




Secular Trends and Geographic Maps of Hepatitis C Virus Infection among 4 Million Blood Donors in Taiwan from 1999 to 2017

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The prevalence of hepatitis C virus (HCV) infection in Taiwan was approximately 4% a decade ago, much higher than the worldwide average. This study aimed to assess the HCV burden among 4 million voluntary blood donors after 2 decades of prevention and treatment policies. We retrieved screening results for anti-HCV and HCV RNA from the Database for Evaluating Voluntary Taiwanese Eligible Donors. First-time blood donors who donated blood after 1999 and repeat donors who donated blood more than once between 2013 and 2017 were included to estimate HCV prevalence and incidence, respectively. The Cox proportional hazards model was used to estimate hazard ratios. Geographic variation in HCV prevalence and incidence in 364 townships was also analyzed. The prevalence study included 3,656,598 first-time donors. The overall crude prevalence of anti-HCV decreased from 15.5 to 4.5 per 1,000 donors between 1999 and 2017. Younger birth cohorts had a significantly lower prevalence of anti-HCV. The majority of townships (64.3%) in Taiwan showed a significantly decreased prevalence. The incidence study included 1,393,014 repeat donors followed for 3,436,607 person-years. Ninety-eight donors seroconverted to HCV RNA positivity, resulting in an HCV incidence of 2.9 per 100,000 person-years. Donors living in townships where HCV RNA prevalence was greater than 2 per 1,000 had at least 2.5-fold greater risk of new HCV infection. *Conclusion:* HCV prevalence in Taiwanese first-time blood donors decreased by 71% in the last 2 decades. However, townships with higher HCV prevalence also showed higher HCV incidence and require more active intervention. (*Hepatology Communications* 2020;4:1193-1205).

Chronic hepatitis C virus (HCV) infection is one of the major etiologies of liver cirrhosis and hepatocellular carcinoma and is also correlated with extrahepatic complications, such as insulin resistance, cryoglobulinemia, and renal disease.⁽¹⁾ The estimated number of viremic infections worldwide is 71.1 million, which accounts for 1% of the world population.⁽²⁾ Surveys from 10 years ago in Taiwan found

that around 4%–5% of the general population was anti-HCV positive^(3,4) along with 1.2% of first-time blood donors.⁽⁵⁾ Both of these HCV prevalence rates were much higher than the worldwide average. It is therefore important to understand the overall HCV transmission routes in Taiwan and to develop strategies for control.

Routine screening for HCV infection among blood donors is essentially active surveillance among

Abbreviations: CI, confidence interval; DAA, direct-acting antiviral; ELA, enzyme immunoassay; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; NAT, nucleic acid test; TBSF, Taiwan Blood Services Foundation; WHO, World Health Organization.

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a healthy general population. This study evaluates the prevalence and incidence of HCV infection among 4 million voluntary blood donors between 1999 and 2017. In addition, about 70%-85% of these voluntary blood donors were repeat donors, and their serial HCV tests can be used to determine HCV incidence. The results from this study will be helpful for implementing direct-acting antiviral (DAA)-based hepatitis C control policies, and the large population of voluntary blood donors coming from all small townships will also allow for an accurate assessment of possible endemic areas.

Because viral hepatitis is a leading cause of death and disability worldwide,⁽⁶⁾ in 2014, the World Health Assembly requested that the World Health Organization (WHO) examine strategies for eliminating hepatitis B and C.⁽⁷⁾ Sustained development goals for viral hepatitis have been proposed to reduce 90% of new hepatitis B virus (HBV) or HCV infections and 65% of associated mortality by the year 2030.⁽⁸⁾ Accordingly, prevention and treatment by DAA agents that cure HCV infection⁽⁹⁾ have been implemented in many countries to combat HCV. However, in order to determine efficacy, it is crucial to obtain continuous prevalence and incidence data on HCV in each country. Our study from a large population of voluntary blood donors paves the way for monitoring the progress of HCV control in Taiwan.

Participants and Methods

STUDY POPULATION AND DESIGN

The Taiwan Blood Services Foundation (TBSF) is a nation-wide establishment that collects blood and also supplies blood components for clinical use. Since 1991, 100% of the blood components have been collected from voluntary nonremunerated blood donations.⁽¹⁰⁾ Each year, approximately 1 million blood donors donate blood, which accounts for 4.5% of the entire population. The proportion of first-time donors was down to 13.9% in 2017 from nearly 30% in 1999, which coincides with the decrease in crude birth rates in Taiwan.⁽¹¹⁾ In 1999, nearly 60% of blood donations were collected through group campaigns. TBSF has since established more fixed donation sites, and in 2017, 53% of blood donations were collected at fixed sites.

During blood donations, the TBSF collected basic demographic characteristics from blood donors, such as sex, date of birth, township of residence, and the site where blood was being donated. A predonation interview was conducted to ascertain eligibility for blood donation. Starting in 1992, donors in Taiwan with a history of recent major surgery, blood transfusion, hepatitis within 6 months, infectious or renal disease, or close contact with patients with hepatitis were temporarily deferred in order to exclude donors

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who may be at higher risk of HCV infection and in the infectious window at the time of blood donation. Those in high-risk groups, including injection drug users, men who have sex with men, patients with hemophilia, patients who have coagulopathy, and their sexual partners, were permanently deferred. Several new criteria for temporary deferral were added in 2006, including tattooing, piercings, needle punching, receiving acupuncture therapy using nondisposable needles, and administration of any plasma-derived medicinal products. Those who received gastroscopy, thoracoscopy, proctoscopy, or other endoscopic examination within 6–12 months were temporarily deferred starting in 2011. The overall deferral rate of predonation interviews during our study period increased from 8.8% in 1999 to 14.2% in 2017, and the deferral rate due to HCV-related risk factors increased from 0.42% in 1999 to 0.88% in 2017.

Postdonation screening tests were conducted to ascertain the presence of blood-borne pathogens, including HBV, HCV, human immunodeficiency virus (HIV), human T-lymphocyte virus, and *Treponema pallidum*. In Taiwan, a universal nucleic acid test (NAT) has been conducted for every donation since 2013. The test is a triplex test that improves sensitivity for detecting HBV, HCV, and HIV. A report of the screening results was delivered to every blood donor. Recommendations for further medical consultation were noted in this report if there were any suspected infections identified during the postdonation screening. We used this routinely collected data to estimate the prevalence and incidence of HCV infections from first-time and repeat donors, respectively.

A computerized database of blood donations in the TBSF has been available since 1999, and we also established a de-identified analytic Database for Evaluating Voluntary Taiwanese Eligible Donors (DEVOTED). In order to estimate the prevalence of anti-HCV and HCV RNA positivity in this healthy population, blood donors whose first donation was between 1999 and 2017 were included in the analysis. Donors with detectable anti-HCV or HCV RNA in their blood donation sample were defined as prevalent cases representing both past and current HCV infection and just current HCV infection, respectively. To estimate the incidence of HCV infection, we examined a cohort of blood donors who donated 2 or more times after the implementation of universal NAT screening (2013–2017) and whose previous

donations were undetectable for both anti-HCV and HCV RNA. Donors with newly detectable HCV RNA during follow-up were defined as incident cases, which demonstrated new viral infection.

This study protocol (PM-106-BB-180) was approved by the institutional review board of the Taiwan Blood Services Foundation, Taipei, Taiwan.

BLOOD SCREENING

All plasma samples collected during blood donations were tested for anti-HCV. The detection of anti-HCV was conducted between 1999 and 2017 using the Murex anti-HCV version 4.0 VK47/48 enzyme immunoassay (EIA) (DiaSorin South Africa [previously Murex Biotech SA], Kyalami, South Africa), which is a third-generation assay. Samples that were repeatedly reactive were interpreted as positive. Ascertainment of HCV RNA positivity was first detected in minipools of eight donations, using the Procleix Ultrio Plus Assay on the Procleix TIGRIS System (Grifols, Emeryville, CA). This is a qualitative nucleic acid amplification test with a 95% probability to detect the WHO HCV reference panel of 5.4 IU/mL for individual tests and a detection limit of 70 IU/mL for the eight-minipool test. Reactive individual samples were resolved from the reactive minipools and then confirmed by discriminatory assays for HCV RNA.

STATISTICAL ANALYSIS

For the prevalence study, only records from first-time donations were included. We estimated the prevalence of anti-HCV per 1,000 donors and its 95% confidence interval (CI) starting in 1999 and the prevalence of HCV RNA starting in 2013. Calendar-year-specific and birth-cohort-specific prevalence were calculated to evaluate period and cohort effects. Age-standardized prevalence and their 95% CIs were calculated according to the WHO 2000–2025 world standard population, using a truncated age range of 17–65 years.

In the incidence study, we calculated the incidence per 100,000 person-years by dividing the number of incident cases by the person-years of follow-up. Person-years of follow-up were counted from the first donation between 2013 and 2017 until the first positive anti-HCV or HCV RNA result or the last blood donation between 2013 and 2017, whichever came first. Cox

proportional hazards models were used to estimate hazard ratios (HRs) with CIs for the association of each factor with the occurrence of new HCV infections. Tests for trend were conducted for ordinal variables.

All statistical tests were two-tailed tests, and statistical significance was defined as $P < 0.05$. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

PREVALENCE AND INCIDENCE MAPS

There are 368 townships located in 22 counties or cities in Taiwan. With over 4 million blood donors included in this study, township-specific maps of prevalence and incidence were possible. We estimated township-specific anti-HCV prevalence between 1999 and 2008 and between 2009 and 2017 in 364 townships. Furthermore, we measured HCV RNA prevalence between 2013 and 2017 in 259 townships and HCV RNA incidence between 2013 and 2017 in 69 townships. Comparisons of the crude anti-HCV prevalence between the two time periods were conducted using the chi-square test or Fisher's exact test. The prevalence and incidence map was plotted using QGIS v2.18 (Quantum GIS Development Team).

Results

PREVALENCE OF HCV INFECTION

A total of 3,656,598 donors donated their blood for the first time between 1999 and 2017. Anti-HCV was detected in 32,566 (0.9%) first-time donors. After NAT screening was implemented in 2013, HCV RNA was detected in 1,232 (0.17%) first-time donors and an additional 22 donors who were anti-HCV seronegative tested positive for HCV RNA (Table 1). These 22 individuals accounted for 1.8% of all HCV RNA-positive donors identified through NAT screening.

Generally, a higher crude prevalence of HCV infection was observed in female first-time donors, but the age-standardized rate was similar between sexes. The prevalence of anti-HCV and HCV RNA both increased with age, from 3.6 and 0.3 per 1,000, respectively, in donors under 20 years old to 31.6 and 11.7 per 1,000 in those over 60 years old. The

prevalence of HCV infection differed among blood centers (Table 1).

The crude prevalence of anti-HCV gradually decreased in the most recent 2 decades from 15.5 per 1,000 donors in 1999 to 4.5 per 1,000 donors in 2017 (Fig. 1A). The age-standardized prevalence was higher than the crude prevalence and decreased from 27.7 per 1,000 donors to 9.2 per 1,000 donors during the same time period (Fig. 1B). After the implementation of NAT screening, the crude prevalence of HCV RNA also showed a decreasing trend from 2.1 per 1,000 donors to 1.4 per 1,000 donors between 2013 and 2017 (Fig. 1A). The age-standardized prevalence decreased from 5.8 per 1,000 donors to 3.9 per 1,000 donors (Fig. 1B).

COHORT EFFECTS

The declining trend in anti-HCV prevalence was mainly due to cohort effects as later-born cohorts became the main blood donors. Younger birth cohorts were associated with lower HCV prevalence. Among three 10-year cohorts with available data, comparing the youngest with the oldest birth cohorts, there was a 58.6%, 64.3%, 72.5%, and 82.5% reduction in anti-HCV prevalence observed in donors aged 50-59, 40-49, 30-39, and 20-29 years old, respectively (Fig. 2). We observed a similar pattern in both sexes.

PREVALENCE MAP

Township-specific anti-HCV prevalence between 1999 and 2008 and between 2009 and 2017 is shown in Fig. 3. Comparing prevalence in the two different periods, 234 townships (64.3%) had significantly lower anti-HCV prevalence between 2009 and 2017, resulting in an average reduction of 8.4 per 1,000 in each township.

However, in the 1999-2008 survey, we noted 54 townships with a relatively high HCV prevalence (exceeding 20 per 1,000 donors) clustering in several small geographic areas. From 2009 to 2017, the number of HCV endemic townships decreased from 54 to seven. Finally, despite these seven townships still retaining a higher prevalence, four showed a significant reduction of 47% or more.

Anti-HCV is widely used in population surveys to estimate the prevalence of HCV. However, detection of HCV RNA represents currently active infection and the ability to transmit the virus in a certain

TABLE 1. PREVALENCE OF HCV INFECTION AMONG FIRST-TIME DONORS

Characteristics	Prevalence of anti-HCV (1999-2017) per 1,000 donors			Prevalence of HCV RNA (2013-2017) per 1,000 donors		
	Case Numbers	Crude Rate	Age-Standardized Rate	Case Numbers	Crude Rate	Age-Standardized Rate
Total	32,566	8.9 (8.8-9.0)	17.1 (16.9-17.4)	1,232	1.7 (1.6-1.8)	4.8 (4.5-5.1)
Sex						
Male	16,495	8.2 (8.1-8.3)	16.7 (16.4-17.1)	513	1.3 (1.2-1.4)	4.8 (4.3-5.3)
Female	16,071	9.8 (9.6-9.9)	17.3 (16.9-17.6)	719	2.2 (2.0-2.3)	4.8 (4.4-5.2)
Age at donation (years)						
<20	5,601	3.6 (3.5-3.7)		97	0.3 (0.3-0.4)	
20-29	8,271	6.6 (6.5-6.8)		165	0.6 (0.5-0.7)	
30-39	5,668	16.4 (16.0-16.8)		249	3.8 (3.3-4.3)	
40-49	7,404	24.2 (23.6-24.7)		272	6.8 (6.0-7.6)	
50-59	4,794	27.0 (26.2-27.7)		356	10.0 (8.9-11.0)	
60+	828	31.6 (29.5-33.7)		93	11.7 (9.4-14.1)	
Blood center						
Taipei	6,374	6.9 (6.8-7.1)	11.4 (11.1-11.8)	230	1.2 (1.1-1.4)	2.9 (2.5-3.3)
Hsinchu	4,502	9.2 (9.0-9.5)	16.2 (15.5-16.8)	166	1.7 (1.5-2.0)	4.3 (3.5-5.1)
Taichung	6,496	8.9 (8.7-9.2)	17.8 (17.3-18.4)	240	1.7 (1.4-1.9)	4.9 (4.2-5.6)
Tainan	7,249	9.7 (9.5-10.0)	26.0 (25.1-26.8)	313	2.1 (1.9-2.3)	7.7 (6.7-8.7)
Kaohsiung	6,313	10.6 (10.3-10.8)	21.2 (20.6-21.9)	223	2.0 (1.7-2.3)	6.1 (5.2-7.0)
Hualien	1,632	8.9 (8.4-9.3)	18.2 (17.0-19.3)	60	2.1 (1.6-2.6)	7.7 (5.5-9.9)

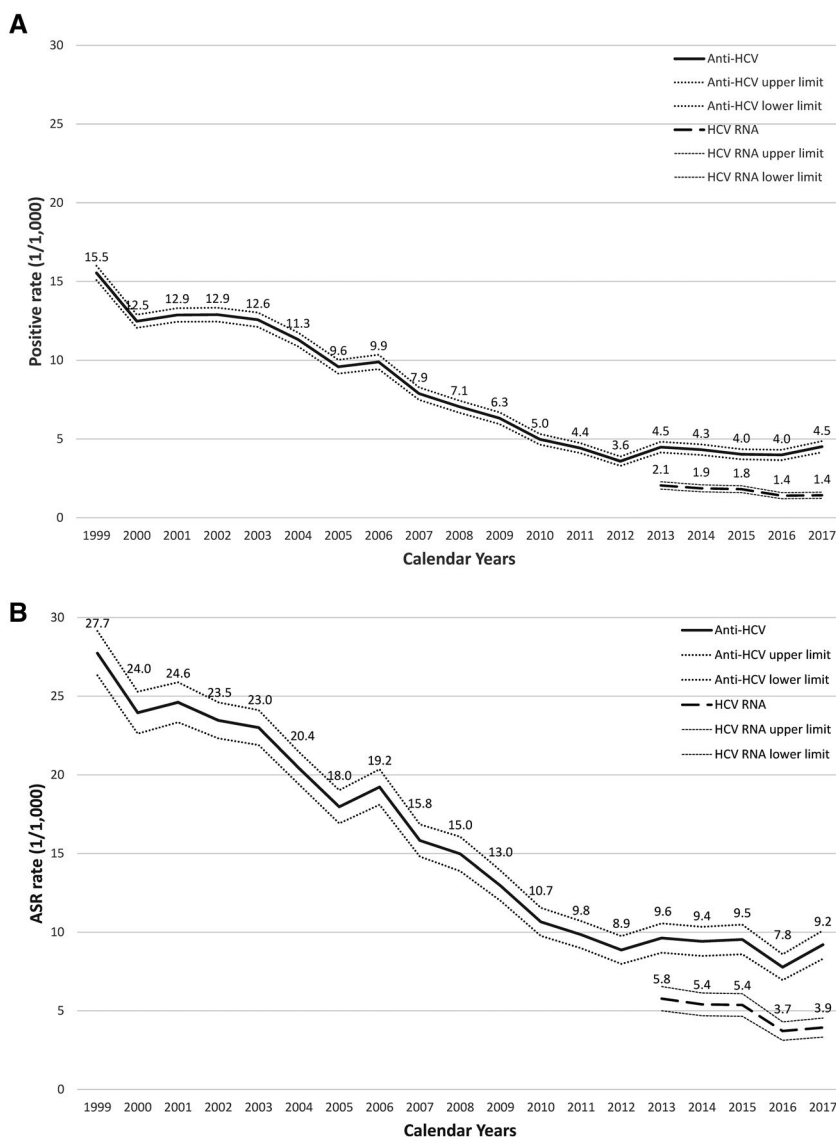


FIG. 1. Prevalence of HCV infection among first-time donors. (A) Crude rates. (B) Age-standardized rate. Abbreviation: ASR, age-standardized rate.

population. Township-specific HCV RNA prevalence between 2013 and 2017 is shown in Fig. 3. Two clusters of townships with higher HCV RNA prevalence were identified near the west coast, one cluster in Miaoli County and another located near the west coast of both Yunlin and Chiayi counties. Nearly 30% of townships in these counties had an HCV RNA prevalence of more than 5 per 1,000 donors. Donors from Miaoli mainly donated blood at sites administered by the Hsinchu blood center, while donors from Yunlin and Chiayi mainly donated blood at sites administered by the Tainan blood center. Therefore,

we also saw a higher prevalence of HCV in these blood centers (Table 1).

INCIDENCE OF HCV INFECTION

A total of 1,393,014 donors who donated blood more than once between 2013 and 2017 were included in the incidence study, and 98 of these donors were identified as newly infected with HCV because of a seroconversion to detectable HCV RNA. During 3,436,607 person-years of follow-up, the overall incidence in these donors was 2.85 per

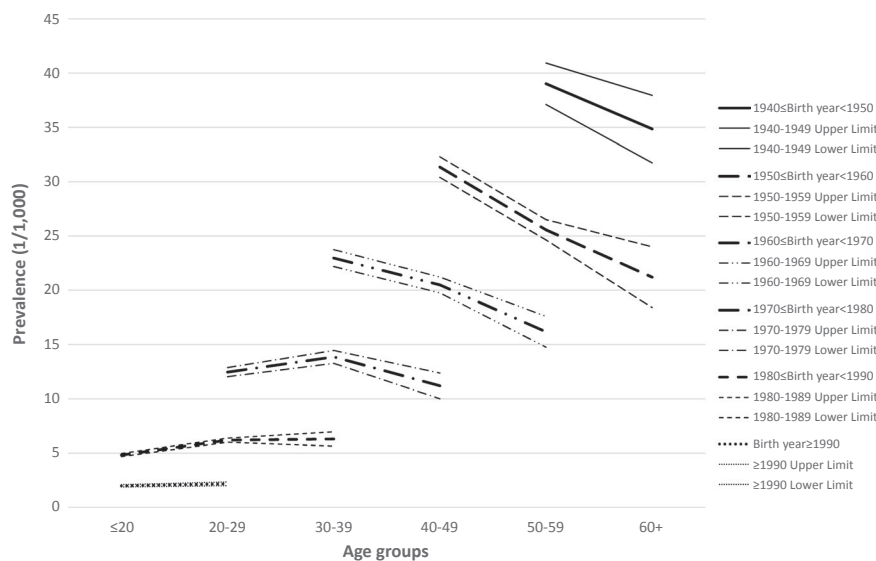


FIG. 2. Prevalence of anti-HCV in different birth cohorts among first-time donors.

100,000 person-years (Table 2). No significant difference in HCV incidence was observed between sexes. Although the estimated incidence increased with age, no significant trend was seen. Donors who donated blood at the Hsinchu, Tainan, and Kaohsiung blood centers had significantly higher risks of acquiring new HCV infections compared with those who donated at the Taipei blood center.

INCIDENCE MAP

Township-specific incidence of new HCV infections is shown in Fig. 4. Donors living in townships where the prevalence of HCV RNA was 2–5 per 1,000 donors and >5 per 1,000 donors had HRs of 2.46 (95% CI, 1.29–4.69) and 8.37 (95% CI, 3.69–18.99), respectively, for new chronic HCV infections compared with those living in townships with a prevalence of <1 per 1,000 donors. Townships with a higher HCV RNA prevalence were correlated with significantly higher HCV incidence (trend $P < 0.0001$) (Table 2).

We further identified a cluster in Chiayi County, a known endemic region,^(4,12) where an incidence rate of at least 10 per 100,000 person-years was seen in eight townships (incidence rates were 142.0, 56.1, 40.1, 38.9, 24.8, 19.7, 19.2, and 12.8 per 100,000 person-years in Liujiao, Taibao, Puzi, Xingang, Zhongpu, Zhuqi, Dalin, and Minxiong townships, respectively). A total of 19 new HCV cases were found in this

region, accounting for 19.4% of all identified cases. The overall incidence in this cluster of townships was 33.6 per 100,000 person-years (95% CI, 18.5–48.7), which was nearly 12 times higher than the incidence for all of Taiwan ($P < 0.0001$). Another cluster was discovered in Taoyuan City, where the incidence was at least 5 per 100,000 person-years in five townships (incidence rates were 15.6, 12.7, 9.7, 7.4, and 5.4 per 100,000 person-years in Yingge, Guanyin, Pingzhen, Bade, and Zhongli, respectively). This area was not previously reported as an endemic area for HCV infection in other studies.^(4,12) A total of 11 new HCV cases were found in this region, accounting for 11.2% of all identified cases. The overall incidence in this region was 8.2 per 100,000 person-years (95% CI, 3.4–13.1), which was nearly 3 times higher than the overall incidence in Taiwan ($P = 0.0005$). Donors from Taoyuan mainly donated blood at sites administered by the Hsinchu blood center. Therefore, we also saw a higher incidence of HCV at the Hsinchu blood center.

Discussion

This study used routine screening data from blood donors to evaluate the prevalence and incidence of HCV infection in Taiwan. A total of 3,656,598 and 1,393,014 blood donors were included in our

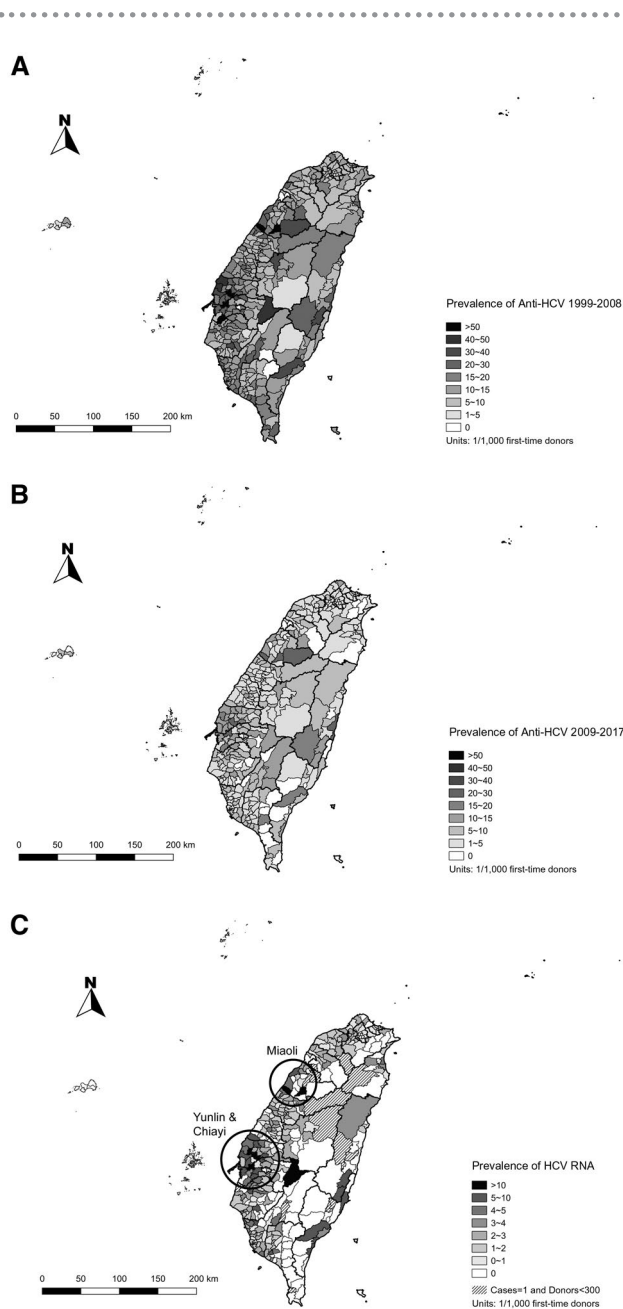


FIG. 3. Township-specific prevalence map of HCV infection among first-time donors. (A) Anti-HCV prevalence between 1999 and 2008. (B) Anti-HCV prevalence between 2009 and 2017. (C) HCV RNA prevalence between 2013 and 2017.

prevalence and incidence studies, respectively, accounting for approximately 25% of the total population aged 17-65 years old. Among this healthy population, we showed a decreasing trend in anti-HCV prevalence during the most recent 2 decades, with a larger reduction occurring among later born cohorts. Once both the prevalence and incidence of HCV RNA

were available after the universal implementation of the NAT, we were able to demonstrate evidence of active HCV infection. We found that the incidence of new HCV chronic infections was low in most townships. However, we identified a few hotspot townships with a clearly higher incidence and found that the risk of incidence was associated with a locally high prevalence of HCV RNA.

We observed obvious cohort effects in anti-HCV prevalence in this study. Anti-HCV prevalence was significantly lower in younger birth cohorts (Fig. 2). Because younger cohorts have become the major source of blood donations, the overall prevalence of anti-HCV has gradually decreased in the recent 2 decades. A series of anti-HCV screenings conducted throughout local Taiwan communities also showed similar results.⁽⁴⁾ Decades ago, a common misconception in Taiwan was that the administration of medications or nutrients was more effective and rapid through injection than through oral intake. Unfortunately, nondisposable syringes were commonly used during that time. As a result, older cohorts were more likely to be exposed to HCV infection.^(13,14) The population attributable risk due to previously unsterile medical injections was estimated to be 57.3%.⁽³⁾ As disposable syringes became widely used after the 1980s and medical and environmental hygiene continued to improve, the prevalence of HCV among the younger population significantly decreased.⁽⁴⁾ In our study, less than 1% of donor cohorts born after 1980 were anti-HCV seropositive.

Anti-HCV is the first assay used to detect HCV infection in many surveys and blood services, but false-reactive results of EIA are common in low-risk and immunocompetent populations, averaging 35%.⁽¹⁵⁾ Generally, the positive predictive value is lower in populations with decreased prevalence.⁽¹⁶⁾ In Taiwan, the proportion of HCV RNA positivity among anti-HCV-positive cases varies. In two surveys that targeted the general population with an anti-HCV prevalence of less than 2%, testing with a third-generation assay showed an HCV RNA positivity rate of less than 45% in both studies.^(17,18) In our study, among first-time donors with reactive anti-HCV results after 2013, 40% were HCV RNA positive. This proportion was similar to that found in an Irish recipient survey (33%)⁽¹⁹⁾ and in the 2007-2012 National Health and Nutrition Examination Study in the United States

TABLE 2. INCIDENCE AND HRS OF NEW HCV INFECTION

Characteristics	Number of Incident Cases	Incidence (1/10 ⁵)		Model 1		Model 2	
		Point Estimate*	95% CI	HR (95% CI)	PValue	HR (95% CI)	PValue
Total	98	2.85	2.29-3.42				
Sex							
Male	60	2.91	2.17-3.65	0.95 (0.63-1.43)	0.81	1.00 (0.66-1.50)	0.99
Female	38	2.76	1.88-3.64	Ref.		Ref.	
Age (years)							
<30	30	2.34	1.51-3.18	Ref.		Ref.	
30-49	47	2.99	2.14-3.85	1.27 (0.80-2.01)	0.32	1.26 (0.80-2.00)	0.32
50+	21	3.59	2.05-5.12	1.58 (0.90-2.77)	0.11	1.54 (0.88-2.70)	0.13
				trend <i>P</i> = 0.11		trend <i>P</i> = 0.12	
Blood center							
Taipei	14	1.29	0.61-1.96	Ref.			
Hsinchu	17	3.40	1.78-5.02	2.70 (1.33-5.48)	0.006		
Taichung	16	2.22	1.13-3.31	1.71 (0.83-3.50)	0.14		
Tainan	34	6.20	4.09-8.31	4.78 (2.56-8.92)	<0.0001		
Kaohsiung	16	2.85	1.45-4.25	2.19 (1.07-4.50)	0.03		
Hualien	1	1.93	0.00-5.72	2.41 (0.32-18.39)	0.40		
Township-specific HCV RNA prevalence (1/1,000)							
<1	12	1.60	0.69-2.51			Ref.	
1 to <2	34	2.15	1.43-2.87			1.33 (0.69-2.56)	0.40
2 to <5	41	4.00	2.77-5.22			2.46 (1.29-4.69)	0.006
≥5	11	13.59	5.45-21.74			8.37 (3.69-18.99)	<0.0001
						trend <i>P</i> < 0.0001	

*Age-standardized incidence rate.
Abbreviation: Ref., reference value.

(46%).⁽²⁰⁾ Nevertheless, we conducted two additional EIA tests for samples that were repeatedly reactive to primary anti-HCV screening between 2010 and 2013 and found that 87% were reactive to one other test. In addition, among anti-HCV-reactive but HCV RNA undetectable samples after 2013, 30% were immunoblot positive. Thus, the estimated false-positive rate in our study may range between 13% and 40% in recent years. As anti-HCV testing did not change during the study period, the prevalence of anti-HCV in recent years may be even lower than our estimates.

After NAT was introduced for blood screening in 2013, we found that the crude prevalence of anti-HCV and HCV RNA among first-time donors in 2017 was as low as 4.5 per 1,000 and 1.4 per 1,000, respectively. This rate was even lower than those reported from population-based surveys conducted nearly 2 decades ago.^(3,4,21) In our analyses, we observed a 71% reduction in the crude prevalence of anti-HCV from 1999 to 2017, mainly because

nearly 80% of first-time donors were under 30 years old and the proportion of donors born after 1980 increased from 43% to 86%. This also resulted in a higher age-standardized prevalence than crude prevalence. Although new deferral criteria for blood donations were added after 2006, only acupuncture was found to be significantly associated with HCV infection in Taiwan.⁽³⁾ In addition, there was no drastic decrease in HCV prevalence after 2006, showing that changes in donor selection criteria may not have contributed to the significant reduction in HCV prevalence observed in our study.

Population-based case-control studies conducted nearly 30 years ago in Taiwan showed an 8-fold to 10-fold increased risk of getting HCV infection among subjects who had received a blood transfusion, and the population attributable risk during that time was 25%,^(14,21) showing that transfusion was once a major route of HCV transmission. As approximately 4%-6% of adults^(14,21) and 1%-5% of

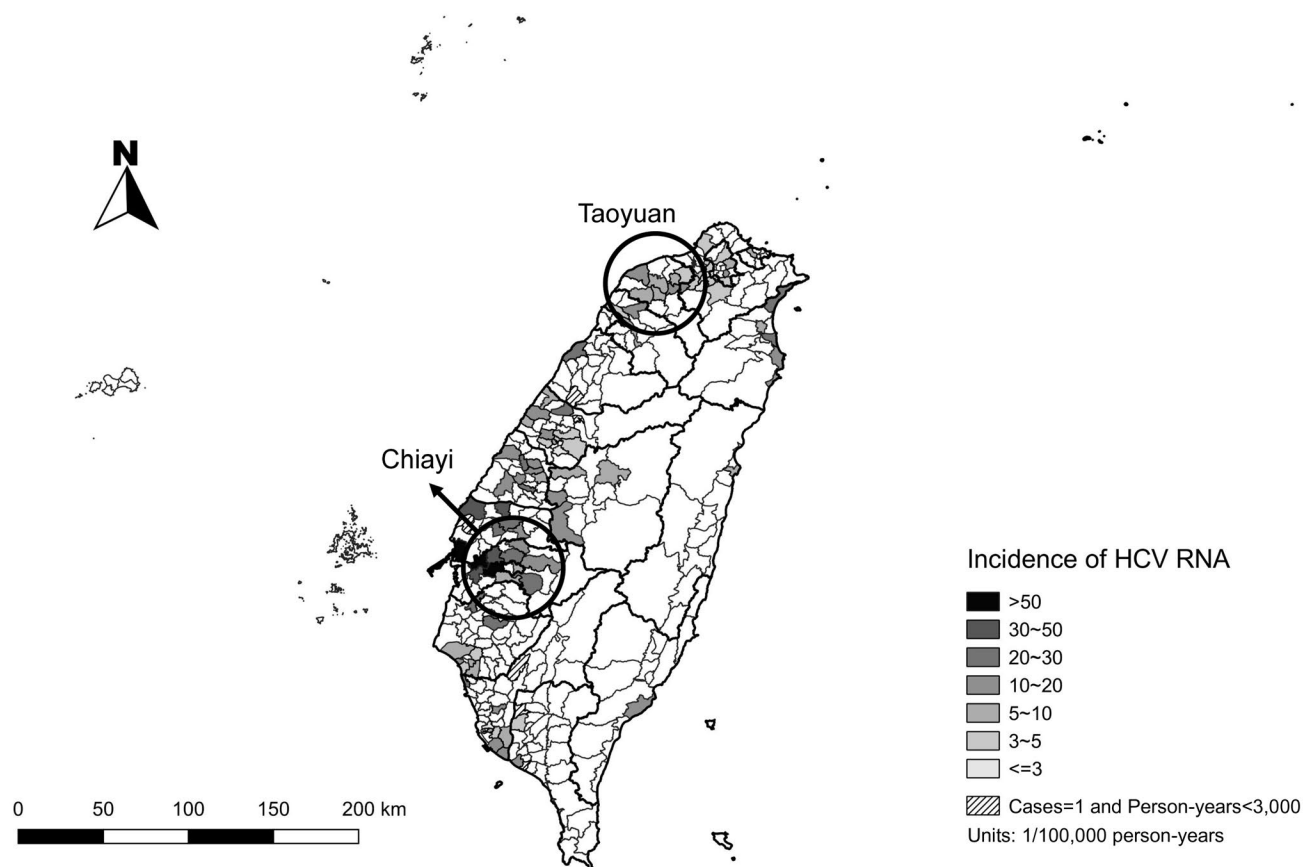


FIG. 4. Township-specific incidence map of HCV infection.

teenagers^(17,22,23) had ever received a blood transfusion, universal blood donor screening for anti-HCV and HCV RNA, which has since screened 1 million blood donors per year, would significantly reduce the risk of HCV infection. Patients with thalassemia benefited the most from blood donor screening; this reduced anti-HCV prevalence among these patients born after 1992 by 74%.⁽²⁴⁾ Our data also showed a continuously decreasing trend since 1999.

Moreover, the advent of antiviral treatment for HCV might also have contributed to the reduction of HCV observed in our study. Based on population prevalence estimated from a series of community-based screening programs and surveys^(4,17,18,21-23,25-34) of 0.2 million residents since 1996, two study groups estimated that approximately 270,000-550,000 patients with HCV need antiviral treatment in Taiwan.^(4,35) Since 1999, an increasing number of local governments and hospitals in Taiwan have initiated their own community-based integrated screenings, which include anti-HCV

tests and are targeted at residents aged 40 years or older. In 2011, the Taiwanese government began including a one-time HCV screening into the preventative health care service for adults aged 40-64 years, and more than 30% of the target population participated. These programs not only provided blood tests but also provided health education and assisted referrals for follow-up and antiviral treatment. Beginning in October 2003, a national program initiated by the Taiwan National Health Insurance (TNHI) began reimbursing pegylated-interferon-alpha (PEG-INF- α) combined with ribavirin for treatment of anti-HCV-positive hepatitis.⁽³⁶⁾ From 2003 to 2017, a total of 95,000 patients with chronic hepatitis C were treated by either PEG-INF- α plus ribavirin or DAA, which accounts for about 20%-35% of the estimated total patient numbers.⁽³⁷⁾ These policies may help reduce the HCV reservoir in the population. New DAAs have been reimbursed by the TNHI for chronic hepatitis C since 2017. This national program

aims to treat 80% of patients with chronic hepatitis C by 2025 as part of a national goal to eliminate HCV infection in Taiwan.⁽³⁷⁾ Our blood donor program will provide evidence of HCV reduction or eventually even elimination in the general population.

The overall incidence of new HCV infections in our follow-up cohort was 2.85 per 100,000 person-years, which was equivalent to rates among repeat donors in other developed countries, such as Japan (0.4-1.86 per 100,000)^(38,39) and European countries (0.4-1.9 per 100,000).⁽⁴⁰⁾ Despite these encouraging findings, there remains a risk for new HCV infection in Taiwan. The geographic maps of HCV incidence in Taiwanese townships revealed two possible HCV transmission routes. One was present in all townships and contributes to a low incidence. This route most likely represents an omnipresent route or behavior carrying a low transmission rate. After the introduction of universal donor screening and ensuring a low-risk donor population to ensure blood safety, transfusions are no longer a significant route of HCV infection. The other pathway, sexual transmission, may account for this route and deserves further study.

In contrast, the clusters of townships with high HCV incidence suggest the presence of another efficient transmission route. Most likely, certain behaviors pertinent to these locations account for higher HCV transmission, including folk medicines involving invasive procedures^(3,41) or clinical practices with unsatisfactory sterilization procedures.⁽⁴²⁾ In the United States and Eastern European countries, a recent resurgence of acute HCV infection was associated with the opioid epidemic and increases in injection drug use.^(43,44) In Taiwan, anti-HCV was detected in more than 90% of incarcerated injection drug users.⁽⁴⁵⁾ Therefore, this transmission route cannot be excluded from hotspot townships. These possible local transmission routes have to be investigated to inform strategies for successful infection control.

Previous multilevel analysis showed that 57.4% of geographic variation in HCV infection comes from ecological factors at the village level, such as the proportion of detectable HCV RNA among anti-HCV-positive residents and the adequacy of health care resources,⁽³³⁾ suggesting that there is potential to reduce local HCV burden through public health interventions. In a highly endemic township where the past prevalence in adults was more than 40%, 1 decade of interventions, including education,

screening, follow-up, and treatment, successfully reduced anti-HCV prevalence among teenagers by 64%.⁽²³⁾ In the present study, we demonstrated a changing pattern of anti-HCV prevalence in 64.3% of townships in Taiwan by comparing township-specific prevalence during two different time periods. In general, we saw lower anti-HCV prevalence across all of Taiwan between 2008 and 2017. This may be due to the overall improvements in medical resources, practices, and health education.

There were other limitations in this study. The estimation of population prevalence using blood donors may be underestimated due to restrictive donor selection criteria that defer high-risk donors who have HIV, are intravenous drug users, or are undergoing hemodialysis. However, our birth cohort-specific prevalence was similar to those seen in a large population screening program.⁽⁴⁾ Because previous screening programs were generally targeted at residents aged 40 years or older, this resulted in selection effects. Therefore, a decreasing trend of anti-HCV seroprevalence by increasing age among donors more than 40 years old was observed in earlier birth cohorts in this study. Homeless individuals and new immigrants may not be covered in this study because they rarely donate blood. Only township-specific prevalence and incidence were available in our study; a more accurate village-specific prevalence may provide more detailed information on geographic variation.^(22,30,33,46) Lastly, 5 years of follow-up and 98 incident cases of HCV infection may not be enough to identify all HCV-affected townships. However, our survey will continue to overcome these limitations.

HCV infection in Taiwan has been continuously decreasing, and younger cohorts born after the 1980s had the lowest risk. Blood transfusions are no longer a major route of HCV infection, and the identification of other routes of transmission in the general population is critical. This study also showed that data from routine blood donor screenings can play a critical role in the surveillance of infection burden and will also guide future interventions. For example, careful interviews of the 98 new cases may shed light on possible transmission routes that can be targeted through active interventions. The geographic HCV hotspots found in our study show the potential for using this approach to plan future prevention, screening, and DAA-treatment policies in hyperendemic areas, with the ultimate goal of hepatitis C elimination.

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