Title

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Demonstration of a population-based HCV serosurvey in Ho Chi Minh City, Viet Nam: Establishing baseline prevalence of and continuum of care for HCV micro-elimination by 2030

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Summary

Background A baseline of hepatitis C virus (HCV) burden and other HCV epidemiological profiles is necessary for HCV micro-elimination in Ho Chi Minh City (HCMC), Viet Nam. This study aimed to determine HCV exposure and prevalence of HCV viremia as well as the proportion of HCV testing and treatment uptake among participants.

Methods From 2019 to 2020, the probability proportionate to size sampling method was deployed to representatively invite approximately 20,000 adults (18 or older) throughout HCMC to free screening and linkage to care for HCV.

Findings In HCMC, the weighted prevalence of anti-HCV was 1·3% (95% CI, 1·1%-1·6%). Individuals born from 1945 to 1964 had the anti-HCV prevalence of 3·6% (95% CI, 3·0%-4·2%) and represented 40·4% of all HCV cases. There were wide variations in anti-HCV prevalence in HCMC, including variations between districts, risk factors, and socioeconomic statuses. A baseline HCV continuum of care for the city demonstrated that only 28·5% (85/298, 95%CI 23·4-33·7%) of persons with anti-HCV (+) were aware of their HCV status, with 77.6% (66/85, 95%CI 68·8-86·5%) diagnosing HCV incidentally, 82·7% (62/75, 95%CI 74·1-91·2%) initiating anti-HCV therapy, and 53.6% (30/56, 95%CI 40·5-66·6%) achieving HCV cures.

Interpretation There remains a considerable disease burden of HCV in HCMC of which a significant proportion was in the age group born between 1945 to 1964. Additionally, there were significant gaps in HCV awareness, screening, and access to care in the community in Viet Nam. Thus, future interventions must have pragmatic targets, be tailored to the local needs, and emphasise screening.

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Keywords: Hepatitis C virus; Ho Chi Minh City (HCMC); Viet Nam; Framework; Micro-elimination; National elimination; 2030; Access to care; HCV screening; HCV baseline linkage to care

Research in context

Evidence before this study

As of October 10, 2021, we searched PubMed, MEDLINE, and Embase for publications written in English or Vietnamese using the keywords, "HCV micro-elimination," "framework for HCV," "framework for HCV micro-elimination," "viral hepatitis micro-elimination," and "Viet Nam." We found no article leveraging the micro-elimination concept in infectious disease to develop baseline data for HCV elimination in Viet Nam.

Added value of this study

This study was the first in Viet Nam to use the micro-elimination concept in infectious disease to establish a baseline for HCV elimination in Ho Chi Minh City (HCMC). HCMC had a population of nine million and represented a microcosm of Viet Nam. The micro-elimination framework relies on accurate prevalence, access-to-care data, and other unique epidemiological characteristics of HCV in HCMC. Future national or city governments can leverage this data to deliver targeted elimination strategies for HCV in HCMC.

Implications of all the available evidence

By providing the real-life data for an HCV micro-elimination framework in a large city such as HCMC, we demonstrated the feasibility of a large-scale comprehensive screening and access-to-care program for HCV elimination in a low- to middle-income country, Viet Nam. Additionally, the study was coordinated by a multi-sector collaboration, including government, public medical institutions, non-profit organisations and civil society, and private sector. Both the HCV micro-elimination framework of HCMC and the multi-partner approach can be adopted into Viet Nam's national and provincial health departments for national HCV elimination strategies in Viet Nam. Furthermore, the overall process deserves to be assessed in other resource-limited HCV endemic countries.

Introduction

Chronic liver disease caused by hepatitis C virus (HCV) remains a significant global public health problem, afflicting approximately 71 million people worldwide.[1] In 2016, the global elimination targets for HCV set by the World Health Organisation (WHO) were 90% of those infected diagnosed, 80% of those eligible treated, 90% reduction in the incidence of new infections, and 65% reduction in liver-related mortality by 2030.[1,2] In 2020, Razavi et al. reported that, among 45 high-income countries, only nine are on track to eliminate HCV by 2030, while three more countries are on track for elimination by 2040. The rest expect to eliminate HCV by 2050 or beyond.[3] In low- to middle-income countries, gaps in HCV elimination progress lag even more staggeringly behind the WHO's targets.[4] Such gaps include the lack of available national epidemiological data, effective national policy, and multi-disciplinary implementation programs for viral hepatitis.

Viet Nam is a lower-middle-income country in Southeast Asia and has an estimated population of 96 million.[5] In a systematic review, Berto et al estimated that, among the general population in Viet Nam, the prevalence of anti-HCV was 1·0% to 4·7%.[6] Data input in this review were mostly based on small-scale, focused, retrospective studies. Similar to the national viral hepatitis profiles, HCMC, with a diverse population of nine million,[5] has no representative, citywide data on HCV disease prevalence or identifiable gaps in the HCV cascade of care to be addressed to promote HCV elimination.

A pragmatic approach in HCV elimination is to break down elimination goals into smaller goals for specific populations or geographic areas. As a result, treatment interventions can be delivered using targeted methods. This concept is known as "micro-elimination".[7] Pursuing micro-elimination has been demonstrated successfully in the treatment of HIV and has recently been promoted for HCV elimination.[7] A valid and successful micro-elimination program is based on reliable epidemiological data, including baseline gaps in the cascade of care to be overcome and monitored, and active involvement of all the stakeholders.[7]

A unique characteristic of HCV in the United States (US) was the discovery of a unique birth cohort (e.g. persons born between 1945 and 1965), that represented 75% of all chronic HCV infections and created a straightforward target for routine HCV screening in the US. Birth cohort-based HCV prevention was the US national standard, endorsed by both the US Centers for Disease Control and Prevention in 2012 and the US Preventive Services Task Force in 2013. Subsequently, birth cohort screening followed by treatment represented an important and cost-effective strategy that has been well documented.[8] Similar to the US birth cohort phenomenon, whether Vietnamese who lived during the Viet Nam War (birth cohort of 1945-65) also exhibited a higher prevalence of HCV infection remained to be determined.

To pave the foundation to achieve the national goals of HCV elimination in Viet Nam,[9] we selected HCMC to establish a baseline assessment to promote HCV

micro-elimination. Specifically for this study, we aimed to determine accurately the prevalence of HCV infection in adult residents (18 years or older) and define the unique baseline epidemiological profiles of HCV with a focus on the cascade of care, in HCMC.

Methods

Study setting and design

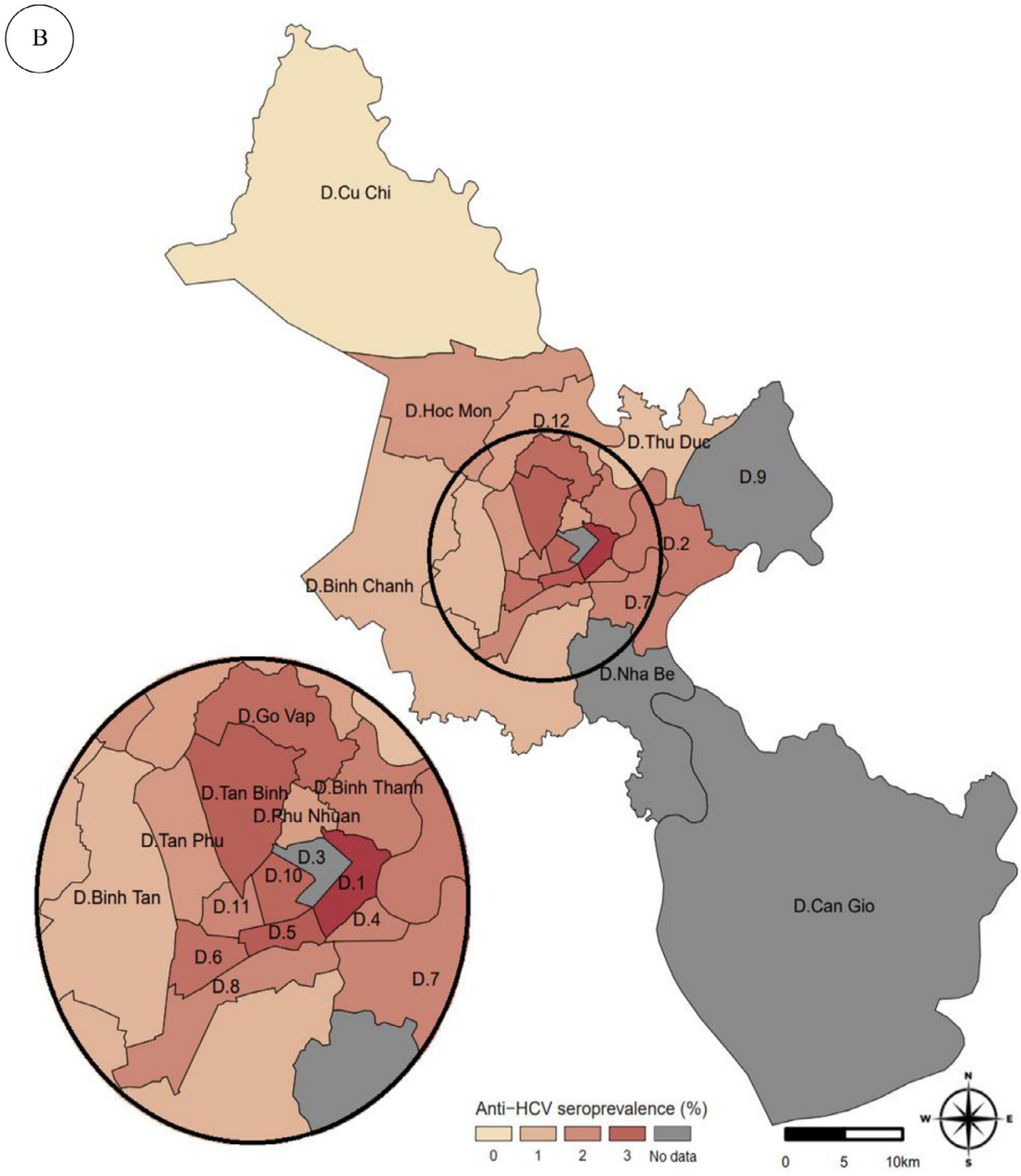
HCMC is located in Southern Viet Nam, with approximately nine million residents in 2019 (Figure 1, ***Panel A***). HCMC is divided into one municipal city, 16 urban districts, and five rural districts, further subdivided into 322 administrative units at the commune level (i.e., 259 wards, 58 communes, and five townlets). HCMC was selected to conduct the study because we have established a track record and infrastructure in the city.

Using multistage cluster sampling, a cross-sectional, representative seroprevalence survey for HCV, with care access coordination, was conducted in HCMC from June 2019 to July 2020. The calculated sample size of 20,000 was adequately powered to estimate the prevalence of anti-HCV in the population. Based on the prevalence of anti-HCV (+) of 3% (95% CI, 2·5%–3·5%) discovered in our prior study[10] and a precision of 0.5%, a sample size of 4,470 participants was required. The sample size estimate was multiplied by 2·5 to account for the design effect of the cluster sampling method and an experience-driven non-response rate of 40%, giving a total estimated sample size of 18,625 participants. The sample was further expanded to 20,000 to allow for potential survey attrition.

The eligibility criteria included adults 18 years or older living in HCMC for at least six months before study entry, irrespective of their knowledge of having active HCV infection or HCV-related sequelae. Participants were excluded if they did not finish all the assessments or were not in the invitation list in the pre-screening stage.

Figure 1. Panel A: ***Map of Viet Nam (red shape) and Ho Chi Minh City (encircled)***.

Panel B: ***Wide variations of anti-HCV prevalences among districts in Ho Chi Minh City, Viet Nam***. The highest prevalence was found in District 1 (3·9%) and the lowest was in District Cu Chi (0·0%). Generally, anti-HCV prevalence was higher in the urban districts (encircled and labelled districts and District 12) than in the suburban districts (District Thu Duc, District 2) and the rural districts (District Cu Chi, Hoc Mon, Binh Chanh). No data was available for District 3, 9, Nha Be, and Can Gio due to early termination.



Note: D.1, District 1; D.Go Vap, District Go Vap; HCV, hepatitis C virus

Figure 1 Continued.

The sample selection procedure had three stages (Figure 2). In the first stage, by applying proportionate to size sampling (PPS), 100 communes were selected without replacements from the sampling frame of 322 communes in HCMC Population Census in 2009. At least two communes were selected from each district of the 24 districts in HCMC. In the second stage, at least two neighbourhoods were chosen with simple random sampling from each commune based on a list of neighborhoods provided by the local administrative government.

In the third stage, selection began with conveniently choosing the first household in the block where the local field coordinators live and then continued door-to-door to the next nearest household on the right until a total of 50 households was obtained. With the expected 200 participants from each commune, two invitation packages were sent out to each household. Two adults from

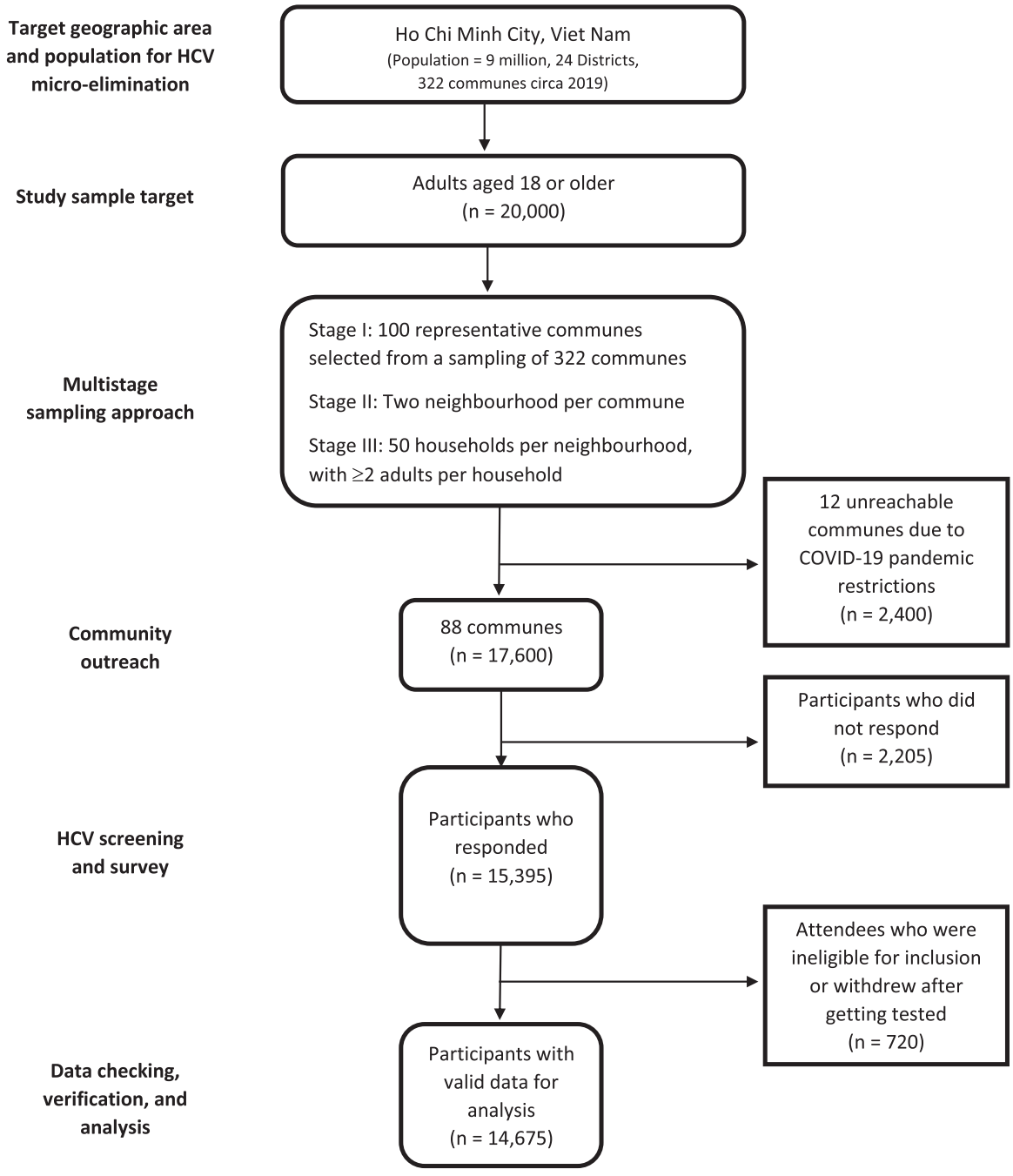


Figure 2. Overview of study sampling frame and participant recruitment.

each household were invited to the screening events. Family members of different genders and ages were encouraged to report to the screening events. Any household that refused to join the study would be skipped. If the two neighbourhoods selected did not achieve the quota, one more neighbourhood would be selected to compensate with the same randomised method.

Study procedures

We hereby outline the study procedures. For further details, please refer to ***Appendix A*** of the Methods.

In the pre-screenings stage, through a priori protocol and under the guidance of a local field coordinator, trained outreach teams visited each household to introduce the study and deliver the invitation package (i.e., invitation letters, study introduction leaflet, consent

forms and survey questionnaire). Prospective participants were encouraged to fill out the questionnaire at home by themselves; those who did not understand or fill out the questions were able to get help during the screening events. In the screening stage, invited screening participants who agreed to the screenings at the communal health station were verified using their personal information and national identifications. Participants had their blood drawn by a certified phlebotomist and provided further consent if they agreed to have their blood stored on the screening day, irrespective of screening results.

In the post-screening and linkage-to-care stage, depending on the screening results, result interpretation, recommendations and provisions for follow-up and management were sent in sealed packages to participants' homes via shipping services. Recommendations were "Further examination needed to confirm HCV infection status and treatment eligibility. You may transmit the disease to others" for those with positive anti-HCV result or "No further examination needed. Protect yourself against HCV infection" for those with anti-HCV (-). Individuals with anti-HCV (+) who had archived sera (n=233) were subsequently tested for HCV RNA. For all confirmed HCV RNA (+), depending on their insurance status, they received one of the two coordination services for clinical management accordingly.

Data collection

The data collected through self-administered paper-based questionnaires included personal information, socio-demographics, medical history, hepatitis B virus (HBV) co-infection, and risk factors for HCV infection. The risk factors for HCV infection included blood transfusion, tattooing, drug abuse, sharing needles, immunosuppression therapy, dialysis, commercial sex, self-identified Lesbian-Gay-Bisexual-Transgender (LGBT), using a condom, and living with those infected with viral hepatitis. Most of these items were answered with "Yes," "No," and "Don't know." For those answering that they had blood transfusions, the questionnaires asked for the time of the first transfusion. The questionnaires, including known risk factors for HCV, had been validated from the previous studies.[11]

All specimens were screened for anti-HCV (Elecsys® Anti-HCV II, Roche Diagnostics) and confirmed by HCV RNA (COBAS® AmpliPrep/COBAS® TaqMan® assays, Roche Diagnostics) if anti-HCV was positive. The anti-HCV status was defined as positive or reactive (COI ≥1.00), negative or non-reactive (COI <0.90), and border (0.90 ≤ COI <1.00)). Those with positive or "border" anti-HCV results who consented to have additional stored blood were further quantitatively tested for HCV RNA. HCV RNA results were then classified as positive (HCV RNA ≥ 15 IU/mL) or negative (HCV RNA <15 IU/mL). Lab results were reviewed and approved by a certified medical doctor at MMC and sent to participants within four weeks after screening.

Baseline HCV continuum of care (CoC) construct

The construct was based on questionnaires at the point of survey. The result of the anti-HCV test was used to form the first stage of CoC, while answers to the questions such as "Are you infected with HCV?", "Have you received any treatment?", and "Have you been cured?" were used to build the second, third, and fourth stages of CoC, respectively. Non-response to a question was classified as missing cases for that stage.

The detailed definitions for the four steps are defined as follows:

1. *Anti-HCV Ab positive:* The number of participants with positive HCV antibody screening at the study entry.
2. *Aware of HCV status:* The number of participants with positive anti-HCV who reported being infected with HCV before the study entry.
3. *Initiated treatment:* The number of participants with positive anti-HCV who reported being infected with HCV and had initiated anti-viral therapy.
4. *Cured:* The number of participants with positive anti-HCV who reported that they had been infected with, treated for, and cured of HCV.

Data management and statistical analysis

Data management was shown in detail in ***Appendix B***. Data cleaning and de-identifying were done in STATA before exporting data for further analysis. Data analysis was performed in R (Version 4.0.5).

To ensure the prevalence of HCV infection representing the HCMC population, the sample was expanded and calibrated in terms of the size and characteristics of the HCMC population. Initially, expansion weight (design-based weight), based on PPS sampling design, was calculated for each commune (PSU, Eq. (1) below). After that, each observation was applied to the expansion weight by the commune in which they lived.

$$d_i = \frac{U}{m * n_i} \quad (1)$$

which:

- d_i: expansion weight for commune (PSU) ith
- U: universal population = Population of HCMC in Census 2009 (filtering adults ≥ 18 years old)
- m: number of communes (PSUs) were selected
- n_i: number of individuals was selected in commune (PSU) ith

Next, the base weights were adjusted for non-response and early study termination. Non-response

weights were calculated as the expected number of participants in each commune divided by observed values. Early termination weights were calculated as the expected number of communes divided by observed values. The adjusted base weights were the product of base weights, non-response weights and early termination weights. Then, the adjusted base weight was applied to each observation.

The following step is the calibration for demographic factors. It was separately calculated in each stratum created by cross-tabulating gender and age group (Eq. (2)). Then, each observation was applied to the calibrated weight by their gender and age.

$$c_j = \frac{U_j}{E_j} \quad (2)$$

which:

- c_j: calibrated weight for stratum *j*th
- U_j: population of HCMC in Census 2019 for stratum *j*th
- E_j: estimated population of stratum *j* based on expansion weight

Lastly, the final weight was the product of expansion weight and calibrated weight (Eq. (3)).

$$w_k = d_i * c_j \quad (3)$$

which:

- w_k: weight values for participant *k* who lives in commune *i* and has demographic characteristics similar to stratum *j*
- d_i: expansion weight for commune (PSU) *i*th
- c_j: calibrated weight for stratum *j*th

For descriptive analysis, weighted frequency and prevalence were calculated. Risk factor responses were dichotomised into: "Yes" or "No/Don't know." Bivariate analyses were done to guide covariate selection for multiple logistic regression. Multiple logistic regression was applied to find independent factors associated with the anti HCV(+) status. Only risk factors for HCV infection were included in multiple regression models as an exposure variable, regardless of their statistical significance in univariate analysis.

Variables were considered potential confounders if they were (1) risk factors of OR associated with anti-HCV positivity with a *p*-value less than 0·20 *AND* (2) associated with the risk factor in the main model with a *p*-value less than 0·20.[12] The "Forward selection" strategy was applied to select confounders for adjustment.[12] Adjustment began with age and sex; then confounders were added one by one to the model. At each step, we added the confounder that makes the most difference among those not yet added. The process stops when variables make less than a 10% difference in the main model effect. The significance level for hypothesis testing was set at 0·05. Missing data were assumed completely at random and not imputed.

Ethics approval

The study was approved by the institutional review boards at Pham Ngoc Thach University of Medicine, HCMC, Viet Nam (Approval No. 2169 DHYKPNT-NCKH, 06/07/2019 and No. 008/HDDD, 01/04/2019) and HCMC Department of Health, HCMC, Viet Nam (Approval No. 3110/SYT-NVY, 06/14/2019).

Role of the funding sources

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Results

The target population invited to the study included 88% (17,600 of 20,000) of persons 18 or older from 88 of 100 cluster sites in HCMC. The high response rate may be partially influenced by the incentive of $2.50 USD given to each screening participant who completed the screening and surveying process. Twelve clusters could not be reached due to the COVID-19 restrictions in Viet Nam since early 2020. Subsequently, 83·4% (14,675 of 17,600) had completed the multi-step screening survey and phlebotomy and were included in the final analysis (Figure 2).

The characteristics of the study participants and weighted prevalence of anti-HCV positivity are shown in Table 1. Females made up 67·7% (9,941 of 14,675) of the participants, 77·1% (11,311 of 14,675) were living in urban districts, and 54·1% (7,934 of 14,675) of the participants were 50 years or older. The weighted prevalence of anti-HCV positivity was 1·3% (95% CI, 1·1%-1·6%), corresponding to 298 of the 14,675 adults enrolled and included in the study analysis. Of the 298 adults with anti-HCV (+) who enrolled in the study, 78·2% (233 of 298) agreed to have their serum stored for HCV RNA testing, of whom 50·6% (118 of 233) were positive. In

Characteristic	Participants, n	Anti-HCV positivity		
		Frequency	Weighted frequency	Weighted prevalence, % (95% CI)
Overall	14,675	298	95,438	1·3 (1·1, 1·6)
Age group				
18-30	1538	2	4125	0·2 (0·0, 0·4)
31-40	1997	23	22,031	1·3 (0·7, 2·0)
41-50	3206	30	15,690	1·2 (0·7, 1·7)
51-60	4002	83	20,052	2·2 (1·6, 2·7)
61-70	2960	125	22,427	4·5 (3·6, 5·4)
>70	972	35	11,113	4·2 (2·0, 6·3)
Gender				
Female	9941	155	31,668	0·8 (0·6, 1·1)
Male	4734	143	63,770	1·8 (1·4, 2·3)
Residence[a]				
Urban districts	11,311	256	82,249	1·5 (1·2, 1·8)
Suburban districts	1238	15	5803	0·7 (0·1, 1·3)
Rural districts	2126	27	7385	0·8 (0·4, 1·2)
Ethnicity				
Kinh	13,493	265	84,610	1·3 (1·0, 1·5)
Chinese	1062	30	7850	1·5 (0·8, 2·2)
Others	81	2	2735	3·6 (0·0, 10·1)
(Missing)	39	1	243	
Employment				
No	6133	156	44,277	1·7 (1·2, 2·2)
Yes	8348	138	51,161	1·1 (0·8, 1·4)
(Missing)	194	4	641	
Marital status				
Single/separated/divorced/widowed	4491	100	32,062	1·1 (0·7, 1·4)
Living together/married	10,123	197	63,134	1·5 (1·2, 1·8)
(Missing)	61	1	243	
Education level				
No formal education	2080	60	16,499	2·6 (1·5, 3·8)
Elementary graduate	3084	73	25,760	2·5 (1·7, 3·3)
Secondary graduate	3766	74	27,054	1·7 (1·1, 2·3)
High school graduate	3263	61	16,045	0·9 (0·6, 1·2)
Undergraduate/graduate/postgraduate	2396	29	9837	0·5 (0·2, 0·7)
(Missing)	86	1	243	
Income level[b]				
No Income	4795	121	32,557	1·6 (1·1, 2·1)
< $ 303 USD/month	7330	131	39,175	1·1 (0·9, 1·4)
≥ $ 303 USD/month	2196	24	17,333	1·1 (0·5, 1·6)
(Missing)	354	22	6373	
Health insurance				
No	1940	29	11,976	0·9 (0·4, 1·4)
Yes	12,496	265	83,462	1·4 (1·1, 1·7)
(Missing)	239	4	498	
Personal history of liver cancer or cirrhosis				
No	14,292	281	92,818	1·3 (1·0, 1·5)
Yes	37	11	2620	16·9 (1·6, 32·3)
(Missing)	346	6	1099	
Personal history of ≥ 1 non-communicable conditions[c]				
No	8930	158	58,875	1·1 (0·8, 1·3)
Yes	5528	136	36,563	2·2 (1·7, 2·7)
(Missing)	217	4	866	

Table 1 *(Continued)*

Characteristic	Participants, n	Anti-HCV positivity		
		Frequency	Weighted frequency	Weighted prevalence, % (95% CI)
Overweight or obesity[d]				
No	6346	133	43,805	1·2 (0·9, 1·5)
Yes	8269	164	51,633	1·4 (1·1, 1·8)
(Missing)	60	1	253	
Heavy drinking[e]				
No	12,376	243	78,963	1·2 (0·9, 1·5)
Yes	1142	26	16,475	1·8 (1·0, 2·6)
(Missing)	1157	29	10,871	
Smoking history				
No	11,431	193	51,940	0·9 (0·7, 1·1)
Yes	2832	96	43,498	2·7 (1·9, 3·6)
(Missing)	412	9	1988	
Anti-HBcT status				
Negative	6087	87	35,742	0·9 (0·6, 1·1)
Positive	8588	211	59,696	1·9 (1·5, 2·3)
History of blood transfusion				
No	13,510	248	81,000	1·2 (1·0, 1·4)
Yes	783	45	11,819	3·5 (2·1, 4·9)
Don't know	98	0	0	-
(Missing)	284	5	2619	
First time receiving blood transfusion				
Before 1992	108	11	2255	9·7 (3·0, 16·3)
1993 to 2006	143	10	2616	5·1 (1·6, 8·7)
2007 to 2013	103	5	1072	2·1 (0·0, 4·2)
2014 until now	168	3	477	0·5 (0·0, 1·1)
Unknown	261	16	5400	4·5 (1·1, 7·9)
History of tattoo(s)				
No	11,350	222	68,284	1·1 (0·9, 1·4)
Yes	3083	73	26,231	2·2 (1·5, 2·8)
(Missing)	242	3	923	
History of intravenous drug abuse				
No	14,251	280	87,355	1·2 (1·0, 1·5)
Yes	227	16	7560	6·0 (2·2, 9·8)
Don't know	21	0	0	-
(Missing)	176	2	523	
History of sharing needles				
No	14,439	291	93,302	1·3 (1·1, 1·5)
Yes	64	4	1579	6·0 (0·0, 13·3)
Don't know	25	0	0	-
(Missing)	147	3	557	
History of immunosuppression therapy or chemotherapy or corticosteroid				
No	12,370	232	76,327	1·2 (0·9, 1·4)
Yes	536	15	4697	3·0 (0·9, 5·1)
Don't know	1541	46	13,553	2·7 (1·7, 3·8)
(Missing)	228	5	861	
History of having renal dialysis				
No	14,484	291	95,131	1·3 (1·0, 1·5)
Yes	21	2	307	6·0 (0, 14·4)
(Missing)	170	5	1819	
History of having sexual intercourse with sex workers				
No	14,266	290	92,678	1·3 (1·1, 1·6)
Yes	70	0	0	-

Table 1 *(Continued)*

Characteristic	Participants, n	Anti-HCV positivity		
		Frequency	Weighted frequency	Weighted prevalence, % (95% CI)
Don't know	185	4	1839	1·8 (0·0, 4·0)
(Missing)	154	4	921	
Self-identification as LGBT				
No	14,429	295	94,968	1·3 (1·1, 1·6)
Yes	67	1	151	0·3 (0·0, 0·8)
(Missing)	179	2	318	
Use of condom during sexual intercourse				
No	11,725	259	77,062	1·5 (1·2, 1·8)
Sometimes	1471	20	8416	0·8 (0·3, 1·4)
Often	689	9	5560	1·0 (0·2, 1·7)
Don't know	44	1	327	1·2 (0·0, 3·7)
(Missing)	746	9	4072	
Living with person(s) infected with HBV/HCV				
No	1672	37	12,418	1·7 (1·0, 2·3)
Yes	364	13	3407	2·3 (0·7, 3·9)
Don't know	242	7	1916	1·7 (0·0, 3·4)
(Missing)	12,397	241	77,697	

***Table 1*: Prevalence of anti-HCV positivity by demographics and risks factors in Ho Chi Minh City, Viet Nam.**
AntiHBcT, anti-hepatitis B virus core total antibody; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; LGBT, Lesbian, Gay, Bisexual, and Transgender; 95% CI, 95% Confidence Interval.
[a] Suburban districts represent District 2, District 9, and Thu Duc district; rural districts represent Binh Chanh district, Nha Be district, Cu Chi district, Can Gio district, Hoc Mon district; urban districts represent the remaining districts.
[b] VND-USD conversion rate: 23102·31 (20/06/21).
[c] Non-communicable disease includes diabetes, hypertension, hypercholesterolemia, nonalcoholic steatohepatitis.
[d] Overweight or obese were defined as BMI > 23·0 as per Asian definition.
[e] Heavy drinking was defined as having AUDIT-3 score ≥ 5 in male and ≥ 4 in female.

the remaining group (*n*=115) who had anti-HCV (+) but negative HCV RNA, 39·1% (45 of 115) reportedly underwent DAA treatment for HCV.

There are wide variations in anti-HCV prevalences within HCMC, including variations between the age groups, districts, immigration status, and socioeconomic standings. Figure 3 shows anti-HCV positivity by year of birth and gender. Notably, the birth cohort born from 1945 to 1964 had a prevalence of anti-HCV (+) of 3·6% (95% CI, 3·0%-4·2%) and represented 40·4% of all HCV cases in HCMC. The seroprevalence reached the highest level at 6·6% (95% CI, 4·0%-9·1%) in males and 3·5% (95% CI, 2·1%-4·9%) in females born during 1950–1954. The other peak was at 3·0% (95% CI, 1·0%-4·9%) in the male birth cohort born from 1980 to 1984.

People with a history of blood transfusion, renal dialysis, advanced liver diseases, intravenous (IV) drug use, needle sharing, and/or tattoos had a 2·0% or higher anti-HCV prevalence. Moreover, the prevalence of anti-HCV positivity was 1·5% (95% CI, 2·2%-2·9%) in urban districts and was 0·7% (95% CI, 0·1-1·3) in suburban districts and 0.8% (95% CI, 0·4-1·2) in rural districts (Table 1). The detailed variations of anti-HCV positivity among districts are presented in Figure 1, **Panel B**. Briefly, District 1, an urban district, was the epicentre of HCV infection with the highest seroprevalence of 3·9% (95% CI, 1·9%-5·9%). Surrounding District 1 includes District 5, District 10, and Tan Binh District, which had a seroprevalence of around 3%.

Table 2 illustrates the crude and adjusted odds ratios of positive anti-HCV across selected variables. Although risk factors such as a history of renal dialysis, taking immunosuppression therapy, or having partners infected with viral hepatitis B or C was associated with an increased likelihood of having positive anti-HCV, the adjusted associations were not statistically significant. After adjusting for confounding, history of blood transfusion, tattoo(s), and IV drug use were significantly associated with HCV (+) status.

Figure 4 shows the flows of patients across the questionnaire-based cascade of testing and access to care. Seventy-eight per cent (233/298) of the participants with positive anti-HCV agreed to have sera archived. Among 298 study participants with positive anti-HCV results, only 28·5% (85 of 298, 95%CI 23·4-33·7%) reported knowing HCV prior to the study entry. Of those, 7·1% (6 of 85, 95%CI 1·6-12·5%) were aware of HCV after experiencing jaundice, whereas 77·6% (66 of 85, 95%CI 68·8-86·5%) were coincidentally diagnosed in routine health check-ups or doctor visits for different health problems. Of those aware of HCV disease, 82·7% (62 of 75, 95%CI 74·1-91·2%) initiated

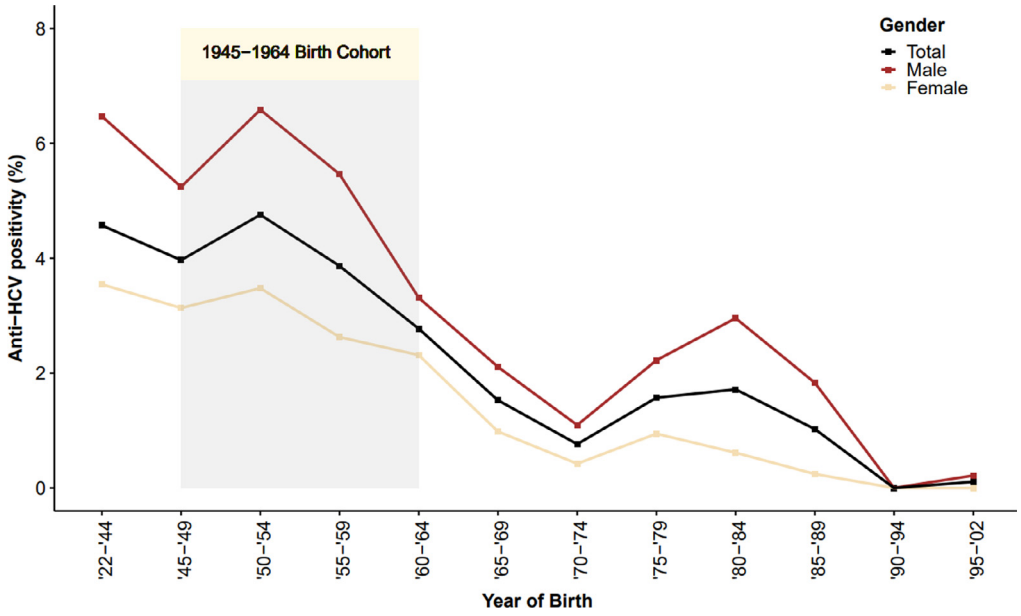

Figure 3. HCV prevalence by age and gender and the birth cohort (1945-1964) phenomenon in Ho Chi Minh City, Viet Nam. Generally, the prevalence in males was over two times higher than in females (1·8% vs 0·8%).

Note: Shaded area highlights those born during 1945−1964, with the prevalence ranging from 2·8% (those born during 1960−1964) to 4·8% (those born during 1950−1954).

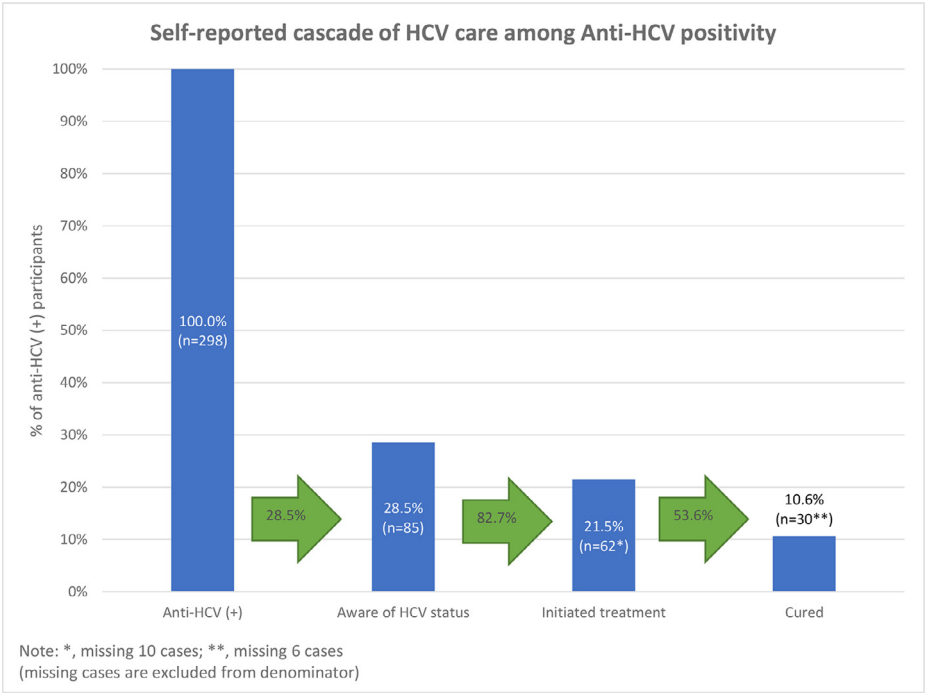

Figure 4. HCV self-reported cascade of care in Ho Chi Minh City, Viet Nam. The chart represents participants who had laboratory evidence of exposure to HCV and sought health care for HCV diagnosis and treatment.

Characteristic	OR	95% CI	*p*-value	aOR	95% CI	*p*-value
Age group						
18-30	..	..		..	..	
31-40	8·5	1·9, 38·9	**0·007**	..	..	..
41-50	7·9	1·8, 35·7	**0·009**	..	..	..
51-60	14·2	3·6, 56·0	**<0·001**	..	..	..
61-70	30·1	7·9, 115·2	**<0·001**	..	..	..
>70	27·7	6·0, 128·8	**<0·001**	..	..	..
Gender						
Female	..	..		..	..	
Male	2·2	1·6, 3·1	**<0·001**	..	..	..
Residence[a]						
Urban districts	..	..		..	..	
Suburban districts	0·5	0·2, 1·2	0·111	..	..	..
Rural districts	0·5	0·3, 0·9	**0·021**	..	..	..
Ethnicity						
Kinh	..	..		..	..	
Chinese	1·2	0·7, 2·0	0·450	..	..	..
Others	3·0	0·5, 17·9	0·243	..	..	..
Income level[b]						
No Income	..	..		..	..	
< $ 303 USD/month	0·7	0·5, 1·0	0·063	..	..	..
≥ $ 303 USD/month	0·7	0·4, 1·2	0·170	..	..	..
Employment						
No	..	..		..	..	
Yes	0·7	0·5, 0·9	**0·025**	..	..	..
Marital status						
Single/separated/divorced/widowed	..	..		..	..	
Living together/married	1·4	0·9, 2·0	0·113	..	..	..
Education level						
No formal education	..	..		..	..	
Elementary graduate	1·0	0·6, 1·6	0·856	..	..	..
Secondary graduate	0·6	0·4, 1·1	0·138	..	..	..
High school graduate	0·3	0·2, 0·5	**<0·001**	..	..	..
Undergraduate/graduate/postgraduate	0·2	0·1, 0·3	**<0·001**	..	..	..
Health insurance						
Yes	..	..		..	..	
No	0·6	0·3, 1·1	0·130	..	..	..
Anti-HBcT status						
Negative	..	..		..	..	
Positive	2·2	1·5, 3·1	**<0·001**	..	..	..
History of blood transfusion						
No/Don't know	..	..		..	..	
Yes	3·0	2·0, 4·6	**<0·001**	2·4	1·6, 3·7	**<0·001**
History of renal dialysis						
No	..	..		..	..	
Yes	4·9	1·1, 21·4	**0·038**	1·2	0·2, 7·4	0·835
History of immunosuppression therapy or chemotherapy or corticosteroid						
No/Don't know	..	..		..	..	
Yes	2·4	1·2, 5·0	**0·021**	1·4	0·7, 2·9	0·338
History of tattoo(s)						
No/Don't know	..	..		..	..	
Yes	1·9	1·4, 2·6	**<0·001**	3·0	2·0, 4·6	**<0·001**

Table 2 *(Continued)*

Characteristic	OR	95% CI	*p*-value	aOR	95% CI	*p*-value
History of intravenous drug abuse						
No/Don't know	..	..		..	..	
Yes	5·2	2·6, 10·1	**<0·001**	2·2	1·1, 4·8	**0·040**
History of sharing needles						
No/Don't know	..	..		..	..	
Yes	4·9	1·4, 17·1	**0·016**	1·0	0·3, 3·7	0·997
Self-identification as LGBT						
No/Don't know	..	..		..	..	
Yes	0·2	0·0, 1·5	0·124	0·4	0·1, 2·4	0·297
Use of condom during sexual intercourse						
Yes	..	..		..	..	
No/Don't know	1·7	1·0, 2·9	0·064	1·1	0·6, 1·9	0·849
Having partner(s) infected with HBV/HCV						
No/Don't know	..	..		..	..	
Yes	1·4	0·7, 3·0	0·393	1·5	0·7, 3·3	0·70

***Table 2*: Association of anti-HCV positivity with HCV related factors in HCMC.**
AntiHBcT, anti-hepatitis B virus core total antibody; aOR = adjusted odds ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; LGBT, Lesbian, Bisexual, Gay, Transgender; OR, odds ratio; 95% CI, 95% Confidence Interval.
[a] Suburban districts represent District 2, District 9, and Thu Duc district; rural districts represent Binh Chanh district, Nha Be district, Cu Chi district, Can Gio district, Hoc Mon district; urban districts represent the remaining districts.
[b] VND-USD conversion rate: 23102·31 (20/06/21).

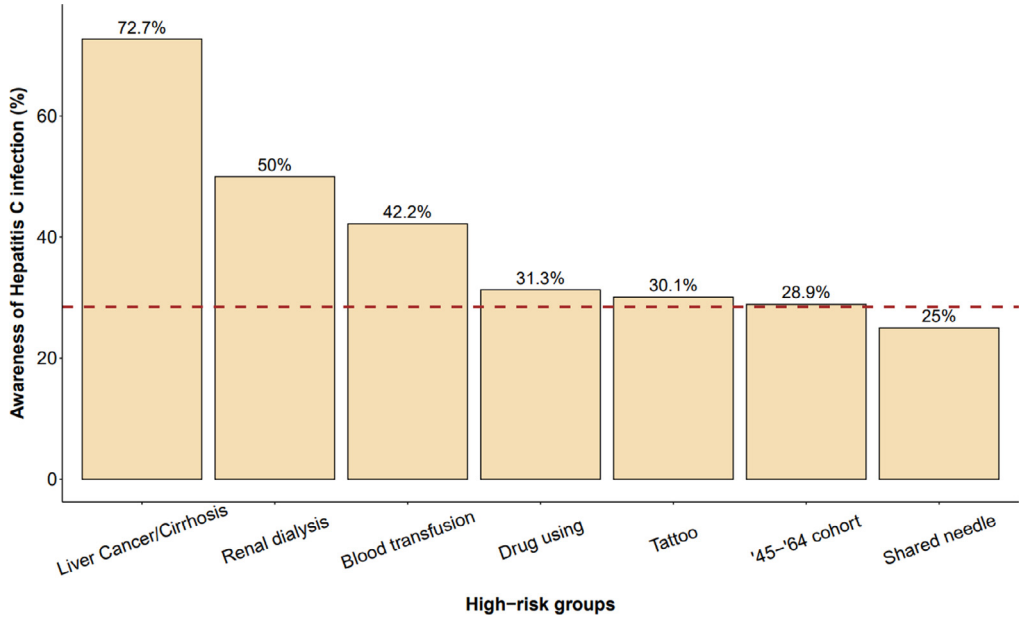

Figure 5. Proportions of HCV infection awareness among high-risk subgroups who had positive anti-HCV. "Aware of HCV status" was defined as the number of participants with positive anti-HCV who reported that they had been infected with HCV before the study entry. Generally, there was a variation in proportions of awareness among high-risk groups for HCV transmission. In the healthcare setting-related groups, 50% of dialysis patients and 42·2% of blood transfusion recipients knew their HCV status. The proportions in those who had high-risk behaviours (drug use, tattooing, shared needle) ranged from 25% to 31·3%, while 28·9% of the 1945-1965 birth cohort. Those having liver cancer or cirrhosis had the highest rate of 72·7%.

Note: The dashed line is a reference and represents 28·5%, which was the average rate of awareness of the study sample.

treatment and 53·6% (30 of 56, 95%CI 40·5-66·6%) had been cured. Among the self-reported cases with HCV cure, 87·5% (21 of 24) were verified to have negative HCV RNA by studying HCV RNA testing results using the archived sera.

The proportions of awareness of HCV status by high-risk subgroups were further elaborated in Figure 5. Those with a history of drug abuse, sharing a needle, tattoos, or those born during 1945-1964 had HCV awareness proportions of around 30% or lower.

Discussion

The overall goal of our study was to establish a baseline for HCV elimination representing a large geographic area in Viet Nam. The results, in turn, can promote national HCV elimination goals in the country. We leveraged the micro-elimination concept that has been successfully demonstrated in HIV and tuberculosis for this HCV baseline assessment.[7] To implement the study, we selected HCMC because we have established a track record and infrastructure to conduct the study. Herein, we further described the HCV epidemiological profiles and discussed strategies that stakeholders could use to leverage this framework for HCV elimination in Viet Nam.

We found that the population-based seroprevalence (i.e., anti-HCV (+)) was 1·3% (95% CI, 1·9-2·6%). By comparison, the US, Japan, India, or Indonesia reported an HCV prevalence to be 1·0%, 2·3%, 0·9%, and 2·1%, respectively.[13,14] Overall, this prevalence corroborates WHO's modelling estimates[15] and the expected decreasing trends in HCV infection nationwide and citywide.[15–17] Interestingly, within HCMC, the prevalence of anti-HCV (+) varied among districts, ranging from 0·0% in District Cu Chi to 3·9% (95% CI, 1·9-5·8%) in District 1, a central district. The discovery of variations in anti-HCV (+) prevalence among the districts may be important to tailor future targeted interventions to a specific area for the most cost-effective outcomes. Thus, further research may need to be conducted to quantify and attribute underlying factors for the variations, of which individual and community factors may play a role.[18]

The HCV viraemic proportion among the persons with anti-HCV (+) was 50·6%. However, the viremic proportion could have been 70·0% (163/233) if we had considered individuals who reportedly underwent direct-acting agent (DAA) treatment before the study enrollment. This large proportion of individuals who had already been treated for HCV before the study entry may explain the low HCV viremic prevalences in previous studies in Viet Nam.[19,20] Provided with the prevalence of anti-HCV (+) and HCV RNA (+) that we discovered in this study, we had estimates of 95,438 adults who had anti-HCV (+) and 49,914 adults who had HCV viremia in HCMC. The incidence of HCV-related sequelae, including decompensated liver cirrhosis and liver cancer, was projected to increase if there were no interventional programs to detect those infected and link them to care in Viet Nam.[15]

For the care continuum, we reported a baseline cascade of care (CoC) based on self-reported survey questionnaires. This CoC revealed a significant gap in disease unawareness among the positive anti-HCV: only 28·5% (85 of 298) of persons with anti-HCV (+) were aware of their HCV status, with 77·6% (66 of 85) diagnosed with HCV coincidentally. Once diagnosed, 82·7% (62 of 75) initiated anti-HCV therapy and 69·8% (30 of 43) had a resultant HCV cure. With the 28·5% of those infected being aware of their status, the WHO target for 2020 of 30% for the HCV diagnosis rate had yet to be achieved.[1] However, 82·5% of those aware received treatment, meaning that the WHO treatment targets for 2030 of 80% were achieved. These statistics suggested that if persons with HCV were aware of their infection status, they would likely seek health care, undergo treatment, and get cured. Therefore, expanding HCV screening and diagnosis rate may be an essential strategy toward HCV elimination in HCMC.

This study further discovered that the 1945–1964 birth cohort had a prevalence of anti-HCV positivity of 3·6% (95% CI, 3·0%-4·2%), higher than the other high-risk groups, and accounted for 40·4% of all positive anti-HCV cases in HCMC. More specifically, the seroprevalence was highest at 6·7% in males and 3·6% in females born during 1950–1954. In line with our study birth cohort data, in a convenient sample, Dunford L et al. described results of HCV in five regions from north to south of Viet Nam: Ha Noi, Hai Phong, Da Nang, Khanh Hoa and Can Tho[21] In this study, HCV patients (n=8,654) were born within a similar birth cohort period (1955 ± 15). Taken together, the Viet Nam birth cohort may represent a significant and straightforward target for HCV screening and thus minimise stigmatisation associated with high-risk behaviour-based screening strategies. As a result, birth cohort screening followed by treatment has been demonstrated as a cost-effective strategy toward HCV elimination goals.[22,23]

Considering the putative increase in the prevalence of anti-HCV positivity in males born from 1970 to 1994, we hypothesise that IV drug abuse in this age group might be a driving factor. This hypothesis comes from evidence of a re-increase in HCV infections in persons who inject drugs (PWID) born around 1980 compared with those born around 1976 in Hai Phong – a northern city in Viet Nam.[24] A similar bimodal distribution of HCV infection incidences was also observed in America, with the first peak in the "baby boomer" birth cohort and the second peak in those in their 20s and 30s attributed to drug use[25] However, the trend should be cautiously interpreted considering the small sample sizes in each year group. Future studies with larger sample sizes for each year group are encouraged to further delineate this putative increase.

In the current study, groups with risky behaviours included a history of advanced liver disease, renal

dialysis, blood transfusion(s), IV drug use, shared needles, and/or tattoos. Among these groups, proportions of being tested for and aware of HCV ranged from 42·2% to 72·7% in those with a history of advanced chronic liver disease, renal dialysis, or blood transfusion. These patients were more likely to be tested for viral hepatitis because they sought medical care for their chronic comorbidities. On the other hand, the proportions in the remaining high-risk groups (i.e., drug use, tattoo, 1945–1964 cohort, and shared needle) ranged from 25% to 31·3%, below WHO's targets for 2020. Considering that these sub-populations are targets for HCV micro-elimination,[26] more efforts should be invested into diagnosis, treatment, and cure.

In multivariate analyses, groups with a history of blood transfusion, tattooing, and/or IV drug abuse are key risk factors for HCV infection in HCMC. This finding was consistent with previous studies.[16,27–29] Nonetheless, concerning blood transfusion and HCV transmission, we expect that blood transfusion will no longer be a problem in the future when a significant downward trend was found between those who first received a blood transfusion before 1992 and those who received one after 2014 (Table 1). The decline might stem from serial releases of the national legislations on blood donor screening in 1992, 2003, and 2013[9] Critical challenges remain for IV drug users—the most affected by HCV in Viet Nam[15]—and those who have tattoos. More attention should be paid to improving the number of needles and syringes distributed to 200 per PWID as targeted by WHO[1] and the accessibility among PWID. Moreover, infection control measures on re-using non-sterile equipment and other sharp instruments should be mandated for tattoo parlours.

There are several limitations to this study. First, due to the ongoing COVID-19 pandemic, we could not reach out to 12 clusters in two urban districts (District 3 and District 9) and two rural districts (Nha Be District and Can Gio District). Nonetheless, since the missing districts were balanced in terms of urban-rural areas and accounted for in the weighting process, the overall estimates were expected to be minimally affected. Second, the role of commercial sex on HCV infection was not examined because none of those with a history of having sex with sex workers had positive anti-HCV, which was likely underreported due to stigmatisation. Finally, the nature of the cross-sectional study design cannot conclude a causal relationship, which might affect the confounding analysis.

In summary, this study has leveraged micro-elimination to document the burden of HCV infection and its baseline continuum of care in HCMC. We encourage future implementation programmes in HCMC to prioritise provision of HCV screening as an intervention. The recommended sub-population for intervention are the birth Viet Nam cohort aged 1945–1964 and other groups with low proportions of testing and awareness (e.g., drug use, tattoo, and shared needles) or geographical groups such as in District 1 and surrounding urban districts in HCMC. Simultaneously, the independent risk factors (i.e., blood transfusion, tattoo, and drug abuse) should be addressed for primary prevention. Last, future studies in Viet Nam should prospectively capture gaps among different steps of the cascade of HCV care to monitor the progress towards HCV Elimination by 2030.

Contributors

TNDP, HKT, DTN, GM, MC and DYD contributed to study design. TK, DL, DVD, TNDP, LP, DTN, AT, AL and HKT contributed to data collection. TK, DL, HKT, TNDP, DXN, AT, AL and DYD contributed to data analysis and manuscript preparation. DYD, GM, RG, WML, HTP, MC, and BTN contributed to funding acquisition. DD and HKT are fully responsible for the overall content for 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

Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices) will be available to researchers who provide a methodologically sound proposal. Proposals should be directed to (Doan Y. Dao, ddoa1@jhmi.edu; Hong K. Tang, hong.tang@pnt.edu.vn) to gain access.

Editor note

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Declaration of interests

Moon Chen Jr received consulting fees from Vietnam Viral Hepatitis Alliance. RGG has received grants or research support in last 2 years from Gilead. RGG has also performed as a consultant or advisor in the past 2 years to Abbott, AbbVie, Altimunne, Antios, Arrowhead, 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 Pharmaceuticals 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 Development, 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, Genlantis, HepQuant, AngioCrine, and HepaTx, outside the submitted work. The rest of the authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100524.

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