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Establishing baseline framework for hepatitis B virus micro-elimination in Ho Chi Minh City, Vietnam – A community-based seroprevalence study

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Summary

Background We conducted a community-based seroprevalence study using three HBV seromarkers (HBsAg, anti-HBs, anti-HBc) in Ho Chi Minh City (HCMC), Vietnam, to (1) determine the prevalence of HBV serologic profiles; (2) document factors associated with HBV infection or susceptibility; and (3) propose strategies toward HBV elimination by 2030.

Methods During 2019–2020, we deployed a multistage cluster design with probability proportionate to size, to recruit 20,000 adults for an HBV screening and linkage to care program citywide. Screening results with interpretation, recommendations, and health education materials were returned to participants. Post-study surveys were conducted within three months to identify gaps in linkage to care.

Findings Of the 17,600 adults invited, 15,275 (86.7%) participated in the study, 14,674 (96.1%) completing all data for final analyses. The prevalence of HBsAg (+) and HBV-naïve were 7.5% and 37.7%, respectively. HBV vaccination rates were 18.7% and about 50% of HCMC population had been exposed to HBV. Of the persons with HBsAg (+), 27.1% linked to care (76% used health insurance). There were wide variations in HBsAg (+) and HBV vaccination rates between districts, risk factors, and socio-economic statuses.

Interpretation The significant disease burden of and gaps in the continuum of care highlight the need and urgency to address the HBV public health problem in Vietnam. Using three screening seromarkers that tailor interventions to the needs of HBV micro-populations could be an effective strategy to pursue HBV elimination goals.

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Keywords: Hepatitis B virus; Ho Chi Minh City (HCMC); Vietnam; Micro-elimination; National elimination; 2030; HBV linkage to care; HBV screening

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Research in context

Evidence before this study

As of May 10, 2022, we searched PubMed, MEDLINE, and Embase for publications written in English or Vietnamese using the keywords, "HBV micro-elimination," "public health framework for HBV," "baseline framework for HBV micro-elimination," "viral hepatitis micro-elimination," and "Vietnam." We found no article leveraging the micro-elimination concept in infectious disease to develop baseline data for HBV micro-elimination in Vietnam.

Added value of this study

This is the first population-based community HBV study to estimate the disease burden and establish a baseline of linkage to care for HBV in Ho Chi Minh City, Vietnam – a low-to-middle-income country. In addition, this study provided recommendations and health education to persons living with chronic HBV to motivate their care seeking behaviors to linkage to care. By using multistage cluster design with probability proportionate to size sampling approach, we were able to estimate the population prevalence of HBV infection statuses after adjusting for complex survey design in data analysis. Furthermore, use of three sero-marker screening panel for HBV (HBsAg, Anti-HBs and Anti-HBc total) enabled us to detail, at a population level, for the first time in Vietnam, different HBV statuses, i.e. HBV susceptible population (negative all three seromarkers), chronic carriers (HBsAg(+)), HBV exposure with immune control (anti-HBc total (+), with or without anti-HBs), and HBV vaccination (anti-HBs(+) without HBsAg). In addition to the current recommendations, focusing on high-risk individuals and childhood HBV vaccination, we highlighted the need to vaccinate all susceptible adults to increase protection from HBV infection.

Implications of all available evidence

By providing the real-life data for an HBV micro-elimination baseline framework in a large city such as Ho Chi Minh City (HCMC), we demonstrated the feasibility of a large-scale comprehensive screening and access-to-care program for HBV elimination in a low-to middle-income country, Vietnam. Additionally, the study was coordinated by a multi-sector collaboration, including government, public medical institutions, non-profit organisations and civil society, and private sector. Next, based on the results of this program, we are planning an interventional program to eliminate HBV in HCMC in the future. Collectively, our practical public health approach can be adopted into Vietnam's national and provincial health departments for national HBV elimination strategies in Vietnam. Furthermore, the overall process deserves to be assessed in other resource limited settings where HBV is endemic.

Introduction

Globally, chronic viral hepatitis B (HBV) remains a significant public health problem, affecting approximately 296 million people, with 1.5 million new infections per year.[1] The majority of the global HBV morbidity and mortality disproportionately afflicts African and Western Pacific Regions.[2] To address the global public health impact of HBV, WHO adopted its first Global Health Sector Strategy in 2016, aiming to eliminate HBV by 2030.[2]

Vietnam is a highly populated low-to-middle income country (LMIC) in Southeast Asia with a significant HBV burden.[2,3] In 2015, Vietnam's Ministry of Health released its first National Action Plan (NAP) for Viral Hepatitis Prevention and Control (2015–2019), which estimated that the prevalence of HBV ranged from 8% to 25%.[4] To implement a successful national HBV elimination program, there was a clear need to generate a framework to better define the gaps in knowledge, treatment and preventive measures, and the extent and seriousness of this public health problem in the population. Of note, in the current Vietnam's NAP for Viral Hepatitis Prevention and Control (2021–2025), the targeted vaccination policy, focusing on high-risk individuals and childhood HBV vaccination, is still recommended.[3] In comparison, the United State's Advisory Committee on Immunization Practices recommended expanding HBV vaccination eligibility to include adults aged 19–59 to increase vaccination and decrease infection.[5]

One of the most pragmatic approaches to HBV national elimination is leveraging the concept of "micro-elimination", which breaks down the elimination into smaller goals for specific populations or geographic areas.[2] This concept has been successfully used for hepatitis C virus (HCV) and HIV.[2] With this in mind, we aimed to establish an HBV micro-elimination framework for Ho Chi Minh City (HCMC) – the largest city in Vietnam by conducting a community-based research program. Specifically, we determined the prevalence and local epidemiological profiles of HBV infection in adult residents (age ≥18), the local acceptability and baseline continuum of HBV care in HCMC.

Methods

Study setting, design, and procedure

Ho Chi Minh City (HCMC) is located in southern Vietnam, with nine million residents in 2019 (Population Census in 2019 (Fig. 1-panel A). Using multistage cluster sampling with proportionate-to-size approach, a cross-sectional, seroprevalence survey for HBV, with

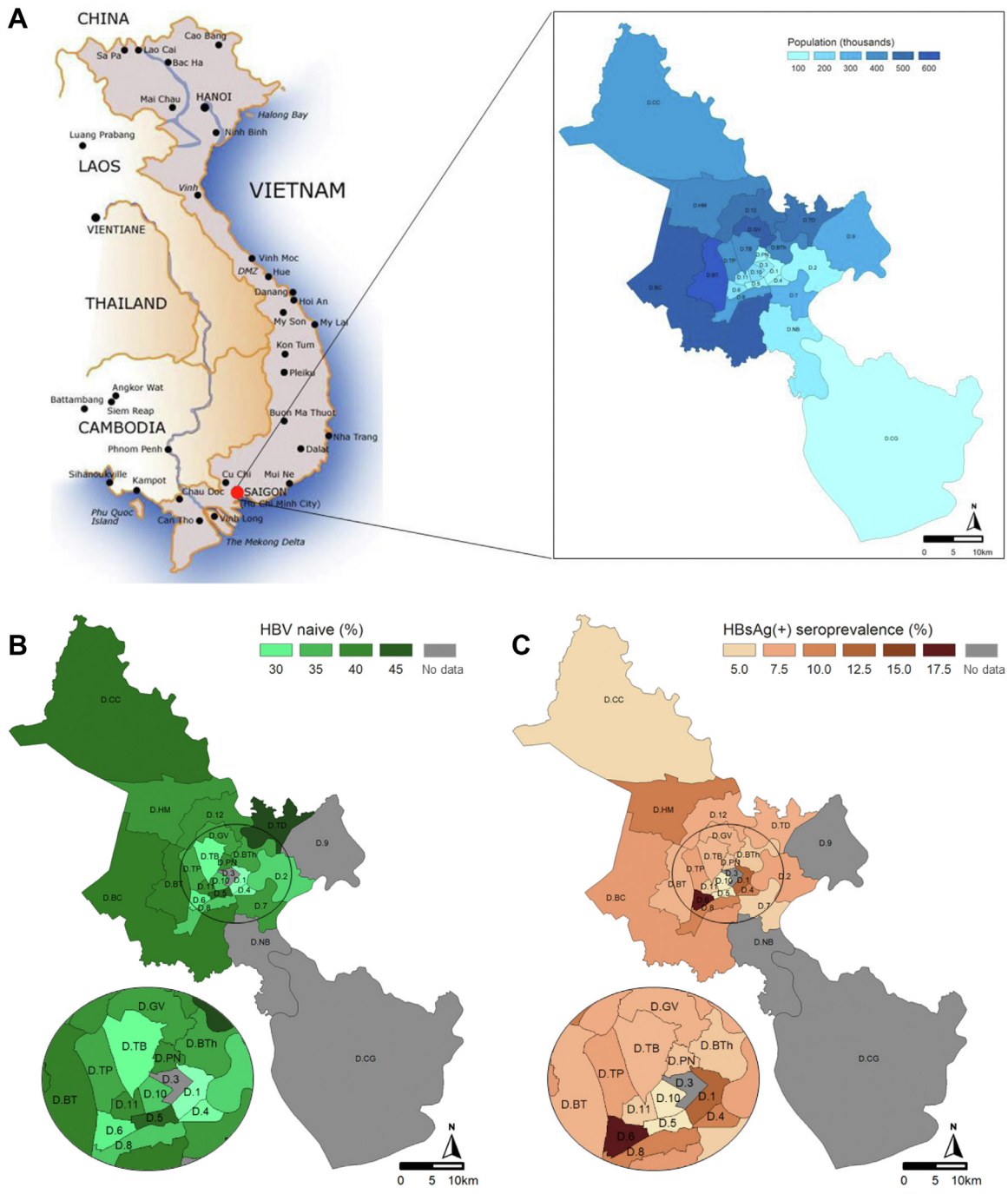

Fig. 1: **Population size and the rates of HBV-naïve and HBsAg (+) across the 24 districts in Ho Chi Minh City, Vietnam.** Panel A depicts the location of Ho Chi Minh City (HCMC – on the left), which is located in southern Vietnam, with its population sizes among the 24 districts in HCMC (enlarging panel – on the right). Panel B illustrates the prevalence of HBV-naïve populations among the 24 districts in HCMC. Panel C illustrates the prevalence of HBsAg(+) among the 24 districts in HCMC. Gray area denotes unreachable sites due to the restrictions secondary to COVID-19 pandemic. Rural areas: Cu Chi (CC), Hoc Mon (HM), Nha Be (NB), Binh Chanh (BC), Can Gio (CG). Urban areas: District 1–12 (D.1-D.12), Tan Binh (TB), Tan Phu (TP), Binh Thanh (BTh), Binh Tan (BT), Go Vap (GV), Phu Nhuan (PN), Thu Duc (TD). Abbreviations: D., district; CC, Cu Chi; HM, Hoc Mon; BC, Binh Chanh; GV, Go Vap; TD, Thu Duc; BT, Binh Tan; TP, Tan Phu; TB, Tan Binh; BTh, Binh Thanh; PN, Phu Nhuan; NB, Nha Be; CG, Can Gio.

care access coordination, was conducted in HCMC from 06/2019 to 07/2020. HCMC was selected to conduct the study because we have established a track record and infrastructure in the city, including our productive working relationships with our local stakeholders in HCMC: 1) our pilot study preceding this study,[6] 2) our other study determining gaps in the cascade of care in viral hepatitis in healthcare workers in HCMC, 3) another study of ours assessing the liver cancer disease burden secondary to viral hepatitis at a tertiary hospital in HCMC, and finally, 4) our annual international scientific conference focusing on viral hepatitis elimination and liver cancer prevention in Vietnam since 2016. The sample size of 20,000 assures an adequate power to estimate the antiHCV and HBsAg prevalence in the population of 2009 (3% for antiHCV(+) and 10% for HBsAg(+) according to prior study,[4,6] after adjusting for 2.5 in design effect at 0.5% precision and an overall expected response rate of 60%. Fig. 2 and Appendix A detailed the study design and procedures.

Those aged ≥ 18 living in HCMC at the selected neighborhood for at least six months before study entry, irrespective of their HBV infection statuses (i.e. HBsAg(+)) were eligible to participate. Only those reported to the screening event would be counted as screening participants. People without verifiable information of residence, outside of the invited neighborhood, or younger than 18 years old were excluded during the data analysis.

Participants completed a self-administered paper-based survey questionnaire and underwent HBV screening at local commune health station (at no cost). Test results were sent to participants' homes in a sealed package within two weeks of the screening event. Participants with HBsAg(+) were contacted three months after the study completion to assess care-seeking behaviors. As each participant received recommendations for next-step depending on their sero-statuses (nothing to do, or get vaccination or get medical consultation and examination), we believed that three months (90 days) after receiving the result would be sufficient to assess care seeking behavior. Written consent was obtained from all participants at study entry. A $2.50USD incentive was provided after the participant completed the survey and phlebotomy. The institutional review boards at Pham Ngoc Thach University of Medicine, HCMC, and the Department of Health-HCMC approved the study (Approval No. 2169 DHYKPNT-NCKH, 06/07/2019 and No. 008/HDDD, 01/04/2019; and (Approval No. 3110/SYT-NVY, 06/14/2019, respectively).

Data collection

At each site, a trained outreach team approached the household to invite potential participants 7–10 days before the screening date at the local commune health station. Participants' demographics and knowledge-attitude-behavior (KAB) were collected using self-administered survey questionnaire and then entered into REDCap. The survey was in Vietnamese language, adapted from the validated survey on the Health Behavior Framework,[7] and piloted on 1400 individuals in 2016.[6] The survey comprised 75 questions about demographics, KAB on HBV transmission, drinking, and smoking behaviors. Height, weight, and waist circumference were collected, and the average of two measurements was recorded. Completeness of survey questionnaire was checked two times before participant left the screening event to avoid missing answers in the questionnaire. Phlebotomies were done at local commune health stations by contracted phlebotomists from Medic Medical Center (MMC) in HCMC. Roche Diagnostics' Elecsys® HBsAg II (clinical sensitivity 99.9%, clinical specificity 99.88% - 99.98%), Anti-HBs II (clinical sensitivity 100%, clinical specificity 99.45% - 99.78%), and Anti-HBc II (clinical sensitivity 100%, clinical specificity 99.31%–100%) assays were analyzed using the Cobas® e 801 system at MMC. Screening results were reported to the research team before returning to participants in a result package. Phone interviews were conducted three months after the study completion based on the phone numbers provided in the survey. All research data were merged and managed in Stata.

Study variable assessments

Different HBV infection statuses based on HBsAg, antiHBs and anti-HBc were shown in Table 1. The "Other" group is the combination of the following three statuses: "immunization", "immune control" and "isolated anti-HBc", and served as the reference group in the multinomial regression analysis. All sociodemographic factors (age, gender, ethnicity, marital status, residency, education, employment, income, health insurance coverage status) and higher risks of HBV infection (history of liver cancer or liver cirrhosis, having family member(s) with HBV and/or HCV, having blood-related risk factors, sex-related risk behaviors) were dichotomized. Age was grouped into three subgroups: 18–30, 31–60, and 61 or older; knowledge was calculated as an individual total score (correct knowledge = 1, incorrect knowledge = 0). Stigma toward HBV infection was dichotomized into negative and positive attitudes (based on the 2 statements: "homeless people are more likely to get HBV", and "HBV infected individuals should be avoided"). Body mass index (BMI) was calculated and classified into two groups: Overweight/Obesity (BMI≥23 kg/m^2) and Underweight/Normal (BMI<23 kg/m^2) for Asian.[8] Waist circumference was dichotomized as normal or abdominal obesity, with the cut-off point ≥90 cm for men, and ≥80 cm for women.[9]

HBV continuum of care was generated using unweighted data from the survey responses and the

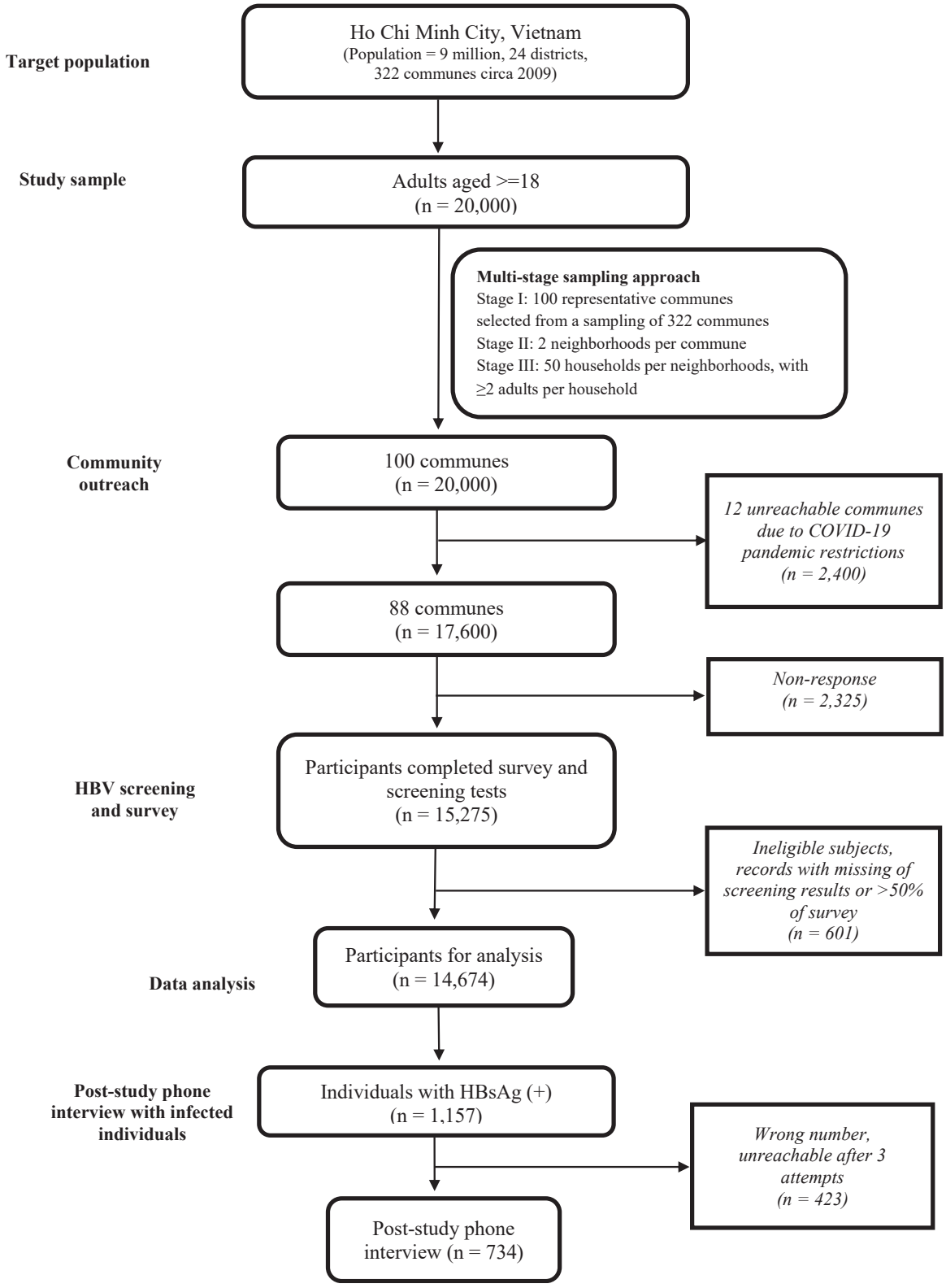

Fig. 2: Overview of study sampling frame and participant recruitment.

HBV Infection status	Combination of sero-markers	Unweighted, n	Weighted, n	Weighted % (95% CI)
HBV-Naive	• HBsAg (–) • Anti-HBs (–) • Anti-HBc (–)	3970	2,751,041	37.7 (36.5–39.0)
Immunization	• HBsAg (–) • Anti-HBs (+) • Anti-HBc (–)	2116	1,360,111	18.7 (17.7–19.7)
Immune control	• HBsAg (–) • Anti-HBs (+) • Anti-HBc (+)	6174	2,250,033	30.9 (29.9–31.9)
Chronic HBV infection	• HBsAg (+) • Anti-HBs(–) • Anti-HBc (+)	1157	546,980	7.5 (6.9–8.1)
Isolated anti-HBc (+)	• HBsAg (–) • Anti-HBs (–) • Anti-HBc (+)	1257	381,643	5.2 (4.8–5.6)
Total		14,674	7,289,808	

Table 1: **Distribution of HBV infection statuses, based on the combinations of three sero-markers (HBsAg, anti-HBs, and anti-HBc Total), in Ho Chi Minh City, Vietnam.**

post-study phone interviews. Based on the question "Are you aware of your HBV status?," we dichotomized those with HBsAg (+) into "diagnosed prior to study entry" and "undiagnosed prior to study entry." People who were diagnosed prior to study entry were classified as "engaged in care" or "not engaged in care." "Engaged in care" included those sought medical care (either from primary care providers or specialists in hepatology/virology) for HBV management, regardless of treatment initiation. The "not engaged in care" group was the combination of those who were "undiagnosed prior to study entry" and those who were "diagnosed but not engaged in care prior to study entry." Using the post-study phone interviews, we identified people in the "not engaged in care" group who later sought care after receiving the study's recommendations. We did not collect information on HBV viral load or medications for those who were diagnosed before entering the study. Those who did not provide or provided a wrong number or were unreachable after three phone call attempts were excluded from the post-study phone interviews analyses. No statistics testing was performed.

Statistical analysis

Univariable analysis were conducted to assess the unadjusted associations between every variable of interest (socio-demographic, anthropometric (BMI and waist circumference), KAB variables) and the outcome variables (HBV statuses: "HBsAg(+)" and "Naive"). We ran multinomial logistic regression with the "Other" group (those who had "isolated anti-HBc" – antiHBc(+) only, or "Immune due to HBV exposure" antiHBc(–)) as reference group. Purposeful selection of variables was included in model building: conceptual (all variables of interest) and statistically significant variables from univariable analyses (with $p < 0.2$) were included in the model building with backward covariates selection to get the parsimonious final model. Statistically insignificant variables were dropped from the full model and variable that changed more than 20% in coefficients between the two fitted models would be retained. We used AIC to compare between models to get the best fit for the data. Complex survey weight for each individual was calculated using design weight, post-survey adjustment (accounted for early termination, age and gender-specific non-coverage of the sampling frame between Census 2009 and 2019), and non-response rates at each site.[10] All analyses were performed using R Statistical Software (v4.0.5)[11] and survey and svyVGAM package to account for complex survey weights.[12] Prevalence of HBV sero-statuses were reported as unweighted and weighted estimates with 95% confidence intervals (CI).

Role of funding sources

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Results

Due to the COVID-19 pandemic restrictions in 02/2020, the study ended earlier than planned; 88 of 100 sites were enrolled. A total of 17,600 people were invited, and 86.8% (15,275/17,600) participated in the study. After eliminating cases with missing information on either the KAB survey or screening results due to ineligibility (3.9% of all participants), 14,674 cases (96% of 15,275) were analyzed. We identified 1157 individuals with HBsAg(+), 63.4% (734/1157) of whom participated in the post-study phone interviews (see Fig. 2).

The weighted prevalence of different HBV infection statuses in HCMC is presented in Table 1 and the district-specific rates of HBV infection and HBV susceptible populations are shown in Fig. 1-panel B and C. The weighted prevalence of HBsAg (+) was 7.5% (95% CI: 6.9–8.1%) while 37.7% (95%CI: 36.5–39.0) were susceptible to HBV and 18.7% (95%CI 17.7–19.7) were protected by HBV vaccination. Approximately 50% of the population had been exposed to HBV with anti-HBc

(+) alone or in combination with HBsAg or anti-HBs. While the distribution of HBV naïve across districts is similar to the population sizes in each district, HBV infection rates varied significantly. Generally, urban and districts with higher proportions of immigrants from other provinces in Vietnam had higher HBV infection rates. The characteristics of the study population are shown in Table 2, comparing across three groups: HBsAg (+), HBV-naïve, and "Other".

HBV-naïve were mostly among those aged 18–30 years (52.9%) while more than two-thirds of the HBsAg (+) were among those aged 31–60 (67.5%). Compared to the HBV-naïve and "Other" groups, the prevalence of HBsAg (+) was higher among males, people with sex partner(s), those with less than high school education, and those having overweight or obesity (BMI ≥23). Knowledge of HBV infection and self-perceived susceptibility to HBV infection among those with HBsAg (+) were highest among the three groups. Approximately 80% of participants in these groups had health insurance coverage.

Table 3 showed result from the multinomial logistic regression analysis, comparing HBsAg (+) vs. "Other" and HBV- naïve vs. "Other". The final model adjusted for the following factors: age, gender, ethnicity, having sex partner(s), residence, education level, employment, income, having health insurance coverage, having a history of liver cancer and/or cirrhosis, knowledge of HBV infection, having family member(s) with HBV and/or HCV, and having blood-related risk factors for HBV infection. Compared to persons in the "Other" group, after adjusting for covariates, the odds of being in the HBV-naïve group was significantly lower among those aged 31 or older, who were male, having sex partner(s), being employed, having health insurance, with slightly lower mean HBV knowledge score, having family members with HBV and/or HCV, and having blood-related risk factors for HBV infections. The odds of being in the HBV-naïve group were higher among people of minority ethnicity, living in the rural areas, and having an income of ≥$110 USD/month (Vietnam per capita income was approximately $2500 USD in 2019). Compared to the "Other" group, persons with HBsAg (+) were less likely to be older than 60 years and more likely to have health insurance. There was no statistically significant difference in the prevalence of HBV infection between the age group of those younger than 30 years and the group aged 30–60 years. However, those with HBsAg (+) were more likely to be male, without high school graduate education level, had slightly higher mean score of HBV knowledge, and were two times more likely to have family member(s) with HBV and/or HCV.

Among 1157 persons with HBsAg(+), 812 (71.2%) were newly diagnosed, and 345 (29.8%) were diagnosed before participating in the study. Of the 345 people who were diagnosed prior to study entry, 165 (14.3% of 1157) cases were engaged in care. Of the 992 people not engaged in care (including 812 cases of newly diagnosed and 180 cases diagnosed but not engaged in care prior to study entry), 629 (63.3%) participated in the post-study phone interviews. Of those, 23.5% (148/629) sought clinical care after receiving the study screening results (Fig. 3). Thus, three months after the study completion, we identified 27.1% (313/1157) of individuals with HBsAg(+) had engaged in care either before (n = 165) or after (n = 148) participating in the study. Of the 313 participants who engaged in care, 262 answered the question about health insurance and 76% (199/262) of those answered reported using health insurance for their medical care.

Discussion

We examined the prevalence of all HBV sero-statuses (HBV naïve, immune control, immunization, isolated antiHBc(+) and HBV infection) to establish a baseline framework toward HBV elimination in HCMC, Vietnam. This framework describes the HBV epidemiological profiles and serves as an exemplary model for baseline assessment to promote national HBV elimination dialog and inform policy change in the country. Additionally, in this manuscript, we discussed strategies that stakeholders could use to leverage this baseline framework toward HBV elimination in Vietnam.

The prevalence of HBV was 7.5% in HCMC, lower than the recent national estimate of 9.2%.[3] Given the diversity of the socioeconomic settings, HBV infection rates varied across districts, ranging from 4.0% to 17.9%. Individuals with HBsAg(+) in this study were more likely to be younger than 60 and were not high school graduates. As higher education levels and older ages were associated with higher adherence to treatment,[13] we highlighted the need for treatment adherence by investing in strategies and efforts to better retain patients in care, especially for the young and low education level group, through care coordination and provision of continuous health education.[13]

Among adults with HBsAg(+), 27.1% (313/1157) engaged in care. Within this group, 14.3% had already followed up with their healthcare providers while the other group 12.8% sought clinical management after being diagnosed through this study (Fig. 3). Our pilot study in 2016 showed that the post-screening follow-up rate among those who received follow-up recommendations with free hepatology evaluation was 14%.[6] The current study results corroborated with the pilot study finding, that is even with provision of health insurance coverage and self-aware of infection status, written interpretation of screening results, recommendations, and health education materials, patient care-seeking

	Overall (n = 14,674)	Naïve (n = 3970)	HBsAg (+) (n = 1157)	Other[f] (n = 9547)
Age[a]				
18-30	36.3 (34.9–37.6)	52.9 (50.8–55.0)	23.4 (19.0–27.9)	26.5 (24.9–28.2)
31-60	53.2 (52.0–54.5)	43.0 (41.0–45.1)	67.5 (63.2–71.8)	58.3 (56.8–59.9)
60+	10.5 (10.1–10.9)	4.1 (3.7–4.5)	9.1 (7.8–10.3)	15.1 (14.4–15.8)
Gender[a]				
Female	52.1 (50.9–53.3)	54.0 (51.7–56.2)	45.1 (41.2–49.1)	51.8 (50.3–53.3)
Male	47.9 (46.7–49.1)	46.0 (43.8–48.3)	54.9 (50.9–58.8)	48.2 (46.7–49.7)
Ethnicity[a]				
Kinh	92.0 (91.3–92.6)	90.0 (88.6–91.3)	93.3 (91.3–95.3)	93.2 (92.4–93.9)
non-Kinh	8.0 (7.4–8.7)	10.0 (8.7–11.4)	6.7 (4.7–8.7)	6.8 (6.1–7.6)
Marriage status[a, b]				
Single/Separated/Divorced/Widowed	40.9 (39.7–42.2)	50.4 (48.2–52.6)	31.0 (26.8–35.1)	35.8 (34.2–37.3)
Married/co-habiting	59.1 (57.8–60.3)	49.6 (47.4–51.8)	69.0 (64.9–73.2)	64.2 (62.7–65.8)
Residence[a]				
Urban	86.8 (86.1–87.6)	86.0 (84.6–87.3)	84.0 (81.2–86.8)	87.8 (86.9–88.7)
Rural	13.2 (12.4–13.9)	14.0 (12.7–15.4)	16.0 (13.2–18.8)	12.2 (11.3–13.1)
High school graduate or higher[a]				
No	46.5 (45.3–47.6)	40.0 (37.9–42.0)	55.1 (50.9–59.3)	49.7 (48.3–51.2)
Yes	53.5 (52.4–54.7)	60.0 (58.0–62.1)	44.9 (40.7–49.1)	50.3 (48.8–51.7)
Employment[a]				
No	36.1 (34.9–37.2)	38.2 (36.1–40.4)	30.2 (26.5–33.8)	35.4 (34.0–36.8)
Yes	63.9 (62.8–65.1)	61.8 (59.6–63.9)	69.8 (66.2–73.5)	64.6 (63.2–66.0)
Income[a,c]				
<110 USD/month	43.3 (42.1–44.5)	42.6 (40.4–44.8)	38.3 (34.5–42.2)	44.5 (43.0–46.0)
≥110 USD/month	56.7 (55.5–57.9)	57.4 (55.2–59.6)	61.7 (57.8–65.5)	55.5 (54.0–57.0)
Health insurance[a]				
Yes	82.1 (81.1–83.1)	79.0 (77.1–80.8)	79.8 (76.2–83.3)	84.6 (83.5.85.8)
No	17.9 (16.9–18.9)	21.0 (19.2–22.9)	20.2 (16.7–23.8)	15.4 (14.2–16.5)
Knowledge of HBV[a]				
Weighted mean score (SD)	4.6 (3.5)	4.3 (3.5)	5.2 (3.8)	4.6 (3.5)
Attitude toward HBV				
Positive	83.8 (82.9–84.7)	83.4 (81.7–85.0)	81.7 (78.4–85.0)	84.4 (83.2–85.5)
Negative	16.2 (15.3–17.1)	16.6 (15.0–18.3)	18.3 (15.0–21.6)	15.6 (14.5–16.8)
Self-perceived susceptibility of HBV infection[a]				
No/don't know	70.0 (68.9–71.1)	71.9 (69.9–73.8)	64.2 (60.2–68.2)	69.5 (68.2–70.9)
Yes	30.0 (28.9–31.1)	28.1 (26.2–30.1)	35.8 (31.8–39.8)	30.5 (29.1–31.8)
History of liver cancer and/or cirrhosis[a]				
No	99.8 (99.7–99.9)	99.9 (99.7–100.0)	98.5 (97.2–99.9)	99.9 (99.8.99.9)
Yes	0.2 (0.1–0.3)	0.1 (0.0-0.3)	1.5 (0.1–2.8)	0.1 (0.1–0.2)
Having family member(s) with HBV and/or HCV[a]				
No/Don't know	87.9 (87.1–88.6)	91.4 (90.2–92.7)	75.2 (71.5–79.0)	87.1 (86.1–88.2)
Yes	12.1 (11.4–12.9)	8.6 (7.3–9.8)	24.8 (21.0–28.5)	12.9 (11.8–13.9)
Any blood-related risk factors[ad]				
Without	78.5 (77.5–79.4)	80.2 (78.6–81.9)	78.3 (75.1–81.5)	77.3 (76.1–78.5)
With	21.5 (20.6–22.5)	19.8 (18.1–21.4)	21.7 (18.5–24.9)	22.7 (21.5–23.9)
Any sexual risk behaviors[ae]				
Without	28.4 (27.3–29.6)	31.5 (29.4–33.6)	27.2 (23.3–31.1)	26.4 (25.0–27.8)
With	71.6 (70.4–72.7)	68.5 (66.4–70.6)	72.8 (68.9–76.7)	73.6 (72.2–75.0)
BMI[a]				
Underweight/normal weight	50.1 (48.9–51.3)	53.2 (51.0–55.4)	47.7 (43.6–51.8)	48.3 (46.9–49.8)
Overweight/obese	49.9 (48.7–51.1)	46.8 (44.6–49.0)	52.3 (48.2–56.4)	51.7 (50.2–53.1)

(Table 2 continues on next page)

	Overall (n = 14,674)	Naïve (n = 3970)	HBsAg (+) (n = 1157)	Other[f] (n = 9547)
(Continued from previous page)				
Waist circumference[a]				
Normal	61.5 (60.4–62.6)	65.9 (64.0–67.9)	60.7 (56.9–64.6)	58.6 (57.2–60.0)
Abdominal obesity	38.5 (37.4–39.6)	34.1 (32.1–36.0)	39.3 (35.4–43.1)	41.4 (40.0–42.8)

[a]$p < 0.05$.[b]Based on marital statuses: those living together or having current marriage were categorized as married/co-habiting. Individuals who reported to be single, separated, divorced, or widowed were defined as single/separated/divorced/widowed.[c]Income of $110USD/month was equivalent to 60% of the minimum wage for urban areas ($180USD/month) or 70% for rural area ($159USD/month) in Ho Chi Minh City as of 2019 according to Vietnam Briefing (posted on November 28, 2019 on https://www.vietnam-briefing.com/news/vietnam-increase-minimum-wage-january-2020.html/).[d]Blood-related risk factors include having blood transfusion, tattooing, sharing needles, using narcotics, or having dialysis.[e]Sex-related risk factors include having intercourse with sex workers, belonging to LGBT (Lesbian, Gay, Bisexual, Transgender) group, or not using condom.[f]Other included immune control, immunization, and isolated antiHBc(+).

Table 2: **Distribution of socio-demographic characteristics and knowledge, attitude, and risk factors according to HBV infection statuses (weighted % (95%CI)).**

behaviors were still insufficient. Thus, active linkage to care with care coordination may be needed to increase the number of persons living with HBV linked to care.

The once daily oral HBV medications with minimal viral resistance typically results in undetectable HBV viral load and reduces risks of HBV transmission and future development of HCC.[14] In Vietnam, HBV anti-viral therapy are widely available and covered 80% by national health insurance.[15] Although we found 79.8% of the HBsAg(+) had health insurance, only 63.6% sought care after knowing their screening results. HBV treatment co-pay in Vietnam was relatively high compared with other Southeast Asian countries,[3,16] raising the affordability concern of universal HBV treatment coverage. Therefore, efforts in improving affordability and accessibility to HBV treatment should focus on lowering antiviral drug prices in addition to increasing the identification of infected individuals in the population. As 87% of the population have health insurance,[17] persons living with chronic HBV should be evaluated and treated if indicated. Given 13% of the population did not have health insurance, inequity in access to HBV care and treatment remained. A discount program with sliding fee scale based on patient's income or on the ability to pay would benefit the low income, underinsured or uninsured people to access care.[18]

Besides linkage to care, a comprehensive HBV program should also include full coverage of vaccination, active case-finding, and monitoring of those who have been exposed to HBV (anti-HBc(+)) for risks of HBV reactivation. While most of the HBV screening programs in Vietnam only used HBsAg with or without anti- HBs,[19] we believe our study was the first to use three HBV seromarkers (HBsAg, anti-HBs, anti-HBc) for a population-based screening in the country. As such, our study was able to additionally provide the prevalence of susceptible population to HBV (i.e. negative for three HBsAg, anti-HBs, and anti-HBc) as well as the prevalence of those who have been exposed to HBV, defined as anti-HBc (+) with or without anti-HBs (+).

As 37.7% of the HCMC adults was susceptible to HBV infection, and less than 20% of the population was vaccinated, we highlighted the need for adult HBV vaccination. Geographically, we found areas in HCMC with large population sizes that also had higher rates of HBV susceptibility (Fig. 1, Panels B&C). With the current sex ratio that higher female than male in the general population of HCMC, adult vaccination may add another layer of preventing mother-to-child transmission of HBV. HBV vaccination is the most effective strategy for preventing HBV transmission.[2] Vietnam has fully implemented its childhood HBV vaccination program through the national extended immunization program since 2003.[3] Recently, the US Centers for Disease Control and Prevention recommended universal HBV vaccination for people aged 19–59.[5] However, the current Vietnam National Guidelines for Diagnosis and Management of HBV Infection recommended targeting HBV vaccination to susceptible or high-risk individuals, and pregnant women as well as childhood vaccination.[20] Taken together, the above findings indicate that in addition to the primary prevention of HBV infection through HBV vaccination, secondary prevention by proactively finding those living with HBV and treating them as indicated is another strategy toward HBV elimination.

Isolated anti-HBc (i.e. anti-HBc (+), HBsAg(–), and anti-HBs (–)) represents one of the following four scenarios relating to HBV: (1) resolved infection, (2) "low-level" chronic infection, (3) false-positive, or (4) resolving acute infection.[19] Since the false positive rate of anti-HBc tests in HBV endemic countries such as Vietnam was very low[21]; its presence almost always indicates a history of HBV exposure.[21,22] We found that 5.2% of the population had isolated anti-HBc. The prevalence of isolated anti-HBc among Asian American was reported to be increased with age, and the total rate was 10.9%,[19] two folds higher than what we found. Although the clinical significance of patients with isolated anti-HBc is not clearly defined, anti-HBc(+) may indicate the persistent presence of HBV covalently closed circular DNA in the liver,[23] putting the patient at risk for reactivation following immunosuppressive agent, antirheumatic medications or cancer

	Naïve vs. Other[a]		HBsAg (+) vs. Other[a]	
	cOR (95% CI)	aOR (95% CI)	cOR (95% CI)	aOR (95% CI)
Age				
18-30	–	–	–	–
31-60	0.37 (0.33–0.42)	0.39 (0.33–0.46)	1.31 (1.00–1.71)	1.17 (0.83–1.66)
60+	0.14 (0.12–0.16)	0.14 (0.12–0.17)	0.68 (0.51–0.90)	0.67 (0.48–0.94)
Gender				
Female	–	–	–	–
Male	0.92 (0.82–1.02)	0.83 (0.73–0.94)	1.31 (1.10–1.56)	1.33 (1.10–1.61)
Ethnicity				
Kinh	–	–	–	–
Non-Kinh	1.52 (1.26–1.84)	1.51 (1.22–1.85)	0.98 (0.70–1.37)	1.08 (0.75–1.55)
Marital status				
Single/separated/divorced/widowed	–	–	–	–
Married/co-habiting	0.55 (0.49–0.61)	0.87 (0.75–0.99)	1.24 (1.01-1.53)	1.00 (0.78–1.29)
Residence				
Urban	–	–	–	–
Rural	1.17 (1.01–1.35)	1.44 (1.22–1.69)	1.37 (1.09–1.72)	1.28 (1.00–1.65)
High school graduate or higher				
Yes	–	–	–	–
No	0.67 (0.61–0.75)	1.00 (0.88–1.14)	1.24 (1.03–1.48)	1.38 (1.12–1.70)
Employment				
No	–	–	–	–
Yes	0.89 (0.80–0.99)	0.80 (0.68–0.95)	1.27 (1.06–1.53)	1.05 (0.82–1.36)
Income				
<110 USD/month	–	–	–	–
≥110 USD/month	1.08 (0.97–1.20)	1.33 (1.13–1.57)	1.29 (1.08–1.54)	1.04 (0.82–1.33)
Health insurance				
No	–	–	–	–
Yes	0.68 (0.59–0.79)	0.81 (0.69–0.94)	0.72 (0.57–0.91)	0.73 (0.57–0.94)
History of liver cancer and/or cirrhosis				
No	–	–	–	–
Yes	1.13 (0.27–4.70)	1.26 (0.33–4.88)	13.74 (4.78–39.46)	14.3 (4.28–47.6)
Knowledge of HBV infection				
Yes?	0.97 (0.96–0.99)	0.98 (0.96–0.99)	1.05 (1.02–1.08)	1.04 (1.01-1.07)
Self-perceived susceptibility of HBV infection				
No/Don't know	–		–	
Yes	0.89 (0.80–1.00)		1.27 (1.06–1.53)	
Having family member(s) with HBV and/or HCV				
No/Don't know	–	–	–	–
Yes	0.63 (0.53–0.76)	0.63 (0.51–0.77)	2.22 (1.78–2.77)	2.04 (1.61–2.59)
Having any blood-related risk factors for HBV infection				
No	–	–	–	–
Yes	0.84 (0.74–0.95)	0.85 (0.74–0.97)	0.94 (0.77–1.15)	0.96 (0.77–1.19)
Having any sexual-related risk factors for HBV infection				
No	–		–	
Yes	0.78 (0.69–0.88)		0.96 (0.78–1.18)	
BMI				
Underweight/normal weight	–		–	
Overweight/obese	0.82 (0.74–0.92)		1.03 (0.86–1.22)	
Waist circumference				
Normal	–		–	
Abdominal obesity	0.73 (0.66–0.81)		0.91 (0.77–1.08)	

[a]Other included immune control, immunization, and isolated antiHBc(+).

Table 3: **Crude and adjusted odds ratios (cORs and aORs) from multinomial logistic regression analyses identifying factors associated with HBV-naïve or HBsAg(+) status.**

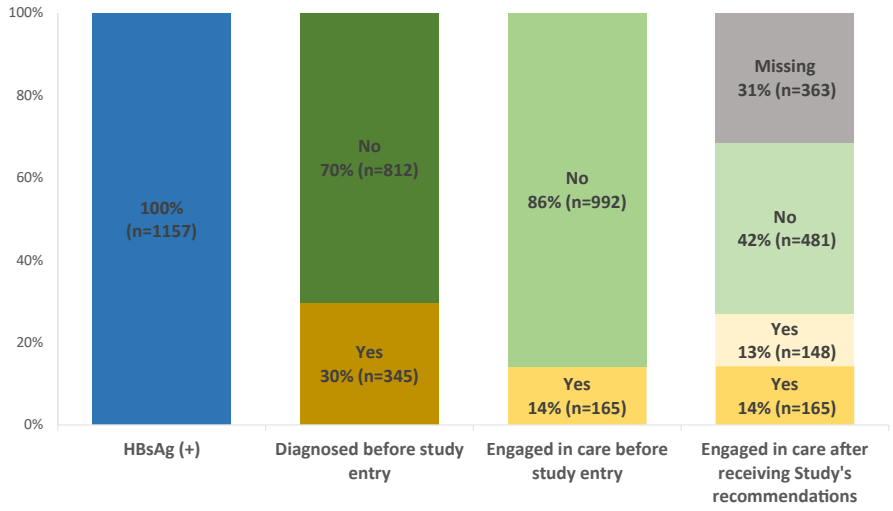

Fig. 3: Baseline HBV continuum of care in Ho Chi Minh City, Vietnam. Notes: "Engaged in care" is defined as those who sought medical care by primary care providers or specialists in hepatology/infectious disease for HBV management, irrespective of whether treatment was initiated or not, after being diagnosed with positive HBsAg.

therapy.[24,25] We recommend using anti-HBc together with HBsAg and anti-HBs to screen for HBV to avoid over-estimating the susceptible population for HBV vaccination. When comparing with "Other" group (defined as the combination of the following three statuses: "immunization", "immune control" and having "isolated anti-HBc"), we found HBsAg (+) group reported twice the odds of having a family member with HBV or HCV while the odds of having a family member with HBV/HCV infection among the Naïve group was 0.63. While vertical transmission of HBV has been historically known as the main mode of HBV transmission in Vietnam,[3,20] our findings suggested that a significant rate of horizontal transmission may occur in the country. A study of Asian American families showed that persons living with chronic HBV were not aware of HBV serostatus in 50% of their family members,[26] which emphasizes that family members with close household contact should be consulted and tested following the identification of an index HBV infected case as recommended by WHO.[27] Tracing the family network of the HBV-infected individual is a convenient approach to identify at-risk individuals and improve early screening or vaccination. However, more definitive studies on family contact tracing for HBV would be needed.

Obesity, insulin resistance, and non-alcoholic fatty liver disease (NAFLD) in Asia have emerged over the last decade. Currently, the population prevalence of NAFLD in Asia is around 25–30%.[28] The prevalence of patients with metabolic risk factor(s) and HBV is unknown and how metabolic risk factors may influence the natural history and treatment response of chronic HBV is to be investigated. We observed 52.3% of persons living with chronic HBV also had obesity (BMI $\geq$ 23) and 39.3% had central obesity (waist circumference $\geq$90 cm in men or 80 in women). More studies are needed to better address the fact that there is a high proportion of metabolic risk factors co-existing with chronic HBV.

To encourage stakeholders who are most knowledgeable about specific populations/specific areas to engage with each other and also promote the uptake of new models of care toward HBV elimination, we formed an alliance before conducting this study.[6] With a rigorous design and planning before execution, the study recruited participants with an 86.8% response rate, which is high for a population-based screening program.[29] While there were incentives ($2.5USD) and free testing, which might encourage people to participate in the study, participating sites and participants provided feedback that our overall program approach is feasible as a community screening program at local health facilities in the long run. Other elements that contributed to its feasibility include the following activities: (1) the strong collaboration with local authorities and government; (2) the creditability of the research team with the endorsement and guidance of HCMC Department of Health; (3) the companionship of local representatives to conduct in-person recruitment of study participants; and (4) the convenience of screening venue (walking distance from home to local health stations) and the timing of screening (weekends).

Our study had several strengths. To our knowledge, this is the first large-scale population-based seroprevalence study conducted in Vietnam. Most investigators have sufficient knowledge, skills and sensitivity to the local cultures to establish trust with stakeholders and

implement a culturally appropriate approach in conducting the study and recruiting patients. Also, we have had a record of successes and well-established infrastructure in Vietnam. Furthermore, we applied multinomial logistic regression that allowed us to use the full sample for all outcome categories to estimate the parameters and variances, as opposed to separate binary logistic regression would reduce the sample size to 2 categories at a time. This statistical approach enabled us to use the strengths of combining three seromarkers in screening. Although we did not perform probability selection of household and within household sample, the design-based weighting strategy (accounting for the probability of primary and secondary sampling unit selection) is adequate to provide meaningful estimation for the prevalence of the disease at individual-level within the community.[30] On the other hand, our study has several limitations. First, even after applying post-stratification weight, our estimation of the prevalence might not truly represent the populations in HCMC due to early termination. Second, self-reporting is subject to recall limitations, and some data such as items about risk behaviors, which were sensitive might not be answered truthfully. Third, no causal inferences between HBV status and other factors can be made due to cross-section design, and unmeasured confounding might remain in the final model. Last, the data on follow-up linkage to care might underestimate the true proportion of people who were eligible for and received clinical management according to their HBV infection because we could not reach all individuals with HBsAg(+) nor confirm their viral load and liver disease status for treatment initiation. There are only 8 years until the 2030 deadline for the global viral hepatitis elimination goal.[14] Without implementing effective interventions in the population, Vietnam is highly unlikely to reach its national elimination goal.[3] We proposed a baseline framework for HBV micro-elimination in HCMC, a model for Vietnam's national effort toward national HBV elimination. With the current national policy of targeted screening for high-risk population,[3,20] prioritizing elimination goals in discrete candidate populations (HBV chronic infection, HBV naïve) through multi-stakeholder engagement could be effective and feasible in Vietnam. Increasing awareness of HBV infection in the community; using three seromarkers (HBsAg, anti-HBs, and anti-HBc) should be adopted to identify those in need of intervention within a single testing encounter (such as people at risk for HBV acquisition need vaccination; while those living with chronic HBV, and/or those at risk for HBV reactivation when exposed to immuno-suppressive agents require thorough medical examination and/or periodic checkup) to link them to care. For individuals living with chronic HBV, in-person care coordination should be implemented. Vaccination should be recommended for adults, ideally to be universally applied, or at least among those living with family member(s) with HBV.

Contributors

TNDP, HKT, DTN, GWM, MCJr, and DYD contributed to study design. TNDP, DVBD, LTBP, TTTP, TBN, and HKT contributed to data collection. TNDP, DHL, and DYD contributed to data analysis and manuscript preparation. DYD, GWM, RGG, WML, MCJr, HTP, and BTN contributed to funding acquisition. DYD is fully responsible for the overall content of the work and the conduct of the study, had access to the data, and controlled the decision to publish. All authors reviewed the manuscript and approved the submitted final version.

Data sharing statement

De-identified participant data relating to the results reported in this paper will be available upon request. Scientific proposal should be sent to the corresponding author to gain access.

Declaration of interests

MC.Jr received consulting fees from the Vietnam Viral Hepatitis Alliance. RGG has received grants or research support in last two years from Gilead. RGG has also performed as a consultant or advisor in the past two years to Abbott, AbbVie, Altimunne, Antios, Arrow head, Dynavax, Eiger, Eisai, Enyo, Genentech, Genlantis, Gerson Lehrman Group, Gilead Sciences, Helios, HepaTX, HepQuant, Intercept, Janssen, Merck, Pfizer, Topography Health, and Venatorx. RGG is on scientific or clinical advisory boards for AbbVie, Antios, Dynavax, Enyo, Genentech, Genlantis, Gilead, Helios, HepaTX, HepQuant, Intercept, Janssen, Merck, Pfizer, and Prodigy. RGG is a member of Topography Health clinical trials alliance. RGG is chair of the clinical advisory board for Prodigy. RGG is an advisory consultant for Fibronostics, Fujifilm/Wako, Perspectum, Quest, and Sonic Incytes. RGG is on data safety monitoring boards for Altimmune, Arrowhead, CymaBay Therapeutics, and Durect. RGG currently has consulting confidentiality agreements with Abbvie, Abbott, Access Biologicals, Active Genome Expressed Diagnostics, ADMA Biologics, AEC Partners, Aligos Therapeutics, Arena Pharma ceuticals Inc, Ark Biopharmaceutical Co Ltd, Arrowhead, Arterys Inc, Alexion, Altimmune, Antios Therapeutics, AprosTx, Audentes Therapeutics, Bayer, Bausch/Salix, Cirina, Consumer Health Products Assoc, CymaBay Therapeutics Inc, DiaSorin Inc, Dova Pharmaceuticals, DRG Abacus, DURECT Corporation, Dynavax, Echosens, Eiger, Eisai, Enyo, Exelixis, Fibronostics Inc, Forty-Seven Inc, Fujifilm Wako Diagnostics, Gilead, HepQuant, HepaTx, IDLogiq, Intellia, Intercept, Inotek, Iqvia, Janssen/J&J, KannaLife, Kezar Life Sciences Inc, LabCorp, Laboratory for Advanced Medicine, Labyrinth Holdings, Life Line Screening, Lilly, MedImmune, Merck, New Enterprise Associates, Ogilvy CommonHealth, Organovo, Patient Connect, Perspectum, Pfizer, Pharmaceutical Research Associates, ProdigY Biotech, Prometheus Laboratories, Refuah Solutions, Regulus Therapeutics, Sagimet Inc, Salix, Saol Bermuda Ltd, Shenzhen HEC Industrial Develop ment, Shionogi Inc, Spring Bank, Tonghua Anrate Biopharmaceutical, Topography Health, Trimaran, Venatorx, and Viravaxx AG. RGG reports activities for Speakers Bureau, focusing on HBV, HCV, HDV and liver cancer; specifically, epidemiology, diagnosis, and treatment. In addition, program presentations on vaccination for HBV and management of complications of cirrhosis. RGG has speaker's contracts to do promotional talks for AbbVie, BMS, Eisai, Genentech, Gilead Sciences Inc., and Intercept. RGG is a minor stock shareholder (liver space noted only) for RiboSciences and CoCrystal. RGG holds stock options in Eiger, Gen lantis, HepQuant, AngioCrine, and HepaTx, outside the submitted work. The rest of the authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2022.100620.

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