

Progressive Scale-up of HBV AND HCV Testing for Hepatitis Elimination in Vietnam

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Vietnam, a low to middle income country of 97 million persons, has the 13th highest national burden of viral hepatitis worldwide.^{1,2} From 2010 to 2016, of 24,091 cases of

HCC from the largest tertiary hospital in Ho Chi Minh City (HCMC), 25% and 62% were caused by HCV and HBV infection, respectively.³

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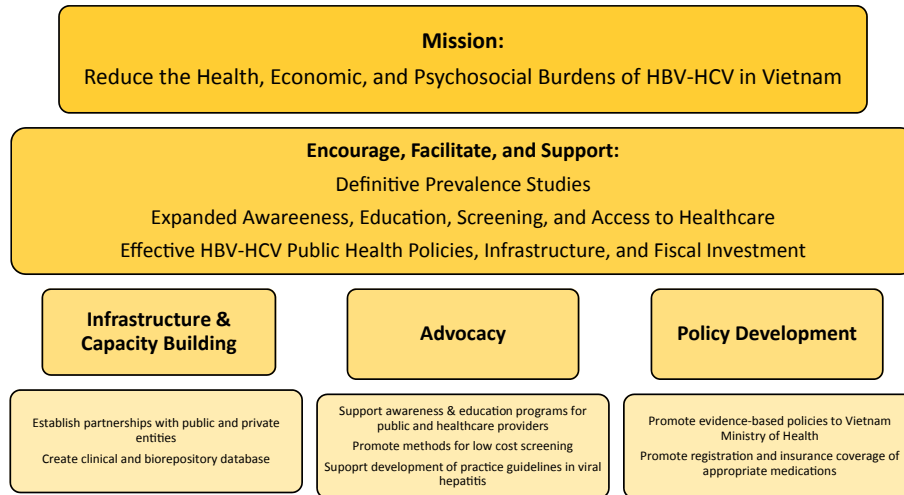


FIG 1 V-VHA's mission and step-wise strategic directions for viral hepatitis elimination in Vietnam. Infrastructural & capacity establishment through local and international partnerships and clinical/biorepository database will serve as a foundation to raise awareness, promote education programs, and support screening and access to care for and policy development on viral hepatitis elimination in Vietnam.

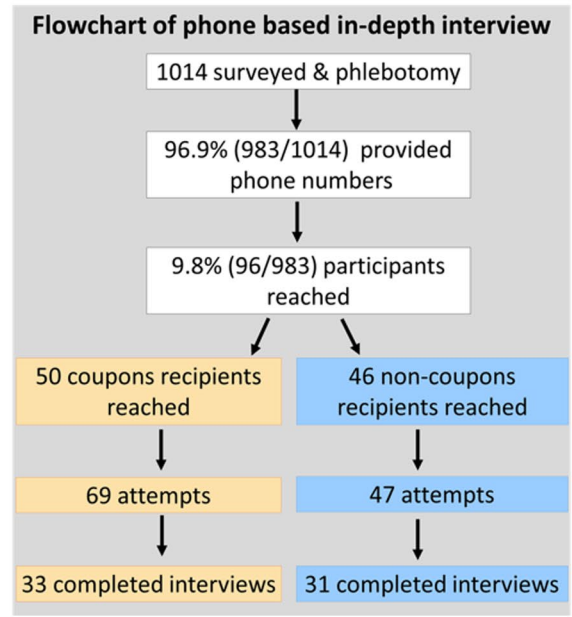


FIG 2 Vietnam (red shape, left panel) is located in South East Asia. Ho Chi Minh City is located in the South of Vietnam (enlarging circle). The right panel represents a flowchart of phone-based interviews for post-program satisfaction and acceptability in the Pilot study.

In 2017, without the scale-up of interventions, an estimated 14,923 cases of HCV decompensated cirrhosis, 8,923 cases of HCV-linked cancer, and 7,123 of HCV-related deaths are projected to occur in 2030 and is expected to continue to rise.⁴ Approximately eight million Vietnamese (8.4% of the population) are chronic HBV carriers, including 3.22 million persons eligible for HBV therapy⁵; but only an estimated 1.34% (43,230) receive recommended treatments for HBV infection.⁵

INITIATIVES DEDICATED TO VIRAL HEPATITIS ELIMINATION IN VIETNAM

To address the urgent needs in viral hepatitis in Vietnam, the Vietnam Viral Hepatitis Alliance (V-VHA), a 501c3 not-for-profit organization, facilitates, advocates, and supports hepatitis prevention, including community education, clinician training for HBV and HCV screening, and linkage to care programs (Fig. 1). This report describes the results of

TABLE 1. RESPONSES TO POST-PROGRAM SATISFACTION SURVEY (PERCENT OF RESPONDENTS) IN THE PHONE-BASED IN-DEPTH INTERVIEWS

Questions	Provision of free coupon with recommendations for further liver disease assessments or HBV vaccination (n = 33)		Provision of screening results only (no follow up needed) (n = 31)	
	Yes	No	Yes	No
Do you think that this program is necessary for you?	84.8	15.2	80.6	19.4
Do you think that this program should be expanded?	100.0	0.0	100.0	0.0
Will you introduce your family members or friends to this program?	82.4	17.6	57.1	42.9
Will you continue to participate in this program if it is extended in the future with partial coverage of screening tests?	81.8	18.2	87.1	12.9
Will you participate if screening tests are free?	96.4	3.6	88.5	11.5
Will you participate if screening locations are close to you but screening tests are not free?	76.9	23.1	46.7	53

For those who **received the program's coupons** for free HBV vaccine series or free liver assessment labs and Hepatology consultation, 13 agreed to answer questions concerning whether they intend to use the coupons. Seventy-seven (10/13) would not use the free coupons due to time constraints, lack of viral hepatitis education, HBV vaccination misconception (no disease, no need for vaccination), lack of transportation, and inability to co-pay for treatment.

a population-based HBV-HCV screening and access to care study (i.e., the Pilot study) in HCMC (Fig. 2, Left Panel). The Pilot study was the first of the three projects conducted by V-VHA from 2016 to 2020 to progressively build the evidence-based framework for the scale-up of HBV- HCV testing and linkage to care in Vietnam (Fig. 2).

The ultimate goal for the three projects was to enroll 20,000 representative adults (18 years or older) from HCMC, with a population of 9 million (HCMC census 2009). To achieve this, a multistage cluster sampling was deployed, with probability proportional to size technique. The 20,000-person enrollment was divided into 3 progressive phases. The Pilot phase representing this report had 1,000 persons. The Cornerstone phase had a total of 5,000 persons (or 4,000 additional persons to the Pilot phase). The Conquering Hepatitis via Micro-Elimination for Vietnam (CHIME for Vietnam) had a total of 20,000 persons. The sample selection procedure had 3 stages. In the first stage, 100 communal clusters were selected without replacements from a sampling frame of 322 communes in HCMC. At least two communes were chosen from each of the 24 districts in HCMC. In the second stage, at least two neighborhoods were selected from each commune with simple random sampling. If the number of households from the two neighborhoods were lower than 100, one more neighborhood would be selected to make it up. In the third stage, selection began with the first household, randomly selected from the list of households in each neighborhood, then continued to the next nearest one on the right to obtain a total of 50 households. With the expected 200 participants from each commune, two invitation letters were sent to each household,

in which we assumed had 2 adults. Any household that refused to join the study would be skipped. If the selection in the two neighborhoods did not achieve the quota, one more neighborhood would be selected to compensate.

For this Pilot report, two neighborhoods from seven selected communes were randomly selected. Invitations were sent to 200 individuals from each commune (100 households per neighborhood). A total of 1,099 of the 1,400 invited participants (79%) reported to the screening sites (commune's health clinics), answered the Knowledge Attitude and Practice (KAP) questionnaires, and agreed to phlebotomy.⁶ Of 1,099 participants, 1,014 (92%) participants completed KAP questionnaires and phlebotomy. For linkage to care, free coupons provided to the screening participants depending on the screening results. Coupons with free three-shot hepatitis B vaccine series were provided to those who had negative for all HBsAg, anti-HBs, and anti-HBcAb. Persons with HBsAg (+) and/or anti-HCV (+) were provided no-cost initial Hepatology consultation, a Fibroscan®, and further liver assessments (comprehensive metabolic panel, complete blood count, INR) as well as HBV and/or HCV viral load. Individuals with anti-HBcAb (+), HBsAg (-), and anti-HBs (+ or -) were counseled on the risks of HBV reactivation if they were to be exposed to immunosuppressive agents. Phone interviews with 96 participants (50 from the coupon receipt group and 46 without coupons) were conducted 6 months after the study to assess participants' satisfaction and the program's acceptability (Fig. 2).

In this Pilot study, we found 3.6 % (36/1,014) were positive for anti-HCV; 7.1% (72/1,014) were HBsAg (+),

evidence of current HBV infection. Anti-HCV Ab (+) participants tended to be older than those with anti-HCV Ab (-) (aged 55 ± 14.30 vs. 47 ± 15.03) ($P < 0.05$). Fourteen percent (5/36) and 25% (18/72) of the persons with anti-HCV(+) and HBsAg(+) were aware of their infection status, respectively. KAP results demonstrated that 52.5% (531/1,011) were aware that HBV or HCV is a risk factor for the development of liver cancer. Six months after receipt of screening results and free coupons, only 11% (32/287) of the eligible participants used coupons for HBV vaccination. In contrast, 14.3% (16/112) of persons with positive HBsAg and/or positive anti-HCV Ab utilized coupons to receive free clinical evaluations for HBV or HCV infection.⁶

Data from the pilot study identified at least 4 opportunities and challenges for scaling up HBV and HCV cascade of care (Table 1). First, the high response rate (79%) in the HBV-HCV screening program in community highlights the feasibility of recruiting participants in community settings. Second, interviews with 96 participants revealed great acceptability (80% or 77/96) of the program in the community. A total of 64 participants (33 in the "coupon" group vs. 31 in the "non-coupon" cohort) completed the satisfaction questionnaires. The results revealed that the inability to pay out-of-pocket for HBV-HCV screening was a significant barrier. Other barriers included a lack of knowledge and awareness about viral hepatitis and sequelae, time constraints, and lack of transportation.

There are several limitations in this Pilot study. The sample size and geographic coverage were not representative of HCMC population. Secondly, the study had unexpectedly low numbers of participants who followed up for no-cost HBV vaccine and clinical evaluations due to financial constraints and lack of knowledge concerning viral hepatitis diagnosis, treatment, and liver cancer prevention. Furthermore, the study had no comparison group for those who were invited but refused or accepted participation.

Despite these limitations, findings from this Pilot study guided the design and implementation of two larger community-based programs: the Cornerstone Program and CHIME for Vietnam. Interim reports of the Cornerstone Program revealed a high rate of HBsAg (7.6%) and anti-HCV antibody (3.48%), respectively.^{7,8} CHIME for Vietnam, started in early 2019, was a comprehensive screening and

linkage to care program that enrolled 20,000 representative adults in HCMC for HBV and HCV.

In summary, Vietnam will require large increases in hepatitis testing and linkage to care to reach goals for hepatitis elimination. The step-wise transition from the Pilot project to the Cornerstone Program and to CHIME for Vietnam emphasizes the logic and feasibility of moving from small to large scale programs in HCMC. Further, from the public health perspective, CHIME for Vietnam study will establish a framework for HBV-HCV elimination in HCMC. This framework is comprised of baseline epidemiological profiles of persons living with chronic HBV-HCV, including the true disease prevalence and baseline linkage to care. Together, these "micro-elimination programs" can guide the set up of large-scaled programs in regions of Vietnam advancing progress toward elimination of HBV-HCV.

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REFERENCES

- 1) Cooke GS, Andrieux-Meyer I, Applegate TL, et al. Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. *Lancet Gastroenterol Hepatol* 2019;4:135-184. [https://doi.org/10.1016/S2468-1253\(18\)30270-X](https://doi.org/10.1016/S2468-1253(18)30270-X).
- 2) Berto A, Day J, Van Vinh Chau N, et al. Current challenges and possible solutions to improve access to care and treatment for hepatitis C infection in Vietnam: a systematic review. *BMC Infect Dis* 2017;17:260. <https://doi.org/10.1186/s12879-017-2360-6>.
- 3) Nguyen-Dinh SH, Do A, Pham TN, et al. High burden of hepatocellular carcinoma and viral hepatitis in Southern and Central Vietnam: Experience of a large tertiary referral center, 2010 to 2016. *World J Hepatol* 2018;10:116-123. <https://doi.org/10.4254/wjv.v10.i1.116>.
- 4) Van Thi Thuy Nguyen TD, Quang NT, Masaya Kato LQ, et al. Estimates and projection of disease burden and investment case for hepatitis C in Viet Nam. *J Viral Hepatitis*, Abstract P2-065 2018. https://doi.org/10.1111/jvh.187_12923.

- 5) Van Thi Thuy Nguyen TD, Quang NT, Masaya Kato LQ, et al. Estimates and projection of disease burden and economic analysis for hepatitis B in Viet Nam. *J Viral Hepatitis*, Abstract P1-011 2018. https://doi.org/10.1111/jvh.07_12923.
- 6) Trang Pham HKT, Mize GW, Le AN, et al. Lessons for a definitive prevalence study design and scalability of comprehensive HBV-HCV screening and access to care pathways in Ho Chi Minh City (HCMC), Vietnam. *Hepatology Supplement*, Abstract 563 2017.
- 7) Pham TND, Mize GW, Phan LT, et al. Tang* and Doan Y Dao* (*Equal Contribution). Demographic and risk factors in Vietnamese patients with HBV in Ho Chi Minh City, Vietnam: a population-based seroprevalence study. *Hepatology, Supplement*, Abstract 2154 2019.
- 8) Pham TND, Dao DVB, Phan L, et al. The burden of and barriers to care for hepatitis C virus (HCV) in Ho Chi Minh City, Vietnam: a comprehensive population-based prevalence study. *Hepatology Supplement*, Abstract 991 2020.