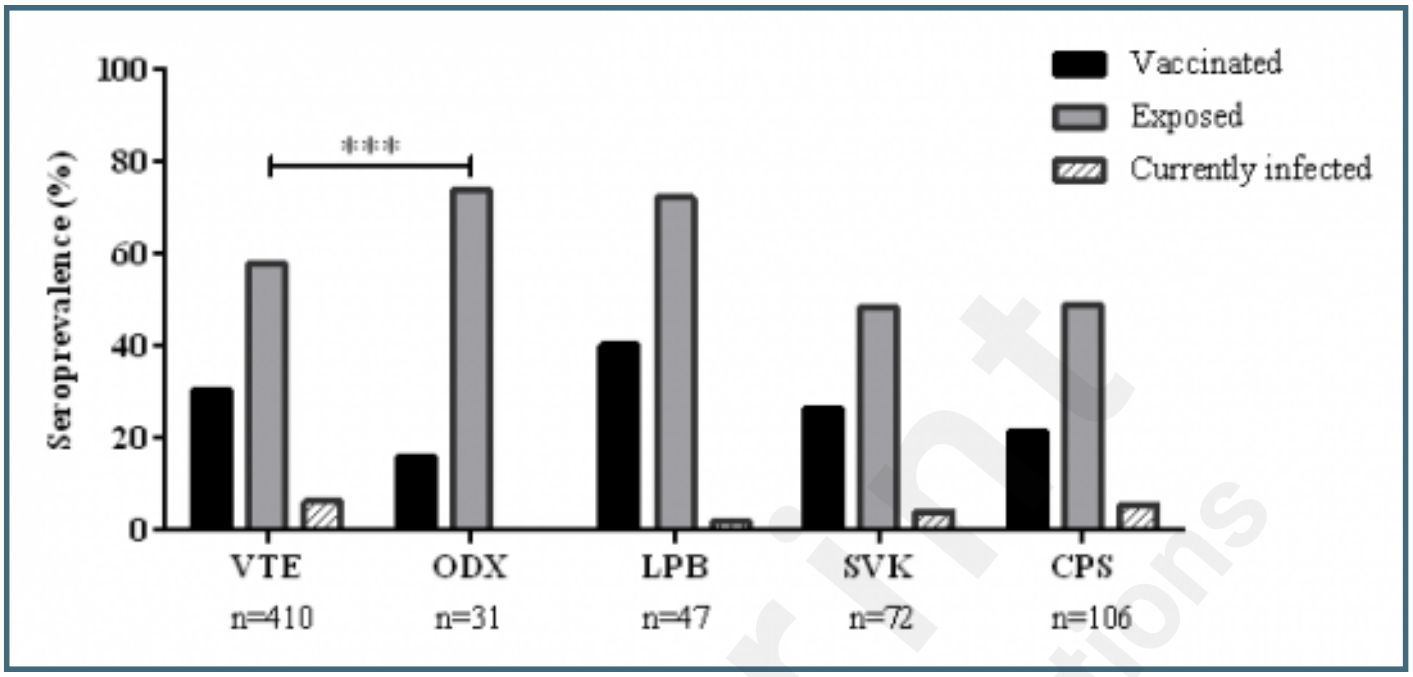
Supplementary Files

Figures

Hepatitis B serology by age group.



Hepatitis B serology by province.



Multimedia Appendixes

Serological profile of hepatitis B.
URL: http://asset.jmir.pub/assets/742e51fe4d54bae10335928f122bc159.docx