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Research Article

Proportion of People Who Are Positive for HBsAg and Anti-HCV Antibody Among Participants in a Community Screening Campaign in Malaysia

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Abstract

Background: The epidemiology of Hepatitis B (HBV) and C (HCV) remains poorly documented in Malaysia. Available statistics are based on data from mostly small studies in special populations.

Objectives: In this study, we provide estimates of the proportion of people who are positive for HBs Antigen (HBsAg) and anti-HCV antibody (Ab) among participants in a community screening campaign.

Methods: A total of 10,914 subjects participated in the hepatitis screening campaign organized by Hepatitis Free Pahang in 2018 and 2019. A low-cost point-of-care test, which has previously been validated, was used to screen for HBsAg and anti-HCV Ab. All screened positive subjects were recalled to undergo confirmatory serologic tests (enzyme-linked immunosorbent assay) and nucleic acid tests (Real-time Polymerase Chain Reaction.

Results: We estimated that 1.17% of adults aged 20 or older who participated in the screening campaign were positive for HBsAg⁺, and only 0.71 percent were positive for anti-HCVAb⁺. Young adults below 30 years of age had a very low proportion of HBsAg⁺ (0.09%). Women had a lower proportion of HBsAg⁺ and HCV-Ab⁺, Chinese had the highest proportion of HBsAg⁺, while Malay had the highest proportion of anti-HCVAb⁺.

Conclusions: Among adult participants of screening in Malaysia, chronic HBV is still common, especially among older and Chinese people. Adults with positive anti-HCV Abs are much less common.

Keywords: Hepatitis B, Hepatitis C, Screening, Point-of-Care Tests, Malaysia

1. Background

The epidemiology of Hepatitis B (HBV) and C (HCV) remains poorly documented in Malaysia. Available data on the number of people who have chronic HBV and positive anti-HCV Abs (1-13) summarized in Tables 1 and 2 below, are based on mostly small studies in unrepresentative populations such as from a single institution (e.g., university, hospital), a single convenient group (e.g., blood donors, students, mothers) or at risk group (e.g., health workers, prisoners, people who inject drugs (PWID) or patients with chronic liver disease or on hemodialysis).

2. Objectives

In this study, we provide estimates of the proportion of people who are positive for HBs Antigen (HBsAg) and

anti-HCV Ab among participants in a community screening campaign.

3. Methods

The study sample population for this study is the people who attended the screening campaign organized by the Hepatitis Free Pahang (HFP). The Ministry of Health's (MOH) Medical and Research Ethics Committee approved the study and all subjects gave oral informed consent. Between 2018 and 2019, HFP organized a total of 109 health fairs to conduct screening, mostly in small towns and villages and largely in the state of Pahang. All attendees at these health fairs registered online to participate in the screening tests. The online data system helped to support the conduct of the screening and administer questionnaire, manage screen-positive subjects for subsequent testing and counseling, facilitate reporting of results through

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Authors (Reference) Year		Population	% HBsAg ⁺	
Ton et al. (1)	1979	Male blood donors	5.5% in all ethnic groups	
Ton et al. (2)	1980	Prisoners	No data in abstract	
Tan et al. (3)	1989	2986 Healthcare employees	2.1% (Chinese 6.3%, Malays 1.8%, Indian 0.9%)	
Gan et al. (4)	1991	STD patients	9.2% for multiple partners 6.8% for without multiple partners	
Ng et al. (5)	2005-2011	2923 newly enrolled university students	0.62% (1.08% those born before 1989 and 0.20% born after 1989)	
Ng et al. (6)	1997-2003	190,077 school children aged 7-12 years	2.5% for children born in 1985 to 0.4% among school children born in 1996.	
Cheang et al. (7)	2002-2010	440 mothers	3.2%	
Yousuf et al. (8)	2007	Blood donors	1.83%	

Table 2. Summary of Data on Percent (%) of People Who Are Anti-HCV Ab Positive in Malaysia Authors % Positive Anti-HCV Ab Year Population Duraisamy et al. (9) Blood donors Blood donors 1.5% 1991-1992 Blood donors; PWID; Patients with liver disease or on Blood donors 1.9%; PWID 30%; Chronic liver disease 8%; Ng et al. (10) 1991 - 1992 Hemodialysis 9.1% hemodialvsis Sinniah and Ooi (11) Blood donors; PWID; Chronic liver disease patients Blood donors 3%; PWID 85%; Chronic liver disease 1.5% 1992 Lee and Ng(12)Children aged 1 to 16 admitted in a hospital 0.6% 1999 - 2000 Haslina et al. (13) Blood donors 0.14% (9/6495) 2008-2009

short messaging service, and capture the data for this study.

To screen HBsAg and anti-HCV Ab, we used a low-cost point-of-care test (POCT, AllTest Biotech) that we have previously validated (14). The tests were conducted by a trained nurse. The procedure was explained, and verbal permission was obtained from the participant prior to the testing. Finger-stick capillary samples were taken from participants, and the tests were performed according to the manufacturer's instructions. In the event of an invalid result, the test was repeated until a valid result was obtained.

All screened positive subjects were subsequently recalled, and 97% returned to undergo confirmatory testing, which were lab-based serologic tests (enzyme-linked immunosorbent assay) and nucleic acid tests for HCV RNA and HBV DNA (Real-time Polymerase Chain Reaction). A trained nurse counseled patients who had a confirmed chronic HBV, or positive anti-HCV Ab on infection transmission, had a risk of liver disease progression, and need for monitoring and treatment. Patients with confirmed chronic HBV, or positive anti-HCV Ab, were also referred to the local health service for further care. Also, HFP funded the direct-acting antiviral drugs for some indigent patients with positive anti-HCV Abs.

3.1. Statistical Methods

The sample size was based on an expected proportion of 2.0% HBsAg⁺ and precision of the estimate as measured

by its 95% exact binomial confidence intervals (CI). For a sample size of 10,000, a proportion of 2.0% can be estimated with a 95% CI of 1.7 to 2.3, which is deemed sufficiently precise. Participants in the screening campaign constituted a convenient sample that was not representative of the general population (female, older subjects, and Chinese were over-represented compared to the population). To estimate the proportion of people who were positive for HBsAg and anti-HCV Ab among participants in the screening campaign, post-stratification (15) was used to adjust the total samples to known population totals for age, gender, and ethnicity based on the Population and Housing Census of Malaysia in 2010. We have undertaken a separate validation study of the POCT used in the screening. Using lab-based serological tests as the diagnostic standard, we determined the POCT for anti-HCV Ab had 98.1% sensitivity and 100% specificity, while that for HBsAg had 95.2% sensitivity and 100% specificity (14). We use these results to estimate the proportion of people who are positive for HBsAg and anti-HCV Ab among participants in the screening campaign, which are corrected for misclassification due to the use of the POCT screening tests (16).

4. Results

A total of 10,912 subjects participated in the hepatitis screening campaign and had screening tests in 2018 and 2019. We could not determine the number of subjects who attended the campaign but did not participate in the screening; hence, we could not estimate the response rate. Table 3 shows the characteristics of all the participants as well as the characteristics of the subjects who were screened positive for HBsAg or anti-HCV Ab. The mean age of the participants was 49 years, there were more female and older subjects, and Chinese were over-represented in the sample. The vast majority of subjects were screened at health fairs organized by local Non-Governmental Organizations (NGO) partners in the state of Pahang.

We estimated that 1.17% of adults aged 20 or older who participated in the screening campaign were positive for HBsAg⁺, and only 0.71 percent were positive for anti- HCV-Ab⁺ (Table 4). Young adults below 30 years of age had a very low proportion of HBsAg⁺ (0.09%). Proportion of subjects who were HBsAg⁺ or anti-HCV Ab⁺ increased with age, and then declined in the oldest age group (age \geq 55 years). Men had a much higher proportion of HBsAg⁺ and anti-HCV Ab⁺ than women. Chinese had the highest proportion of HBsAg⁺, while Malay had the highest proportion of anti-HCV Ab⁺.

5. Discussion

We found that 1.17% of Malaysian adults who participated in the screening campaign were HBsAg⁺, and only 0.71% were anti-HCV Ab⁺. Chronic HBV has long been endemic in the Asia-Pacific region, including in Malaysia, as found in this study, though the prevalence has declined in many countries since the advent of universal vaccination in the 1990s (17). Our estimate of 1.17% HBsAg⁺ in adults is consistent with recent estimates in adults from large population-based studies (as opposed to institution-based studies or studies on special populations such as blood donors, students, PWIDs) in other Asia-Pacific countries such as China (18), Korea (19), Thailand (20) and India (21). The exception is Mongolia (22), which reported a high prevalence of 10.6% in adults in a recent national serosurvey.

Positive anti-HCV Ab is highly endemic in Central Asia and Mediterranean but not in the Asia-Pacific region (17). However, few recent population-based studies on HBV have been conducted in Asia. Our low estimate of anti-HCV Ab⁺ proportion (0.71%) is consistent with the 0.4% reported in China (23), 0.94% in Thailand (24) and 0.87% in India (25). Similar to HBV, Mongolia has an exceptionally high prevalence (11.1%) of anti-HCV Ab⁺ subjects in the Asia-pacific region (26). Our study is one of the largest seroprevalence surveys ever conducted in Malaysia. The large sample size is necessary to provide more precise age-sex and ethnicspecific estimates. We found the males had higher proporTable 3. Characteristics of Subjects Who Participated in the Hepatitis B and C Screening Campaign in 2018 - 2019 $^{\rm a}$

Characteristics	All Subjects	HBsAg ⁺	Anti-HCV Ab ⁺	
Total number	10,912	200	52	
Number known positive, %	-	145	15	
Age (y)				
Mean \pm SD	49 ± 15	52 ± 12	49 ± 11	
Median (IQR)	50 (37,60)	51(42,61)	50 (40,58)	
20-30	1416 (13)	3(2)	3(6)	
30 - 39	1877 (17)	36 (18)	10 (19)	
40 - 49	2182 (20)	57(28)	13 (25)	
50 - 59	2610 (24)	46(23)	15 (28)	
> 60	2827(25)	58 (29)	11 (21)	
Gender			()	
Male	4400 (40)	103 (51)	28 (54)	
Female	6512 (60)	97(49)	24 (45)	
Ethnicity			. ,	
Malay	1782 (16)	11(5)	20 (38)	
Chinese	8519 (78)	183 (92)	30 (57)	
Indian	556(5)	4(2)	1(2)	
Others	55 (1)	2 (1)	1(2)	
Screening method				
Opportunistic at Clinic/Pharmacy	1111 (10)	36 (18)	11 (21)	
Health fairs	9801 (90)	164 (82)	41 (79)	
Location of screening by state				
Pahang	8715 (80)	190 (94)	44 (85)	
N. Sembilan	1263 (12)	7(4)	4 (8)	
Perak	477(4)	2 (1)	1(2)	
Selangor-WP	383 (4)	1(1)	3(5)	
Melaka	74 (1)	-	-	

^a Values are expressed as No. (%) unless otherwise indicated.

tion of HBsAg⁺ and anti-HCV Ab⁺, which is expected. Similarly, Chinese had a higher proportion of HBsAg⁺, while Malay had higher anti-HCV Ab⁺.

The age trend in the proportion HBsAg⁺ showed an inverted U shape. The lower proportion of HBsAg⁺ in the oldest age group could be explained by pre-mature mortality from progression to cirrhosis and hepatocellular carcinoma (17). The low proportion of HBsAg⁺ in young adults below 30 years of age is likely due to the protective effect of universal HBV vaccination, which has been introduced in Malaysia since 1989. However, 0.9% of young adults aged 20-30 were positive for HBsAg suggesting persistent peri-

	HBsAg ⁺ , %	95% CI	Anti-HCV Ab ⁺ , %	95% CI
11	1.17	1.5 - 0.83	0.71	0.97 - 0.44
By age (y)				
20-30	0.09	0.28 - 0.03	0.13	0.5 - 0.03
30 - 40	1.81	3.18 - 1.02	0.58	1.24 - 0.27
40 - 54	1.59	2.35 - 1.06	1.56	2.6 - 0.93
\geq 55	1.37	2.23 - 0.83	0.58	1.44 - 0.23
3y gender				
Male	1.49	2.18 - 1.02	0.92	1.5 - 0.57
Female	0.82	1.24 - 0.54	0.48	0.86 - 0.27
By Ethnicity				
Malay	0.74	1.33 - 0.4	1.16	1.81 - 0.74
Chinese	2.25	2.64 - 1.92	0.37	0.55 - 0.24
Others	0.98	2.34 - 0.41	0.23	0.95 - 0.06
3y age-gender (y)				
Male				
20-30	0.18	0.55 - 0.06	0.05	0.37 - 0.01
30 - 40	2.12	4.62 - 0.96	0.78	2.06 - 0.3
40 - 54	2.07	3.47 - 1.2	2.41	4.38 - 1.3
\geq 55	1.85	3.41-1	0.41	1.77 - 0.09
Female				
20-30	0	0 - 0	0.2	1.07 - 0.04
30 - 40	1.46	3.17 - 0.66	0.35	1.1 - 0.11
40 - 54	1.07	1.73 - 0.66	0.67	1.63 - 0.28
≥ 55	0.89	1.99 - 0.4	0.74	2.36 - 0.23

natal transmission. Elimination of HBV infection as a public health threat requires a reduction in the prevalence of HBsAg⁺ subjects to less than 0.1% in children five years of age (27). This cannot be achieved through universal HBV immunization of newborns alone. Interventions are necessary to prevent mother-to-child transmission of HBV, including antiviral prophylaxis (27, 28). Antenatal screening for HBsAg, which has been discontinued in Malaysia, should be reinstated, and WHO recommendation on the use of antiviral prophylaxis in pregnancy should be implemented (27).

Our study had several limitations. First, the study subjects were not a probability sample and is not representative of the population. Hence, there were more female and older subjects than in the general population, Chinese and Pahang residents were over-represented as a result of the conduct of the campaign through local NGOs, most of which were local faith or ethnic-based organizations in Pahang. Post-stratification was required to adjust the sampling weight to reflect the age, sex and ethnicity distribution of Malaysia. Second, subjects known to have hepatitis may be more or less willing to participate in screening. This source of bias applies to probability samples as well. Such subjects may be more or less willing to consent to be tested in a probability sampling survey. However, the risk of this bias was reduced in our study by pooling the data from numerous (109) screening events or venues conducted in numerous rural and urban locations spread over a wide geographical region. Third, for operational and cost reasons, we have used a POCT for screening instead of labbased serology tests. The POCT has been validated, and the proportion estimates reported here are corrected for the misclassification bias due to the use of POCT.

Footnotes

Authors' Contribution: TOL and ZZL contributed to the subject matter expertise. They also contributed to the writ-

ing of the manuscript. TOL, ZZL, JST, ACT conceived the idea behind this study and contributed to the study design, survey conduct, data analysis, and interpretation, and report writing. All authors read and approved the final manuscript.

Conflict of Interests: All authors are voluntary members of Healthy Malaysia (HM) and Hepatitis Free Pahang (HFP), the sponsors of this research. None of the authors are employees or paid any fees by HM/HFP, nor do they own shares in HM/HFP. There is no patent arising from this research. Teck-Onn Lim is a member of the editorial board of this journal. The journal confirmed that Teck-Onn Lim was completely excluded from all review processes.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after publication. The data are not publicly available in the absence of pubic data repository in Malaysia.

Ethical Approval: The Ministry of Health's (MOH) Medical and Research Ethics Committee approved the study (NMRR ID 16-2391-33614).

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Informed Consent: All subjects gave informed consent.

References

- Ton SH, Lopez CG, Hasnah H. Prevalence of anti-HBc in Malaysian male blood donors and its correlation with DNA polymerase activity. *Southeast Asian J Trop Med Public Health*. 1979;10(1):1–6. [PubMed: 483004].
- Ton SH, Lopez CG, Noriah R. HBeAG and anti-HBe in the Malaysian population and in Malaysian prisoners. *Southeast Asian J Trop Med Public Health*. 1983;14(2):252–4. [PubMed: 6635764].
- 3. Tan TC, Vadivale M, Ong CN. Prevalence of hepatitis B surface antigen and antibody among health care employees in Negri Sembilan, Malaysia, 1989. *Asia Pac J Public Health*. 1992;**6**(3):134–9. [PubMed: 1342800]. https://doi.org/10.1177/101053959200600303.
- Gan CY, Yap SF, Ngeow YF, Wong HC. Hepatitis B infection among Chinese STD patients in Kuala Lumpur, Malaysia. Sex Transm Dis. 1991;18(2):84–8. [PubMed: 1862464]. https://doi.org/10.1097/00007435-199118020-00006.
- Ng KP, Ngeow YF, K R, M R. Hepatitis B seroprevalence among University of Malaya Students in the Post-universal Infant Vaccination Era. *Med J Malaysia*. 2013;68(2):144–7. [PubMed: 23629561].
- Ng KP, Saw TL, Baki A, Rozainah K, Pang KW, Ramanathan M. Impact of the Expanded Program of Immunization against hepatitis B infection in school children in Malaysia. *Med Microbiol Immunol.* 2005;**194**(3):163–8. [PubMed: 15834754]. https://doi.org/10.1007/s00430-004-0231-4.
- Cheang HK, Wong HT, Ho SC, Chew KS, Lee WS. Immune response in infants after universal hepatitis B vaccination: a communitybased study in Malaysia. *Singapore Med J.* 2013;**54**(4):224–6. [PubMed: 23624451]. https://doi.org/10.11622/smedj.2013078.

- Yousuf R, Rapiaah M, Ahmed SA, Rosline H, Salam A, Selamah S, et al. Trends in hepatitis B virus infection among blood donors in Kelantan, Malaysia: a retrospective study. *Southeast Asian J Trop Med Public Health*. 2007;**38**(6):1070–4. [PubMed: 18613548].
- 9. Duraisamy G, Zuridah H, Ariffin MY. Prevalence of hepatitis C virus antibodies in blood donors in Malaysia. *Med J Malaysia*. 1993;**48**(3):313–6. [PubMed: 7514258].
- Ng KP, Saw TL, Wong NW, Goh KL, Chuah SY, Nagaratnam M. The prevalence of anti-HCV antibody in risk groups and blood donors. *Med J Malaysia*. 1995;**50**(4):302–5. [PubMed: 8668047].
- Sinniah M, Ooi BG. Hepatitis C-the Malaysian story. Singapore Med J. 1993;34(2):132-4. [PubMed: 8266152].
- Lee WS, Ng KP. Seroprevalence of anti-HCV in an urban child population: a preliminary study from Kuala Lumpur. *Singapore Med J.* 2001;42(3):100–1. [PubMed: 11405558].
- Haslina MN, Khairiah Y, Zainy DZ, Shafini MY, Rosnah B, Marini R. Seroprevalence of hepatitis C virus infection among blood donors in a teaching hospital in northeastern Malaysia. Southeast Asian J Trop Med Public Health. 2012;43(3):668–73. [PubMed: 23077846].
- 14. Radzi Ah M, S. Tan S, Mohamed R, Jaya F, K S, C. Aun A, et al. Hepatitis Screening and Treatment Campaign in Malaysia-Validation of Low-cost Point of Care Screening Tests and Nucleic Acid Tests for Hepatitis B and C. *Euroasian J Hepatogastroenterol.* 2018;8(2):101-7. [PubMed: 30828549]. [PubMed Central: PMC6395483]. https://doi.org/10.5005/jp-journals-10018-1273.
- Kessler RC, Little RJ, Groves RM. Advances in strategies for minimizing and adjusting for survey nonresponse. *Epidemiol Rev.* 1995;17(1):192–204. [PubMed: 8521937]. https://doi.org/10.1093/oxfordjournals.epirev.a036176.
- Yanagawa T, Gladen BC. Estimating disease rates from a diagnostic test. *Am J Epidemiol*. 1984;119(6):1015–23. [PubMed: 6731428]. https://doi.org/10.1093/oxfordjournals.aje.a113806.
- Wong MCS, Huang JLW, George J, Huang J, Leung C, Eslam M, et al. The changing epidemiology of liver diseases in the Asia-Pacific region. *Nat Rev Gastroenterol Hepatol.* 2019;16(1):57–73. [PubMed: 30158570]. https://doi.org/10.1038/s41575-018-0055-0.
- Cui F, Shen L, Li L, Wang H, Wang F, Bi S, et al. Prevention of Chronic Hepatitis B after 3 Decades of Escalating Vaccination Policy, China. *Emerg Infect Dis*. 2017;23(5):765-72. [PubMed: 28418296]. [PubMed Central: PMC5403029]. https://doi.org/10.3201/eid2305.161477.
- Lee H, Lee H, Cho Y, Oh K, Ki M. Changes in seroprevalence of hepatitis B surface antigen and epidemiologic characteristics in the Republic of Korea, 1998-2013. *Epidemiol Health*. 2015;**37**. e2015055. [PubMed: 27048173]. [PubMed Central: PMC4835708]. https://doi.org/10.4178/epih/e2015055.
- Posuwan N, Wanlapakorn N, Sa-Nguanmoo P, Wasitthankasem R, Vichaiwattana P, Klinfueng S, et al. The Success of a Universal Hepatitis B Immunization Program as Part of Thailand's EPI after 22 Years' Implementation. *PLoS One*. 2016;11(3). e0150499. [PubMed: 26938736]. [PubMed Central: PMC4777547]. https://doi.org/10.1371/journal.pone.0150499.
- Chowdhury A, Santra A, Chakravorty R, Banerji A, Pal S, Dhali GK, et al. Community-based epidemiology of hepatitis B virus infection in West Bengal, India: prevalence of hepatitis B e antigen-negative infection and associated viral variants. *J Gastroenterol Hepatol.* 2005;20(11):1712-20. [PubMed: 16246191]. https://doi.org/10.1111/j.1440-1746.2005.04070.x.
- Dashdorj N, Dashtseren B, Bold B, Yagaanbuyant D. P29: Epidemiological study of prevalence and risk factors for HBV among apparently healthy Mongolians. *Viral Hepat J.* 2014;21:21–48. https://doi.org/10.1111/jvh.12333_28.
- Chen YS, Li L, Cui FQ, Xing WG, Wang L, Jia ZY, et al. [A seroepidemiological study on hepatitis C in China]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2011;**32**(9):888–91. Chinese. [PubMed: 22340876].

- Wasitthankasem R, Posuwan N, Vichaiwattana P, Theamboonlers A, Klinfueng S, Vuthitanachot V, et al. Decreasing Hepatitis C Virus Infection in Thailand in the Past Decade: Evidence from the 2014 National Survey. *PLoS One*. 2016;**11**(2). e0149362. [PubMed: 26871561]. [PubMed Central: PMC4752320]. https://doi.org/10.1371/journal.pone.0149362.
- Chowdhury A, Santra A, Chaudhuri S, Dhali GK, Chaudhuri S, Maity SG, et al. Hepatitis C virus infection in the general population: a community-based study in West Bengal, India. *Hepatology*. 2003;**37**(4):802–9. [PubMed: 12668973]. https://doi.org/10.1053/jhep.2003.50157.
- Dashtseren B, Bungert A, Bat-Ulzii P, Enkhbat M, Lkhagva-Ochir O, Jargalsaikhan G, et al. Endemic prevalence of hepatitis B and C in Mongolia: A nationwide survey amongst Mongolian adults. *J Viral Hepat.* 2017;**24**(9):1–9. [PubMed: 28211256]. https://doi.org/10.1111/jvh.12697.
- 27. World Health Organization. Prevention of Mother-to-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis in Pregnancy. Geneva, Switzerland: World Health Organization; 2020. eng.
- Dusheiko G. A Shift in Thinking to Reduce Mother-to-Infant Transmission of Hepatitis B. N Engl J Med. 2018;378(10):952-3. [PubMed: 29514035]. https://doi.org/10.1056/NEJMe1801662.