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%-86.3%) 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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Chronic liver disease caused by hepatitis C virus (HCV) remains a significant global public health problem, afflicting approximately 71 million people worldwide. 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. 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. In low- to middle-income countries, gaps in HCV elimination progress lag even more staggering behind the WHO’s targets. 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. 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%. 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, 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”. Pursuing micro-elimination has been demonstrated successfully in the treatment of HIV and has recently been promoted for HCV elimination. 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.

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. 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, we selected HCMC to establish a baseline assessment to promote HCV identification.
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.
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
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.13

All specimens were screened for anti-HCV (Elecys® 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) above. After that, each observation was applied to the expansion weight by the commune in which they lived.

\[
d_i = \frac{U}{m + n_i} \tag{1}
\]

which:

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

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.

\[ c_j = \frac{U_j}{E_j} \]

where:
- \( c_j \): calibrated weight for stratum \( j \thinspace \)
- \( U_j \): population of HCMC in Census 2019 for stratum \( j \)
- \( E_j \): estimated population of stratum \( j \thinspace \) based on expansion weight

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

\[ w_k = d_j * c_j \]

where:
- \( w_k \): weight values for participant \( k \) who lives in commune \( i \) and has demographic characteristics similar to stratum \( j \)
- \( d_j \): expansion weight for commune (PSU) \( j \thinspace \)th
- \( c_j \): calibrated weight for stratum \( j \thinspace \)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 risk factor in the main model with which:

Adjustment began with age and sex; then a strategy was applied to select confounders for adjustment. A “Forward selection” of 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).

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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, 81.4% (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 | 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                            |                 |          |                    |                                 |
| 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                         |                 |          |                    |                                 |
| No Income                            | 4795            | 121      | 32,557             | 1.6 (1.1, 2.1)                  |
| < $ 303 USD/month                    | 7330            | 131      | 39,175             | 1.0 (0.9, 1.4)                  |
| ≥ $ 303 USD/month                    | 2196            | 24       | 17,333             | 1.0 (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 | 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 | 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 | Frequency | Weighted frequency | Weighted prevalence, % (95% CI) |
|----------------------------------------|-----------------|-----------|--------------------|---------------------------------|
| **Overweight or obesity**              |                 |           |                    |                                 |
| 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**                     |                 |           |                    |                                 |
| 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                                     | 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             |                                 |
| **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                             | 96              | 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 (0.0, 14.4)                 |
| *Missing*                              | 170             | 5         | 1819               |                                 |
| **History of having sexual intercourse with sex workers** | | | | |
| No                                     | 14,266          | 290       | 92,678             | 1.3 (1.1, 1.4)                  |
| Yes                                    | 70              | 0         | 0                  | -                               |

Table 1 (Continued)
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 3.3% (95% CI, 2.1%-4.9%) in females born during 1950–1954. The other peak was at 5.0% (95% CI, 1.0%-9.9%) 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 0.5% (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. Seventy-eight per cent (233/298) of the participants with positive anti-HCV (364 of 75, 95% CI 7.4-11.2%) were aware of their positive test result. 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 | 6.7, 33.7   | <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**                              |      |             |         |      |             |         |
| 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**                           |      |             |         |      |             |         |
| 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)
Table 2: Association of anti-HCV positivity with HCV related factors in HCMC.

| 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  | 1.4, 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                         |     |                 |         |      |        |         |
| Yes                                   | 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: 23,102.31 (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. 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, 1.0-2.6%). By comparison, the US, Japan, India, or Indonesia reported an HCV prevalence to be 1.0%, 2.3%, 0.9%, and 2.1%, respectively. Overall, this prevalence corroborates WHO’s modelling estimates and the expected decreasing trends in HCV infection nationwide and citywide.

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.

The HCV viraemic proportion among the persons with anti-HCV (+) was 50.6%. However, the viremic proportion could have been 70.0-6% (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. 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.

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. 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. 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.

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. 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. 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 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 20139 Critical challenges remain for IV drug users—the most affected by HCV in Viet Nam15— 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 WHO1 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, ddoi@jhmi.edu; Hong K. Tang, hong.tang@pnt.edu.vn) to gain access.

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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 affiliations.

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Supplementary materials

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