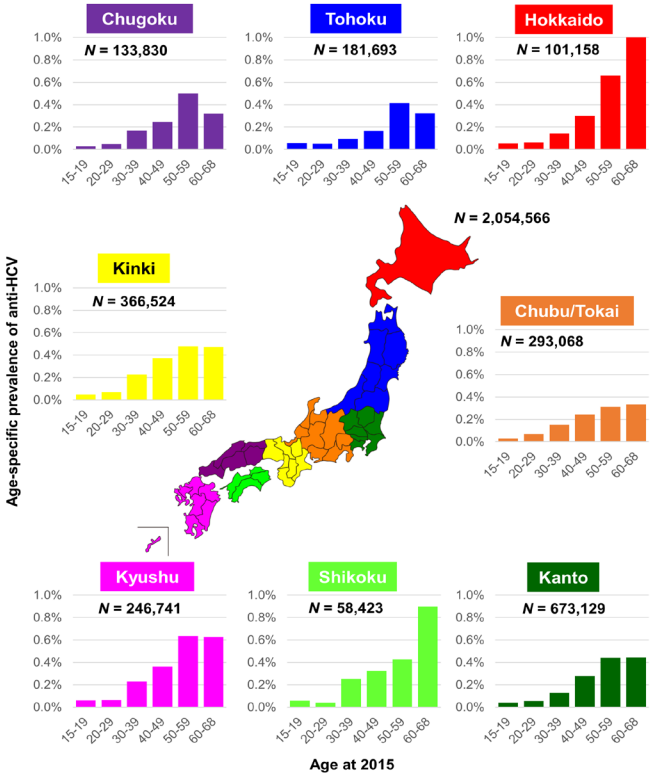
Print ISSN: 2434-9186 Online ISSN: 2434-9194

NCGM

Global Health & Medicine

Volume 3, Number 5
October, 2021

Towards HCV elimination – Perspectives from Japan and Asia



Age-specific prevalence of anti-HCV among first-time blood donors during 2012-2016 in Japan (Page 265)

Print ISSN: 2434-9186
Online ISSN: 2434-9194
Issues/Year: 6
Language: English

Global Health & Medicine

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Online ISSN: 2434-9194
Issues/Year: 6
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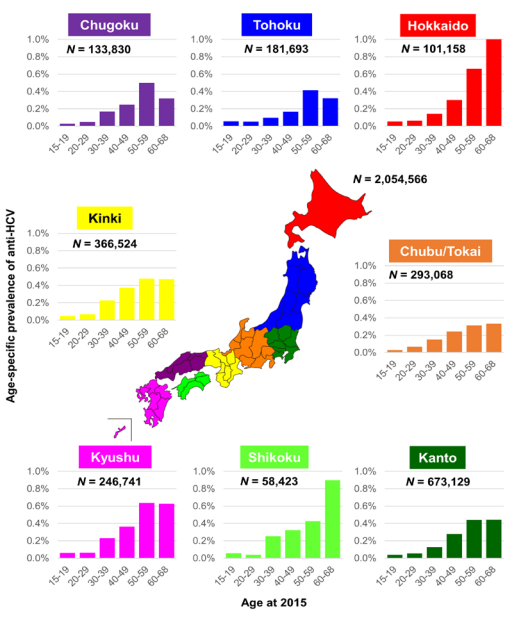

Age-specific prevalence of anti-HCV among first-time blood donors during 2012-2016 in Japan. In this figure, Japan is geographically divided into eight main regions and the age specific prevalence of anti-HCV is shown for each region in the bar graph and each color in the map represents its corresponding region. (Page 265)

Global Health & Medicine. 2021; 3(5):249-252.

EDITORIAL

DOI: 10.35772/ghm.2021.01078

Messages from Japan policy for viral hepatitis

Tatsuya Kanto*

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Abstract: In Japan, the estimated number of chronic HBV infections was 1.1-1.2 million and that of chronic HCV was 0.9-1.3 million in 2015. The mortality of hepatocellular carcinoma (HCC) had been increasing and hit a peak at around 2002, which subsequently started to decrease. Japan has a national action plan for addressing viral hepatitis called, "Basic Act on Hepatitis Measures", established in 2009. "Basic Guidelines for Promotion of Control Measures for Hepatitis" was issued in 2011 and was updated in 2016, comprising 9 principles in order to promote measures to prevent hepatitis B and C. According to these guidelines, national and local government share screening costs for testing HBV and HCV for those residents who are over 40 years old. Thus, out-of-pocket expenses from examinees are free of charge or reduced to a minimum. In addition, for patients with chronic hepatitis B or C being treated: drug prices of nucleotide analogues, interferon treatment or direct antiviral agents, and examination expenses should be covered by a special program for viral hepatitis. From December 2018, the special coverage program of medical expenses, shared by central and local government, has started for patients with HBV- or HCV-induced liver cancer and decompensated cirrhosis. However, in the cascade-of-care of viral hepatitis in Japan, significant gaps still remain in the diagnosis, treatment and transition to patients in need. Several advantages have prevailed in Japanese health care systems for patients with viral liver disease compared to those in other countries in the Western Pacific Region. Therefore, Japan should take a lead in helping the implementation of a practical hepatitis action plan for each country in need.

***Keywords*:** viral hepatitis, liver cancer, decompensated cirrhosis, Basic Act on Hepatitis Measures

On the globe, approximately 257 million people are infected with hepatitis B virus (HBV) and 71 million with hepatitis C virus (HCV) as of 2015, respectively (*1*). Both viruses are hepatotropic and principally of a non-cytopathic nature, and the majority of the endemic areas are in developing countries. Once infected, substantial populations progress to a chronically-infected state that eventually develops liver cirrhosis and hepatocellular carcinoma (HCC) within decades. Liver cirrhosis and liver cancer are responsible for 94% of deaths associated with hepatitis infections. Liver cancer is the second most common cause of cancer deaths in the Asia-Pacific Region, and approximately 78% of liver cancer causes are a result of chronic viral hepatitis B or C (*1*). Viral hepatitis is the seventh-leading cause of mortality globally, responsible for 1.45 million deaths in 2013 (*2*). One quarter of the world's population lives in the Western Pacific, but the Region bears 40% of the world's deaths caused by hepatitis. Consequently, hepatitis kills more than 1,500 people every day in the Region (*1*).

Regardless of the success of hepatitis B (HB) vaccination, which has reduced the prevalence of HBsAg in the under 5 years old population in several countries, millions of people across the Region still continue to live with chronic hepatitis B or C and the risk of cirrhosis and liver cancer. We now have effective medicines, such as direct acting antivirals (DAAs) and nucleot(s)ide analogues (NAs) to manage and treat chronic hepatitis C or B, respectively. The high price of DAAs has been a major barrier for access to treatment across the Region. In response to the social movement and WHO's designation of some DAAs as essential medicine, a mega-pharma agreed to tiered pricing and provided generic licensing to several pharmaceutical companies. Currently, generic DAAs are commercially available in designated low- or middle-income countries where people can get access to DAAs at reasonable prices. In order to achieve WHO targets of viral hepatitis elimination by 2030, various barriers still need to be overcome, depending on the policy and socio-economic circumstances in each country.

In this special topic issue of *Global Health & Medicine*, experts from countries in Asia and Pacific contribute reviews covering current status of elimination efforts in the epidemiological, clinical and policy settings in this region. As for a preface, I summarize here the outline of the policy for viral hepatitis in Japan.

National hepatitis action plan in Japan

In 2015, the estimated number of individuals with chronic HBV infection was 1.1-1.2 million and that of chronic HCV infection was 0.9-1.3 million in Japan (*3*). Annual incidence of deaths in 2014 from liver cirrhosis was approximately 10 thousand and that from liver cancer was 29 thousand, respectively. And 70% of deaths from liver cirrhosis or cancer were caused by hepatitis B and C. Therefore, in Japan, it has been an important health issue for the management and care of patients with chronic hepatitis B or C infection.

Japan has a national plan for addressing viral hepatitis called, "Basic Act on Hepatitis Measures", established in 2009 (Act No.97 of the year 2009) (*4*). Following 2011, "Basic Guidelines for Promotion of Control Measures for Hepatitis" was issued by the government, comprising 9 principles of measurement, in order to promote prevention of hepatitis B and C (*5*). There are set targets and government has allocated funding for the plan. The Ministry of Health and Labour and Welfare (MHLW) in Japan has appointed working groups for viral hepatitis, "The Council for Promotion of Hepatitis Measures", including epidemiologists and clinical researchers. Based on "Basic Act on Hepatitis Measures", every prefecture and government have selected linked regional core centers for treatment of liver disease (hereafter referred to as regional core centers) along with achieving cooperation of specialized medical institutions, so that there is no bias by region, and it will be equally improved. Consultation Center for Liver diseases has been installed in all regional core centers corresponding to the consultation from the patient and their family. The Hepatitis Information Center was established in The National Center for Global Health and Medicine (NCGM), The Research Center for Hepatitis and Immunology in 2008. Some of the roles of the Hepatitis Information Center are the support for sharing medical information between regional core centers, the training of medical personnel and the provision and dissemination of up-to-date information regarding hepatitis (*6*). Along with the update of "Basic Guidelines for Promotion of Control Measures for Hepatitis" in 2016, The Hepatitis Information Center has been assigned to take more responsibility to promote linkage for care of hepatitis patients, by active participation in the collaboration among regional core centers, specialized medical institutions and central/local governments. In cooperation with the nationwide awareness-raising program, "*Shitte Kan-en*" project, Hepatitis Information Center and regional core centers have contributed to the synthesis and distribution of the hepatitis educational program to the young generations (*7*).

Screening and diagnosis of viral hepatitis in Japan

Testing for viral hepatitis is an initial step of the linkage to care for patients with hepatitis B or C. In Japan, national and local government share screening costs for testing hepatitis B and C for those residents who are over 40 years old (Figure 1). Thus, out-of-pocket expenses from examinees are free of charge or reduced to the minimum. From 2001 to 2014, approximately 17 million persons have taken a hepatitis virus test in this country. Test results for hepatitis B and hepatitis C are notified to patients, and positives are encouraged to visit medical institutions and to get registration to the follow-up system in some prefectures. Intensive medical examinations are necessary for positive test patients for the diagnosis of liver disease with active viremia, to determine whether they should be treated or not with anti-viral agents. For this purpose, medical expenses are covered by local governments for positive testers, which are even found at workplaces, and pre-surgical or maternal check-ups, who agree to participate in the follow-up program (Figure 1) (*8*).

Linkage from diagnosis to treatment in viral hepatitis in Japan

The nationwide questionnaire analysis on viral hepatitis testing in FY2017 disclosed that the screening rates of HBV or HCV were 71.0 % and 61.6 %, respectively. Of particular importance, people who clearly remember having taken a hepatitis test were limited to 20.1 % for HBV and 18.7 % for HCV, respectively. This survey demonstrated that about 40 % of the participants were unaware of test experience in FY2017. What is worse, even if the test results were positive, approximately 30 % of the people were unaware of the test results and failed to seek medical institutions (*9*). Such a gap in the linkage to care for viral hepatitis should be one of biggest hurdles for viral hepatitis elimination in Japan.

Hepatitis medical care coordinators (HMCC) are specialized personnel who are expected to support patients and their families in every aspect of the cascade of care. Through the end of March 2019, 16,546 HMCCs were certified in Japan. Actual roles of HMCCs are the following: *i*) sharing updated information of viral hepatitis, *ii*) introduction to consultation services, encouraging to undergo examinations and treatment, etc., and *iii*) coordinating in promoting appropriate medical care. HMCCs with various occupations are working at regional core centers, specialized hospitals, public health centers, pharmacies and municipal offices (*10*). HMCCs are unique health professionals who could play significant roles in filling the gaps between diagnosis, treatment and care of viral hepatitis.

Antiviral treatment in Japan – clinical guidelines and subsidy program

In clinical practice in Japan, optimization of DAAs treatment has been done based on HCV genotypes,

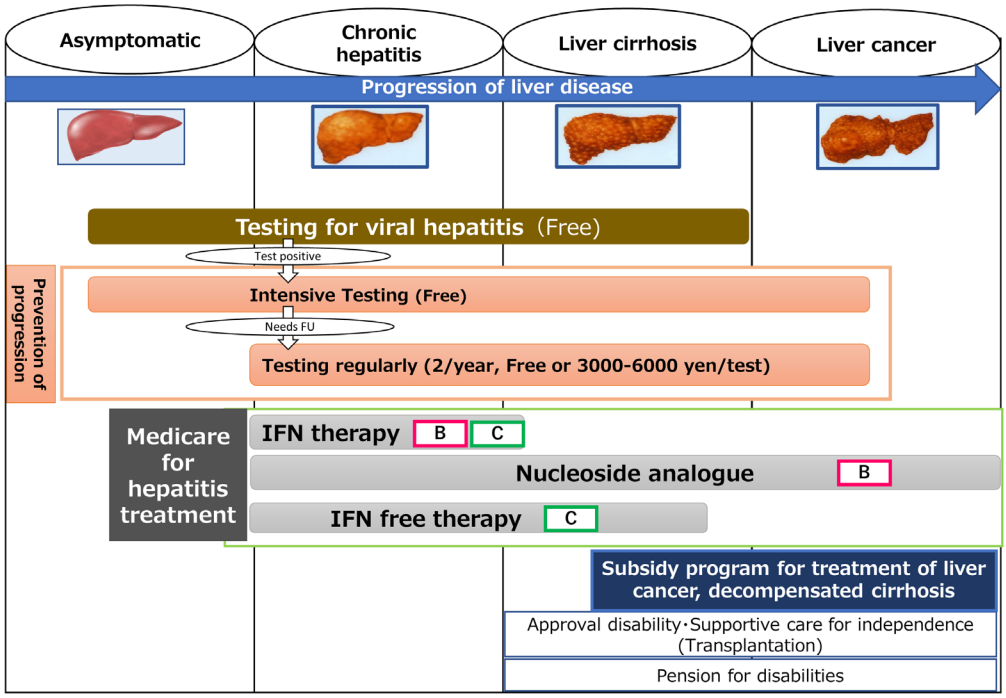

Figure 1. National Hepatitis Program in Japan. In Japan, lifelong support is provided to patients with viral hepatitis. People can take viral hepatitis test for free in most cases. If they are diagnosed as HBV or HCV positive, they can get more intensive examinations including ultrasonography, in order to decide whether they need anti-viral treatment. In the specialized institutions or regional core centers, they can get interferons or direct-acting antivirals, medical expenses, which are covered by special subsidy programs. From 2018, a special subsidy program for the treatment of liver cancer and decompensated cirrhosis was started. If the condition of patients deteriorates with progression to liver cirrhosis, they are supported by special pension programs. The format is adapted from the information from the Ministry of Health, Labor and Welfare in Japan.

stages of liver disease (chronic hepatitis or compensated/decompensated cirrhosis), prior experience with DAAs and the pattern of resistance-associated substitutions (RAS) on treatment. Of particular importance, meticulous care is needed for the treatment of patients with prior DAA failure and decompensated liver cirrhosis. Such tailored DAA treatment is guided by the *Guidelines for the management of hepatitis C virus infection*, updated and issued from Japan Society of Hepatology, which have been updated in pace with the registration of novel DAAs (*11*).

There are no barriers to prescribing antiviral drugs or DAAs to patients with hepatitis C with the public health insurance. In addition, for the treatment cost for chronic hepatitis B or C, drug prices for nucleotide analogues, interferon (IFN)-based treatment or IFN-free DAAs and examination expenses should be covered by the special program for viral hepatitis (Figure 1). The national and local government altogether cover the amount in excess of ten or twenty thousand yen (approximately 100-200 USD) of the cost of treatment (depending on the amount of tax payment) (*8*). As for the eligibility of using such a coverage program, the patients have to submit an application to the prefecture office with recommendation from a designated hepatologist or gastroenterologist (*12,13*). The sustained viral response (SVR) rate using DAAs, including patients with decompensated cirrhosis, has been dramatically improved.

Perspectives

Recently, patients with new or re-infection with HCV are on the rise because of the expansion of persons who inject drugs in some countries, the trend of which has been most significant in younger generations. In order to overcome such tall barriers to eliminate viral hepatitis, the development of a long-awaited protective/therapeutic HCV vaccine could be one of the remedies. Several beneficial advantages have prevailed in Japanese health care systems for patients with viral liver disease compared to those in other countries in the Western Pacific Region. In my personal opinion, Japan should take a lead in supporting implementation of a practical hepatitis action plan or education programs for healthcare workers, such as HMCCs, adjusted for each country where in need.

Funding: None.

Conflict of Interest: Tatsuya Kanto received lecture fee from AbbVie and Gilead Sciences.

References

1. World Health Organization. WHO Global hepatitis report, 2017. *https://www.who.int/publications/i/item/global-hepatitis-report-2017* (accessed May 27, 2021).

2. Stanaway JD, Flaxman AD, Naghavi M, *et al*. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet. 2016; 388:1081-1088.
3. Tanaka J. Report on epidemiological studies to assess the status of hepatitis virus infection and to contribute to designing measurements against the elimination of viral hepatitis. Japan: MHLW scientific research subsidy, Research Project for Emergency Measures to Conquer Hepatitis FY2019. *https://mhlw-grants.niph.go.jp/node/61182* (accessed May 10, 2021). (in Japanese)
4. Ministry of Health, Labour and Welfare. Basic Act on Hepatitis Measures. *http://www.japaneselawtranslation.go.jp/law/detail_main?re=&vm=01&id=1995* (accessed March 31, 2021). (in Japanese)
5. Ministry of Health, Labour and Welfare. Basic Guidelines for Promotion of Control Measures for Hepatitis. *https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/pdf/hourei-27.pdf* (accessed March 31, 2021). (in Japanese)
6. Setoyama H, Korenaga M, Kitayama Y, Oza N, Masaki N, Kanto T. Nationwide survey on activities of regional core centers for the management of liver disease in Japan: Cumulative analyses by the Hepatitis Information Center 2009-2017. Hepatol Res. 2020; 50:165-173.
7. Takeuchi Y, Ohara M, Kanto T. Nationwide awareness-raising program for viral hepatitis in Japan: the "Shitte kan-en" project. Glob Health Med. 2021; 3:301-307.
8. Korenaga M and Kanto T. Testing, diagnosis of viral hepatitis, and the follow-up policy in Japan. Glob Health Med. 2021; 3:308-313.
9. Ministry of Health, Labour and Welfare. FY2011 Report on the Current Extent of Hepatitis Testing. *https://www.mhlw.go.jp/stf/houdou/2r9852000002gd4j-att/2r9852000002gd60.pdf* (accessed May 10, 2021). (in Japanese)
10. Isoda H, Eguchi Y, Takahashi H. Hepatitis medical care coordinators: Comprehensive and seamless support for patients with hepatitis. Glob Health Med. 2021; 3:343-350.
11. Tahata Y, Sakamori R, Takehara T. Treatment progress and expansion in Japan: From interferon to direct-acting antiviral. Glob Health Med. 2021; 3:321-334.
12. Setoyama H, Tanaka Y, Kanto T. Seamless support from screening to anti-HCV treatment and HCC/decompensated cirrhosis: Subsidy programs for HCV elimination. Glob Health Med. 2021; 3:335-342.
13. Oza N, Isoda H, Ono T, Kanto T. Current activities and future directions of comprehensive hepatitis control measures in Japan: The supportive role of the Hepatitis Information Center in building a solid foundation. Hepatol Res. 2017; 47:487-496.

Received June 23, 2021; Revised September 21, 2021; Accepted October 4, 2021.

Released online in J-STAGE as advance publication October 16, 2021.

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Global Health & Medicine. 2021; 3(5):253-261.
REVIEW
DOI: 10.35772/ghm.2021.01065

Regional progress towards hepatitis C elimination in the Western Pacific Region, 2015-2020

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Abstract: Chronic hepatitis C (HCV) infection is a major global public health threat and in 2019 there were an estimated 58 million infected globally and 290,000 deaths. Elimination of viral hepatitis B/C as a public health threat by 2030 is defined as a 90% incidence reduction and a 65% mortality reduction. The Western Pacific region is one of the most affected regions with 10 million people living with HCV, one-fifth of the global burden. We review progress towards HCV elimination in the Western Pacific region since 2015. Key developments in the region, which comprises of 37 high-and-middle-income countries, include the following: 20 countries have national hepatitis action plans, 19 have conducted recent disease burden and investment cases, 10 have scaled-up hepatitis services at primary health care level, and in 11 countries, domestic financing including social health insurance support DAA costs. We highlight six countries' experience in navigating the path towards HCV elimination: Cambodia, China, Malaysia, Mongolia, Philippines, and Viet Nam. Future initiatives to accelerate elimination are expanding access to community-based testing using HCV point-of-care tests among at-risk and general populations; adopting decentralized and integrated HCV one-stop services at harm reduction sites, detention settings and primary care; expanding treatment to include children and adolescents; address stigma and discrimination; and ensuring sustainable financing through domestic resources to scale-up testing, treatment and prevention. The COVID-19 pandemic has a significant impact on hepatitis response across the region on community and facility-based testing, treatment initiation, monitoring and cancer screening, which is projected to delay elimination goals.

***Keywords*:** hepatitis C, Western Pacific, regional progress, hepatitis elimination, hepatitis action plans

Introduction

Chronic hepatitis C infection (HCV) is a major global public health threat and cause of liver disease globally, with a disproportionately high burden in low-and middle-income countries (LMICs) (*1-3*). HCV infection is most commonly associated in LMICs with unsafe injection or inadequate infection control practices in health-care facilities, and in high-and middle-income countries (HMICs), most HCV transmission occurs among people who use unsterile equipment to inject drugs (*2,3*). In 2019, an estimated 58 million persons were chronically infected with HCV and there were 290,000 HCV-related deaths (*3*). On 28 May 2016 during the 69th World Health Assembly, 194 Member States made a historic commitment to eliminate viral hepatitis as a public health threat by 2030 with the launch of the first-ever Global Health Sector Strategy (GHSS) for Viral Hepatitis 2016-2021 (*1*). This strategy outlined a set of global impact targets - a reduction in hepatitis B/C-related mortality by 65% and in incidence of chronic hepatitis B (HBV) and HCV infections by 90% to achieve the goal of elimination of viral hepatitis through scale-up of five key synergistic preventative and testing/treatment programmatic interventions.

The global response and opportunities for HCV elimination have been transformed by advances in treatment in 2014 with the advent of curative, short-course direct acting antiviral (DAA) therapy, followed by dramatic 1000-fold reductions in cost of 12-weeks treatment to under USD$ 100; and simplification of the diagnostic pathway with widespread availability of rapid diagnostic testing for HCV antibody and now access to laboratory-based as well as point-of-care nucleic acid testing (NAT) for confirmation of HCV viraemia with associated recent cost reductions (*4*).

There has been further support for the scale-up of testing and treatment through a rapid sequence of guideline updates from professional societies such as American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL) and Asian Pacific Association for the Study of the Liver (APASL) (*5-8*) as well as from the World Health Organization (WHO) in 2014, 2016 and

2018 leading to recommendations for a "treat all" approach regardless of stage of disease using a few pan-genotypic regimens and adoption of a public health approach (*9*).

Although good progress has been made in several champion countries in scale-up of treatment access and of preventative approaches to reduce transmission, such as blood and injection safety, globally, we are far from achieving the 2030 service delivery coverage targets of 90% diagnosis and treatment of 80% of those infected. As of 2019, only around 20% of persons with HCV infection had been tested but now 62% of those diagnosed have been treated, as a result of the marked increase in the cumulative number treated, from 5 million in 2017 to almost 9.4 million in 2019 (*3*). To achieve the targets for global elimination by 2030, a substantial scale-up in testing and treatment is needed, with simplification of the care pathway.

The 2018 WHO guidelines on care and treatment of persons with chronic hepatitis C infection endorsed eight key good practice approaches to simplify service delivery of viral hepatitis prevention, care and treatment, and improve access to effective hepatitis services, and implement the "Treat All" approach (Table 1) (*9*). However, until recently, most of the evidence to inform the simplified approaches of decentralization, integration and task-shifting were based on HIV literature and experience where adoption of these approaches had such a catalytic impact on antiretroviral treatment scale-up (*10*). There are even greater opportunities for simplification with HCV infection, as short course curative treatment requires minimal expertise and monitoring. A recent comprehensive WHO-led systematic review of 142 studies now provides a strong evidence-base supporting these approaches in HCV care (*11*). Full decentralization of HCV testing and treatment at the same site compared to no or only partial decentralization was associated with increased linkage and treatment uptake, especially among persons who inject drugs. Task-shifting to primary care providers was associated with high rates of HCV cure compared to specialist-delivered care in all subpopulations. The feasibility and effectiveness of other emerging models of care to achieve elimination has been demonstrated in different settings, including a comprehensive "educate, test and treat" in a high burden rural general population settings in Egypt (and now also in Pakistan) that achieved high testing and treatment coverage and 90% reduction in HCV incidence (*12,13*); a same day test-and-treat model (*14*); and micro-elimination initiatives in most affected populations such as people who inject drugs, people living with HIV, persons on haemodialysis, and in prisons (*15*).

The WHO Global Hepatitis Programme also undertook in collaboration with key partners a global project in 2019 to collate good practices and lessons learned from different aspects of national viral hepatitis responses. Key success factors identified in planning the response included strong political will and leadership, effective community mobilization and engagement, and development of comprehensive and costed national plans. Optimal forecasting, national registration and strategic procurement approaches for both drugs and diagnostics through forecasting, as well as exploiting opportunities for diagnostic integration, and simplified integrated service delivery at harm reduction sites and in primary care, supported by a well-trained workforce accelerates service delivery.

Implementing the Regional Action Plan for Viral Hepatitis 2016-2020 towards HCV elimination

The Western Pacific Region comprises 37 high-and middle-income countries and is highly diverse in its hepatitis epidemiology across the large countries and small island states. WHO estimates that in 2019, 126 million people were living with chronic HBV infection (defined as hepatitis B surface antigen (HBsAg) positive) (116 million) and chronic HCV (HCV viraemic prevalence) (10 million) in the

Table 1. Eight good practice principles for simplified service delivery of viral hepatitis prevention, care and treatment

No.	Eight practice principles
1	Comprehensive national planning for the elimination of HCV infection based on local epidemiological context, existing health-care infrastructure, current coverage of testing, treatment and prevention, and available financial or human resources.
2	Simple and standardized algorithms across the continuum of care from testing, linkage to care and treatment.
3	Strategies to strengthen linkage from testing to care, treatment and prevention.
4	Integration of hepatitis testing, care and treatment with other services (*e.g.* HIV services) to increase the efficiency and reach of hepatitis services.
5	Decentralized testing and treatment services at primary health facilities or harm reduction sites to promote access to care. This is facilitated by two approaches: *i*) task-sharing, supported by training and mentoring of health-care workers and peer workers; *ii*) a differentiated care strategy to assess level-of-care needs, with specialist referral as appropriate for those with complex problems.
6	Community engagement and peer support to promote access to services and linkage to the continuum of care, which includes addressing stigma and discrimination.
7	Strategies for more efficient procurement and supply management of quality-assured, affordable medicines and diagnostics.
8	Data systems to monitor the quality of individual care and coverage at key steps along the continuum or cascade of care at the population level.

region, accounting for 40% of the global HBV burden (296 million) and 17% of the world's 58 million HCV burden (*3*). Half of the global burden of death due to hepatitis B and C are in this region, mostly due to cirrhosis or liver cancer from chronic hepatitis infection. The incidence of liver cancer is especially high, and five out of 10 countries with the highest incidence of new cases of liver cancer globally include Mongolia, Lao People's Democratic Republic, Cambodia, Viet Nam and China (*16*). Table 2 summarizes regional progress in 2019.

On 14 October 2015, as part of Resolution WPR/RC66.1, the Regional Action Plan for Viral Hepatitis in the Western Pacific 2016-2020, was launched to help countries in the Region develop their national responses to viral hepatitis (*17*). The framework consists of five priority areas (advocacy and awareness, evidence-based policy, data and surveillance, stopping transmission, and the treatment cascade) and follows a systems approach. This was followed in October 2017, with a further preventative initiative towards elimination - the Regional Framework for Triple Elimination of Mother-to-Child Transmission (EMTCT) of HIV, Hepatitis B and Syphilis in Asia and the Pacific 2018-2030 (triple elimination, WPR/RC68.R2). This outlines an integrated and coordinated approach towards triple elimination, and includes the additional intervention of antiviral prophylaxis for HBV EMTCT to help achieve the global 2030 target of 0.1% HBsAg prevalence among children aged 5 years by 2030 (*18*). This integrated platform will also be important in the future for prevention of HCV mother-to-child transmission, pending the outcome of ongoing trials on the safety and efficacy of DAAs in pregnancy.

Since the launch of the Regional Action Plan for Viral Hepatitis in 2015, national action plans are now in place for 20 countries, and disease burden and investment cases have been developed in 19 countries. Drug prices have also been reduced substantially, and hepatitis medicines have been included in national health insurance systems in many countries. Hepatitis services are being scaled up at primary health care level in 10 countries and strategic information plans were developed by seven countries.

Developing a comprehensive national plan using a "whole systems" approach

A key feature of the WHO Western Pacific regional response and support to countries in their journey towards elimination of viral hepatitis as a public health threat is the adoption of a "whole systems" approach in developing a comprehensive national hepatitis response under the umbrella of Universal Health Coverage (UHC) (*19*). A systems approach recognizes that all parts of a health system are interrelated and interactions among the multiple parts and stakeholders are dynamic. National plans play a vital initial role in establishing a comprehensive viral hepatitis response. A specific costed national strategy or action plan allows Member States to identify priority areas and mobilize resources to mount an effective response. By the end of 2020, 20 countries had developed or drafted their national action plans for HBV and HCV (Figure 1) (*20*). Concurrently, these countries have also established national steering committees or working groups that support governance

Table 2. Monitoring regional hepatitis progress in the Western Pacific Region, 2021

Targets	Interventions	Global 2020 targets (Regional targets in parentheses)	Global 2030 targets	Western Pacific Region at the end of 2019
Impact	Incidence and prevalence among the general population	-30% (< 1% HBsAg in five-year-olds born after HBV immunization started)	-90% 0.1% HBsAg in children aged 5 years or less	HBV prevalence in children younger than 5 years: 0.3% HBV prevalence: 5.9% HBV incidence: 140,000 cases HCV prevalence: 0.5% HCV incidence: 230,000 cases
	Mortality	-10%	-65%	HBV deaths: 470,000 HCV deaths: 77,000
Service coverage	3 dose hepatitis B vaccination	9% (95% by 2017)	90%	94%
	Birth dose hepatitis B vaccination	50% (95% by 2017)	90%	84%
	Safe blood (screened donations)	95%	100%	100%
	Safe injections	100%	100%	98.8% safe injections
	Harm reduction	200 injection sets/PWID	300 injection sets/PWID	57 injection sets/PWID (2015 base-line)
	Tested	30%	90%	HBV: 21.4 million (18%) HCV: 3.5 million (25%)[±]
	Treatment	HBV: 5 million HCV: 3 million	80% eligible treated	HBV: 5.6 million (5%) HCV: 1.5 million (10%)[±]

[±]2015 baseline data was used as the denominator (number of people living with hepatitis C). PWID: people who inject drugs. Source: WHO, 2021.

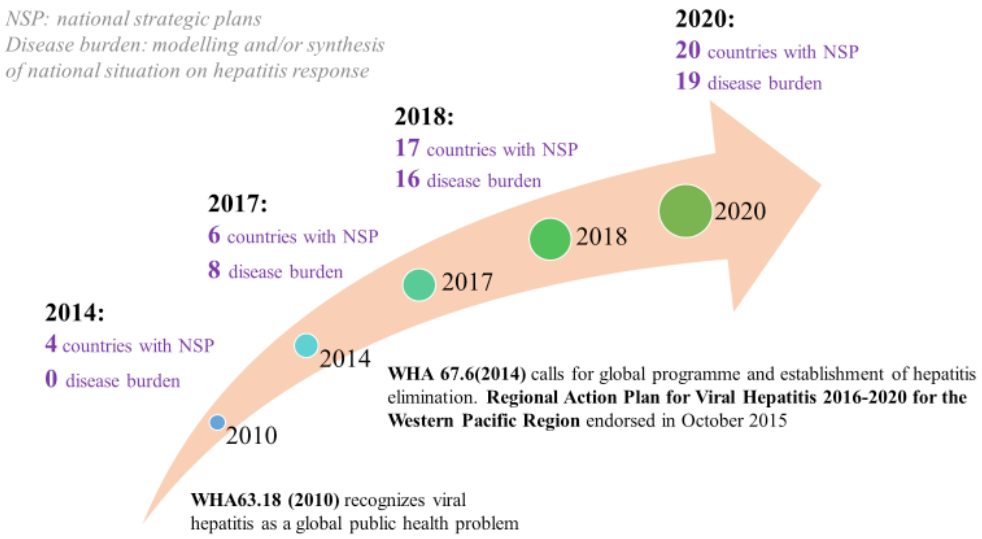

Figure 1. Scaling-up national action plans, Western Pacific Region, 2014-2020.

and coordination of the multiple stakeholders, programmes, partners and civil society organizations to deliver on the target indicators for hepatitis elimination. The majority of these groups include representation of patient and civil society organizations which contribute both to policy and guideline development, as well as help expand the scope, reach and acceptability of hepatitis services (*21*).

Integration of financing of hepatitis care with existing social health insurance programmes

By the end of 2020, most countries with existing social health insurance or government-financed universal coverage systems had incorporated financing of hepatitis care and, in particular, the costs of HCV DAA medicines (Table 3). This represents marked progress from the baseline of 2015 where only six countries funded the costs of direct-acting antiviral medicines - all of them high-income countries in the Western Pacific region, and a significant step to ensure sustainability of services needed to achieve elimination. Lessons learned from vertically funded programmes in transitioning to integrated financing and service delivery such as HIV, tuberculosis (TB) and malaria illustrate the complexities for decision makers in balancing the public health, political, economic and social needs (*22*).

Country profiles on national viral hepatitis response

Implementation of these good practices to achieve elimination by 2030, is highly varied and adapted to the context of each country. The following section focusses on progress in six selected middle-income countries, accounting for more than 95% of the HCV burden in the region.

Cambodia

Cambodia has the fifth highest incidence of liver cancer globally and an estimated prevalence of 1.6% HCV viraemic infection. At the end of 2019, Cambodia launched its first-ever national strategic plan for viral hepatitis 2020-2024, just before the onset of the COVID-19 pandemic (*WHO Cambodia, personal communications*). In-country partners such as Medecins sans Frontieres- France (MSF-F) have established simplified models of HCV care at community level since 2016 in two provinces (*23,24*), and provided testing for about 135,000 people and treatment for 18,000 people by the end of 2020 (*MSF-F Cambodia, personal communications*). The programme also provided training of healthcare workers and task-shifting to non-specialists and nurses, strengthening of laboratory capacity, active case finding as well as implementation research to provide evidence for national decision-making. In addition, financial support from The Global Fund to Fight AIDS, TB and Malaria (Global Fund) to support diagnosis and HCV cure of HIV-HCV co-infected patients in the national HIV programme, was secured by the National Centre for HIV/AIDS, Dermatology and STDs (NCHADS) as mortality of co-infected persons is significantly higher. Resourcing the national plan and scaling up to achieve hepatitis elimination is an ongoing challenge and especially amidst the COVID-19 pandemic. Although domestic financing allocation for HCV services would ensure sustainability, external donor support will likely be needed to achieve the 2030 elimination targets. Sustainable financing will also need to leverage more diverse sources of government revenues for health and include innovations and efficiencies such as cheaper generic DAAs, central or pooled procurement to enable lower bulk volume prices

Table 3. Coverage of hepatitis treatment through domestic resources (social health insurance and government financing) at the end of 2020 for selected countries in the Western Pacific Region

Country	HBV	HCV-DAA
Australia	Financed	Financed
Brunei Darussalam	Financed	Financed[#]
Cambodia	OOP	OOP
China	Financed	Financed
Hong Kong SAR	Financed	Financed
Japan	Financed	Financed
Lao PDR	OOP	OOP
Macao SAR	Financed	Financed
Malaysia	Financed	Financed
Mongolia	Financed	Financed
New Zealand	Financed	Financed
Papua New Guinea	OOP[‡]	OOP
Philippines	[*]	OOP[*]
Republic of Korea	Financed	Financed
Singapore	Financed	Financed
Viet Nam	Financed	Financed

OOP: out-of-pocket; PDR: People's Democratic Republic; SAR: Special Administrative Region (China). [#]Brunei Darussalam: transitioned to DAA and "Treat All" from mid-2020. [‡]Papua New Guinea: hepatitis B (HBV) testing and treatment pilot established in Oro province since 2019. [*]Philippines: pilots for HBV and hepatitis C (HCV) testing and treatment started with government financing in 2019, with HBV national expansion in April 2020. Source: WHO Western Pacific Region, 2021.

for medicines and diagnostics. There is also a need to empower communities in promoting health literacy to reduce transmission, address stigma and discrimination and optimize patient compliance with DAA treatment and achieve cure (*25*).

China

China has one of the largest burden of HCV with an estimated 7.6 million HCV infections at the start of 2016 (*3*). Investment cases for HCV elimination demonstrated good returns on investment and cost savings (*26,27*). The 2017-2020 national plan for prevention and control of viral hepatitis articulated a framework for action by multiple stakeholders. As availability of imported and domestically developed DAAs accelerated from 2015, attempts to improve patient access and mitigate the financial burden of these high-priced medicines were piloted in multiple provinces (*28,29*). Central price negotiations for hepatitis C medicines led by the National Healthcare Security Administration resulted in a more than 85% reduction for a three-month treatment course from US$ 10,000 to US$ 1-2,000 at the end of 2019 (*30*). This price reduction also enabled the inclusion of three DAA combinations (sofosbuvir/ledipasvir, sofosbuvir/velpatasvir and elbasvir/grazoprevir) in the national health insurance package from January 2020, enabling further expansion of access to treatment. Development of the national HCV elimination plan 2021-2030 is in progress.

Malaysia

In its commitment to achieving UHC and elimination of viral hepatitis as a public health threat by 2030, Malaysia used compulsory licensing as a policy tool to improve access to affordable treatment (*31*). With access to cheaper DAA generics, prices have decreased by more than 50-80% since 2015, and the number of patients treated in the public sector have doubled. The country is rapidly expanding new clinical service capacity to deliver HCV testing, treatment and monitoring at primary and community care facilities (*32*). In addition, strategic partnerships between government and Drugs for Neglected Diseases *initiative* (DND*i*) with the Foundation for Innovative New Diagnostics (FIND) have supported active research in diversification of HCV treatment options using a combination of sofosbuvir and ravidasvir as a new low-cost pan-genotypic regimen as well as the 'how' to deliver decentralized diagnosis, linkage to care, treatment initiation and cure at community level health facilities (*33*). Strong civil society input and engagement to support national expansion of services working with vulnerable groups and building empowered communities accelerates the country's UHC journey of getting to elimination (*34*).

Mongolia

Mongolia has the highest liver cancer incidence globally, mostly due to HBV and HCV, and was the first lower-middle-income country in the Asia and the Pacific region to commit to hepatitis elimination (*35*). The Healthy Liver Programme 2017-2020 strategy encompassed an ambitious plan to eliminate HCV and control HBV and hepatitis delta virus (HDV) by 2020 (*36*). A systematic phased approach with provision of care and treatment to priority populations through progressive service expansion was developed. The costs of HBV, HCV and HDV screening, diagnosis and treatment were covered under the national social health insurance programme. By 2019, the programme had screened over 1 million people and treated more than 30,000 through delivery of integrated services at primary care facilities across the country (*37*). Screening for liver cancer through ultrasonography is included as part of the essential package of primary healthcare services enabling decentralized access and routine surveillance across the country. Given the high burden of HBV, HCV and HDV, the national programme also offers, uniquely, routine antenatal HBV, HCV and HDV screening as part of integrated triple elimination of mother-to-child transmission of HIV, syphilis and viral hepatitis.

Philippines

With over 600,000 people infected with chronic HCV,

the Philippines embarked on piloting models of service delivery to enhance reaching those most affected including people who inject drugs and those incarcerated (*38*). Supported by WHO and funded by government, a pilot was launched mid-2019 in Cebu, Central Visayas Region, providing community-based HCV services offering free screening, viral load testing and treatment as a one-stop approach (*39*). Early experience from this and other pilot sites highlighted the need to accelerate universal offer of screening to all at-risk populations including people living with HIV, individuals who have ever injected drugs and incarcerated people. Expansion of availability of testing and treatment is now planned for other regions of the country beyond the current pilot sites and to engage private providers to significantly enhance service access.

Viet Nam

With liver cancer as the top cause of cancer deaths (*40*), Viet Nam established a 2015-2019 national plan outlining the core areas for prevention, testing and treatment for viral hepatitis which was updated for 2020-2024. Entry of DAAs in 2017 through fast-track drug registration mechanisms and importation of generic options has improved affordability (*41*). In 2019, social health insurance included coverage of four DAAs at a reimbursement rate of 50% of drug costs, significantly improving access and reducing financial burden to patients (*42*). However, DAA prices remain high because of in-country mark-ups which may include shipping, insurance, import duties and in-country taxes, and storage *etc.* (*43*).

What's next at the cusp of the decade of elimination by 2030

With the exception of certain early adopter countries such as Malaysia and Mongolia, many of the HCV elimination initiatives in the region were first established in 2019 and therefore the majority of services for screening, diagnosis, treatment and care are still in the initial phases of expansion. Discussions from the Expert Consultation on Viral Hepatitis Elimination in the Western Pacific held in December 2020, noted the tremendous progress made and recommended acceleration of coordinated integrated programming needed to achieve elimination. This includes immunization, maternal and child health, HIV/sexually transmitted infections, noncommunicable diseases and cancer control (*44*). A multi-dimensional, public health approach for prevention and treatment of viral hepatitis and chronic liver disease alongside addressing harmful use of alcohol and obesity (non-alcoholic fatty liver disease, NAFLD) is also required (*45*). There is need to strengthen national responses in access to hepatitis testing and care and achieve more systematic testing of the adults, adolescents and children in high-burden countries or high priority populations, ensure screening for liver cancer particularly among those with cirrhosis even following cure, simplify models of care and delivery, deliver decentralized and integrated services at primary care, task-shift routine care to non-specialists, and promote HCV-self testing use and multiplex rapid diagnostics in different population groups, as well as strategic placement of point-of-care HCV viral load platforms (*11,46-49*). Increasing use of pooled procurement will also be important to reduce costs of tests and medicines, as well as improved governance over existing data systems to enable better reporting to the Global Reporting Systems for Hepatitis (GRSH) (*50*).

COVID-19 has significantly strained health systems in all countries across the world as countries prioritize their response to the pandemic and to providing universal vaccination against SARS-CoV-2 (*51*). Public health interventions to control the pandemic such as physical distancing and re-organization of services and resources have affected the full continuum of HCV services, but especially routine testing, testing campaigns, clinics visits for treatment initiation, monitoring and cancer care (*52*). Community outreach, integral to providing care for the most vulnerable and at-risk individuals, were suspended in most countries (52,53). Studies documenting the impact of COVID-19 on essential service delivery including hepatitis care indicate acute and critical reduction of hepatitis services, but also suggested that many countries had implemented mitigation strategies to protect patients and providers (54). Innovations arising from COVID-19 response include increasing use of digital and e-health with tele-consultations, multi-month prescriptions, more flexible provision of opiate substitution therapy, and greater use of multi-disease diagnostic platforms - both high throughput lab-based and point-of-care. There is also an increasing recognition that investment in health and ensuring UHC (and so in turn, greater economic and national security) can provide opportunities and lessons to support a "building forward better" future for hepatitis elimination in the coming decade.

In 2022, WHO will launch the next Global Health Strategy for Viral Hepatitis 2022-2030, alongside those for HIV and syphilis, and work is also in progress on the WHO framework for multi-disease elimination. The updated strategy will include new epidemiological data and 2025 targets to bridge the gap between the 2020 targets and 2030, alignment with new political commitments including those on primary health care and on universal health coverage, shifts towards domestic rather than donor-driven funding, technological advances and innovations, and shift to increasing community delivery and differentiated services, while highlighting areas where responses have stagnated and the need to deliver more regionalized and population-specific responses (*55*). WHO has recently developed

interim guidance with criteria and measurement approaches for countries seeking validation of elimination of viral hepatitis as a public health threat (*56*). Overall, the guidance proposes the use of absolute impact targets (rather than the relative reduction targets as originally defined in the 2016 global health sector strategy for viral hepatitis for validation of HCV elimination. These include an absolute annual HCV incidence of ≤ 5 per 100,000 persons and of ≤ 2 per 100 people who inject drugs, and an HCV-related annual mortality rate of ≤ 2 per 100,000 persons (*56*).

The Western Pacific Region has a shared vision for WHO's work with countries and partners outlined in the "For the Future: towards the healthiest and safest region" (*57*). This vision requires transformation and future-proofing health systems taking a whole-of-systems approach for health and wellbeing. To get to hepatitis elimination in the next decade, there is need to recognize that COVID-19 will continue to impact the region for a very long time. This also confers opportunities to pivot, adapt and re-design investments in health systems and services to benefit all populations beyond COVID-19 while preparing for future public health emergencies (*58*). Consolidated efforts of governments, donors, partners and communities will be needed to shape this future and build the common vision towards hepatitis elimination by 2030. The future is yet to be written.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. World Health Organization. Global Health Sector Strategy on Viral Hepatitis 2016-2020. *https://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf;jsessionid=5BF52293B12E4CCFB85FCE3FDE10440A?sequence=1* (accessed May 20, 2021).
2. World Health Organization. Progress report on HIV, viral hepatitis and sexually transmitted infections 2019. Accountability for the global health sector strategies, 2016-2021. *https://apps.who.int/iris/bitstream/handle/10665/324797/WHO-CDS-HIV-19.7-eng.pdf?ua=1* (accessed May 20, 2021).
3. World Health Organization. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. *https://apps.who.int/iris/rest/bitstreams/1348210/retrieve* (accessed May 26, 2021).
4. UNITAID. Technology and market landscape: hepatitis C medicines. *https://unitaid.org/assets/HCV-Medicines-Landscape_Aug-2017.pdf* (accesssed May 20, 2021).
5. AASLD-IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015; 62:932-954.
6. AASLD-IDSA HCV Guidance Panel. Hepatitis C guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. Clin Infect Dis. 2018; 67:1477-1492.
7. Ghany MG, Morgan TR; AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C guidance 2019 update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America recommendations for testing, managing, and treating hepatitis C virus infection. Hepatology. 2020; 71:686-721.
8. Omata M, Kanda T, Wei L, *et al*. APASL consensus statements and recommendation on treatment of hepatitis C. Hepatol Int. 2016; 10:702-726.
9. World Health Organization. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. *https://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf?ua=1* (accessed May 20, 2021).
10. Bemelmans M, van den Akker T, Ford N, Philips M, Zachariah R, Harries A, Schouten E, Hermann K, Mwagomba B, Massaquoi M. Providing universal access to antiretroviral therapy in Thyolo, Malawi through task shifting and decentralization of HIV/AIDS care. Trop Med Int Health. 2010; 15:1413-1420.
11. Oru E, Trickey A, Shirali R, Kanters S, Easterbrook P. Decentralisation, integration, and task-shifting in hepatitis C virus infection testing and treatment: a global systematic review and meta-analysis. Lancet Glob Health. 2021; 9:e431-e445.
12. Shiha G, Soliman R, Mikhail NNH, Easterbrook P. An educate, test and treat model towards elimination of hepatitis C infection in Egypt: Feasibility and effectiveness in 73 villages. J Hepatol. 2020; 72:658-669.
13. Shiha G, Soliman R, Mikhail NNH, Easterbrook P. Reduced incidence of hepatitis C in 9 villages in rural Egypt: Progress towards national elimination goals. J Hepatol. 2021; 74:303-311.
14. Shiha G, Soliman R, Serwah A, Mikhail NNH, Asselah T, Easterbrook P. A same day 'test and treat' model for chronic HCV and HBV infection: Results from two community-based pilot studies in Egypt. J Viral Hepat. 2020; 27:593-601.
15. Mangia A, Cotugno R, Cocomazzi G, Squillante MM, Piazzolla V. Hepatitis C virus micro-elimination: Where do we stand? World Journal of Gastroenterology. 2021; 27:1728-1737.
16. World Cancer Research Fund. Liver cancer statistics. *https://www.wcrf.org/dietandcancer/liver-cancer-statistics/* (accessed May 22, 2021).
17. World Health Organization Regional Office for the Western Pacific. Regional Action Plan for Viral Hepatitis in the Western Pacific 2016-2020: a priority action plan for awareness, surveillance, prevention and treatment of viral hepatitis in the Western Pacific Region. *https://apps.who.int/iris/bitstream/handle/10665/208337/97892906177617_eng.pdf?sequence=1&isAllowed=y* (accessed May 22, 2021).
18. World Health Organization Regional Office for the Western Pacific. Regional Framework for the Triple Elimination of Mother-to-Child Transmission of HIV, Hepatitis B and Syphilis in Asia and the Pacific, 2018-2030. *https://apps.who.int/iris/bitstream/handle/10665/274111/9789290618553-eng.pdf?sequence=1&isAllowed=y* (accessed May 23, 2021).
19. World Health Organization Regional Office for the Western Pacific. Western Pacific Regional Strategy for Health Systems Based on the Values of Primary Health

Care. *https://apps.who.int/iris/handle/10665/207483* (accessed May 22, 2021).
20. World Health Organization Regional Office for the Western Pacific. Implementation progress of the regional action plan for viral hepatitis in the Western Pacific 2016-2020: progress report, June 2019. *https://www.who.int/westernpacific/health-topics/hepatitis/implementation-progress-of-the-regional-action-plan-for-viral-hepatitis-in-the-western-pacific-2016-2020* (accessed May 23, 2021).
21. Coalition Plus. The essential role of communities in HCV elimination: A summary of the three-part virtual meeting held December 8-10, 2020. *https://www.coalitionplus.org/wordpress/wp-content/uploads/2021/05/Activist-Meeting-Summary-Final-Version.pdf* (accessed May 24, 2021).
22. World Health Organization Regional Office for the Western Pacific. Health financing regional profile 2018: transitioning to integrated financing and service delivery of priority public health services. *https://iris.wpro.who.int/bitstream/handle/10665.1/14332/9789290618638-eng.pdf* (accessed May 24, 2021).
23. Medecins Sans Frontieres. Cambodia: MSF provides first free Hep C care in the country https://msf-seasia.org/MSF-provides-first-free-Hepatitis-C-care-in-Cambodia (accesssed May 23, 2021)
24. Zhang M, O'Keefe D, Craig J, Samley K, Bunreth V, Jolivet P, Balkan S, Marquardt T, Dousset JP, Le Paih M. Decentralised hepatitis C testing and treatment in rural Cambodia: evaluation of a simplified service model integrated in an existing public health system. Lancet Gastroenterol Hepatol. 2021; 6:371-380.
25. Clinton Health Access Initiative. Cambodia experience: developing a hepatitis C financing strategy. *https://www.hepatitisfinance.org/wp-content/uploads/2020/12/Cambodia_Financing_reportFINAL.pdf* (accessed May 23, 2021).
26. Adee M, Zhuo Y, Zhan T, Chen Q, Toumi A, Ayer T, Nwankwo C, Zhong H, Puenpatom A, Chhatwal J. A tool to inform hepatitis C elimination: A case for hepatitis C elimination in China. Clin Liver Dis (Hoboken). 2021; 17:99-106.
27. Heffernan A, Ma Y, Nayagam S, Chan P, Chen Z, Cooke GS, Guo Y, Liu C, Thursz M, Zhang W, Zhang X, Zhang X, Jia M, Hallett TB. Economic and epidemiological evaluation of interventions to reduce the burden of hepatitis C in Yunnan province, China. PLoS One. 2021; 16:e0245288.
28. Zhang P, Guo R, Lian J, Zhi M, Lu C, Wu W, Wang L, Chan P, Chen Z, Sun J. Unblocking barriers of access to hepatitis C treatment in China: Lessons learned from Tianjin. Ann Glob Health. 2020; 86:36.
29. Zhou HY, Liu S, Zheng SJ, Peng XX, Chen Y, Duan C, Zheng QF, Wang Z, Duan ZP. Coverage of different health insurance programs and medical costs associated with chronic hepatitis C infection in mainland China: a cross-sectional survey in 20 provinces. Hepatol Med Policy. 2016; 1:7.
30. World Health Organization Regional Office for the Western Pacific. Minimising the financial burden of hepatitis C. *https://www.who.int/china/activities/minimising-the-financial-burden-of-hepatitis-c* (accessed May 24, 2021).
31. World Health Organization Regional Office for South East Asia. UHC technical brief: Country experiences in using TRIPS safeguards: Part 1. *https://apps.who.int/iris/rest/bitstreams/1140143/retrieve* (accessed May 23, 2021).
32. Chan H, Hassali MA, Md Said R, Abu Hassan MR. Treatment coverage and drug expenditure in hepatitis C patients from 2013 to 2019: A journey of improving treatment accessibility in Malaysia through government-led initiatives. Hepatitis Monthly. 2020; 20:e107372.
33. FIND and DND*i* team up to support Malaysian MOH efforts to simplify and decentralize hepatitis C screening & treatment. *https://dndi.org/press-releases/2018/find-dndi-malaysianmoh-efforts-hepatitisc-screening-treatment/* (accessed May 25, 2021).
34. Positive Malaysian Treatment Access and Advocacy Group (MTAAG+) and Treatment Action Group (TAG). Hepatitis C virus diagnostics advocacy workshop: summary report. *https://hepcoalition.org/IMG/pdf/malaysia_summary_report_hcv_diagnostics_advocacy_workshop.pdf* (accessed May 24, 2021).
35. Urgent need to increase hepatitis testing and treatment: Mongolia showcases impressive progress, inspiring hope and opportunities. *https://www.who.int/westernpacific/news/detail/26-07-2018-urgent-need-to-increase-hepatitis-testing-and-treatment* (accessed May 27, 2021).
36. World Health Organization Regional Office for the Western Pacific. Action on hepatitis in Mongolia. *https://www.who.int/westernpacific/news/feature-stories/detail/action-on-hepatitis-in-mongolia* (accessed May 26, 2021).
37. World Health Organization. Accelerating access to hepatitis C diagnostics and treatment: Overcoming barriers in low- and middle-income countries. *https://apps.who.int/iris/rest/bitstreams/1328465/retrieve* (accessed May 25, 2021).
38. Center for Disease Analysis. Polaris Observatory: Philippines profile: hepatitis C. *https://cdafound.org/dashboard/polaris/dashboard.html* (accessed May 23, 2021).
39. Belarmino ZC, Carbajosa JC. Center offers free treatment for hepatitis. *https://www.pressreader.com/philippines/the-freeman/20190626/281676846446060* (accessed May 24, 2021).
40. Nguyen TP, Luu HN, Nguyen MVT, Tran MT, Tuong TTV, Tran CTD, Boffetta P. Attributable causes of cancer in Vietnam. JCO Glob Oncol. 2020; 6:195-204.
41. WHO welcomes progress in access to Hepatitis C treatment in Viet Nam. *https://www.who.int/vietnam/news/detail/10-05-2017-who-welcomes-progress-in-access-to-hepatitis-c-treatment-in-viet-nam* (accessed May 25, 2021).
42. Boeke CE, Adesigbin C, Agwuocha C, *et al.* Initial success from a public health approach to hepatitis C testing, treatment and cure in seven countries: the road to elimination. BMJ Glob Health. 2020; 5:e003767.
43. Clinton Health Access Initiative. Hepatitis C market report. *https://3cdmh310dov3470e6x160esb-wpengine.netdna-ssl.com/wp-content/uploads/2020/05/Hepatitis-C-Market-Report_Issue-1_Web.pdf* (accessed May 23, 2021).
44. World Health Organization Regional Office for the Western Pacific. Expert consultation on viral hepatitis elimination in the Western Pacific Region, 1-3 December 2020 Virtual meeting. *https://iris.wpro.who.int/bitstream/handle/10665.1/14717/RS-2020-GE-36-virtual-eng.pdf* (accessed May 23, 2021).
45. Kasai T. Time to act to make elimination of viral hepatitis

a reality. Lancet Gastroenterol Hepatol. 2020; 5:102-103.
46. Thu N, Thuy Cao, Huyen N, Dung N, Kinh N, Sacks J, Boeke C, Tebor J, Ramers C. Preliminary cure rates from the national HCV pilot program in Vietnam. Global Hepatitis Summit 2018; 14-17 June 2018; Toronto, Canada, 2018.
47. Lazarus JV, Pericas JM, Picchio C, Cernosa J, Hoekstra M, Luhmann N, Maticic M, Read P, Robinson EM, Dillon JF. We know DAAs work, so now what? Simplifying models of care to enhance the hepatitis C cascade. J Intern Med. 2019; 286:503-525.
48. Government of South Australia. Nursing model of care for viral hepatitis management in South Australia. *https://www.sahealth.sa.gov.au/wps/wcm/connect/f5dc9e63-ad02-4d51-801c-164efc46143d/NursingMOCViralHepatitisManagementSA-CDCB-04122017.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-f5dc9e63-ad02-4d51-801c-164efc46143d-nwL2B6x* (accessed May 23, 2021).
49. Lloyd AR, Clegg J, Lange J, Stevenson A, Post JJ, Lloyd D, Rudge G, Boonwaat L, Forrest G, Douglas J, Monkley D. Safety and effectiveness of a nurse-led outreach program for assessment and treatment of chronic hepatitis C in the custodial setting. Clin Infect Dis. 2013; 56:1078-1084.
50. World Health Organization. Global reporting system for hepatitis 2018. *https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hepatitis/strategic-information/global-reporting-system/docs/default-source/hq-hiv-hepatitis-and-stis-library/ghrs---global-hepatitis-reporting-system/GRSH-Data_entry_manual* (accessed July 2, 2021).
51. OECD/World Health Organization. Chapter 2. The impact of the COVID-19 outbreak on Asia-Pacific health systems. 2020. *https://www.oecd-ilibrary.org/sites/aaa5448f-en/index.html?itemId=/content/component/aaa5448f-en* (accessed August 3, 2021).
52. Laury J, Hiebert L, Ward JW. Impact of COVID-19 response on hepatitis prevention care and treatment: Results from global survey of providers and program managers. Clin Liver Dis (Hoboken). 2021; 17:41-46.
53. Care Consortium. Community-led rapid survey COVID-19 impact on key populations, people Living with HIV and Global Fund Sub-Recipient Organizations in Sri Lanka. *https://apcaso.org/apcrg/wp-content/uploads/2020/07/English-Final_COVID-19-Impact-Survey-Report-1.pdf* (accessed May 23, 2021).
54. World Health Organization. Second round of the National pulse survey on continuity of essential health services during the COVID-19, January-March 2021. *https://apps.who.int/iris/rest/bitstreams/1343409/retrieve* (accessed May 23, 2021).
55. World Health Organization. EB148/37 Global strategies and plans of action that are scheduled to expire within one year: The global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections, for the period 2016-2021, report by the Director-General. https://apps.who.int/gb/ebwha/pdf_files/EB148/B148_37-en.pdf (accessed May 28, 2021).
56. World Health Organization. Interim guidance for country validation of viral hepatitis elimination. *https://www.who.int/publications/i/item/9789240028395* (accessed May 23, 2021).
57. World Health Organization Regional Office for the Western Pacific. For the future : towards the healthiest and safest Region. A vision for the WHO work with Member States and partners in the Western Pacific. *https://iris.wpro.who.int/bitstream/handle/10665.1/14476/WPR-2020-RDO-001-eng.pdf* (accessed May 24, 2021).
58. Kasai T. From the "new normal" to a "new future": A sustainable response to COVID-19. Lancet Reg Health West Pac. 2020; 4:100043.

Received June 4, 2021; Revised July 2, 2021; Accepted August 3, 2021.

Released online in J-STAGE as advance publication August 13, 2021.

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Global Health & Medicine. 2021; 3(5):262-269.
REVIEW
DOI: 10.35772/ghm.2021.01069

Epidemiology of viral hepatitis C: Road to elimination in Japan

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Abstract: Although HCV infection was the main cause of HCC in Japan contributing 70% over two decades after its first cloning in 1989, it was markedly decreased to 49% in 2013 and expected to decrease continuously. Based on blood donor national database, the new incident cases were 0.4/100,000 person-years, the prevalence was 0.13% and the total number was 890,902-1,302,179 in 2015. Establishment of blood donor screening with anti-HCV measurement and nucleic acid test introduced by Japanese Red Cross as pioneer, high-level medical and surgical care, and the government's policy under the Basic Act on Hepatitis Control have changed its epidemiology and outbreak trend and also enforced the disruption of potential transmission cascades. HCV prevalence among the younger generation was extremely low in all regions, and the predominant age for HCC has shifted to over 60 years old population. Considering such changes, HCV induced HCC occurrence is supposed to be ultimately suppressed in the near future. However, taking into account society changes, regulating intravenous drugs users and monitoring high-risk groups such as tattoos, and men who have sex with men are indeed required in Japan. Understanding the epidemiological changes in HCV is important in assigning, modifying, and designating effective response systems. Selective or national action plans, strategic approaches, and cooperation between government sectors have a positive impact on HCV prevention and control. A dramatic decrease in total number of HCV carriers, increase in number of people treated with highly effective DAA, and subsequent high SVR indicates Japan might achieve WHO's target of HCV elimination by 2030.

***Keywords*:** disease burden, elimination, countermeasure, Japan

Introduction

Hepatitis C virus (HCV) is a positive sense, single-stranded RNA virus sharing the same family of *Flaviviridae* with yellow fever virus, West Nile virus and Dengue virus (*1,2*). HCV has accounted for a major public health burden worldwide and the World Health Organization (WHO) reported that an estimated 71 million people have chronic HCV infection with an attributable death of 399,000 people due to HCV related liver cirrhosis (LC) and hepatocellular carcinoma (HCC) in 2016 (*3*). Moreover, HCV is the major cause of HCC and has contributed to 70-80% of LC and 15% of HCC worldwide (*4*). Therefore, WHO set a global elimination target of viral hepatitis B and C by 2030. Concerning HCV, three major terminal points were set as follows: 80% increase of those eligible to be treated, 90% reduction in incidence of new infection and 65% reduction in HCV-related mortality.

HCV was discovered as the cause of non-A, non-B hepatitis and it was first cloned in 1989 (*1,5*). HCV particles are 50-80 nm in diameter and the HCV genomes comprised of 5'-3' single stranded RNA of 9.6 kilo base pairs bearing ten different open reading frames (ORF) encoding for the production of core, E1, E2, p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B (*6*). HCV isolates can be classified into seven genotypes (1 to 7) and a number of subtypes and its various geographical distribution (*7*). The virulence, transmissibility and sensitivity to antiviral therapy might be greatly influenced by its genotypes. The dominant genotype of HCV in Japan is genotype 1b followed by genotype 2a and 2b (*8-10*). At times, HCV genotype 2b comes across over genotype 1b among those born after 1970 while genotype 2a is constantly found in all age groups in Japan (*8,9,11*). A similar pattern of genotype distribution was also found in hemodialysis patients and a change in genotype distribution from genotype 1b to 2a/2b was also reported among those who started dialysis after 1991 (*12*). In this review article, we would like to express the epidemiology of HCV in Japan.

Countermeasures against HCV in Japan

After cloning of HCV, the diagnostic assays and the treatment for HCV have been gradually developed.

In Japan, screening of antibodies to HCV (anti-HCV) by first generation recombinant enzyme linked immunosorbent assay (ELISA) was started among blood donors since November 1989 (*13*) and replaced by second generation passive hemagglutination (PHA) in April 1992 (*14*). Until 2007, the Japanese Red Cross Society (JRC) used either PHA method (second generation) (HCV-PHA "Dynabot") or PA method (Ortho HCV Ab PA Test II) and substituted with CLEIA method (chemiluminescent enzyme immunoassay, Lumipulse Presto Ortho HCV, Fujirebio Ltd.) in 2008 and CLIA method (chemiluminescent immunoassay, Abbott Architect) in 2018 respectively. JRC uses unique reagents and diagnostic criteria for HCV screening uniformly throughout the country. Moreover, nucleic acid testing (NAT) to screen for HCV RNA was added to HCV screening as a parallel test in October 1999 by JRC (*14,15*).

Later, the Ministry of Health, Labour and Welfare (MHLW) of Japan introduced the initial 5-year project (2002-2006) for the national screening of HBV and HCV among all residents at and over 40 years old (*16*). Later, the aforementioned screening systems are continuing with their prosperity. The screening system for HCV uses the combination of anti-HCV measurement and HCV RNA detection using NAT at the same time. The screening is targeted to explore asymptomatic cases in the general population. It is a unique and effective screening strategy having the benefit of early diagnosis of HCV infection.

Since 2004, JRC implemented the look-back system, in which all collected blood products were partly stored for 10 years with the aim to reconfirm the components of blood products when a blood donor tested positive for infection has a previous record of blood donation and if that blood product was already sent to medical institutions according to the guidelines for look-back system on blood products (*17*).

Aiming to improve the medical care service for liver disease, the regional core specialty hospitals for liver disease were established in all prefectures of Japan in 2007 under the notification of the Health Bureau of the MHLW (*18*). All the core hospitals conduct the following activities: *i*) provision of general medical information on liver disease, *ii*) gathering and sharing information on medical institutions in the prefecture, *iii*) organizing workshops and lectures to medical personnel and health education to local residents, and providing consultation support on liver disease, and *iv*) setting up a forum for consultation with specialist medical institutions on liver disease. In 2008, the medical expense subsidy system was installed in Japan and then the Basic Act on Hepatitis Measures has been formulated since 2010 (*16*).

Interferon-based treatment of HCV infection was started in 1992. The interferon free first-generation Direct Acting Antiviral (DAAs) were introduced in 2014 and then the second generation DAAs have been phasing in since 2015. The development of oral drug DAAs, which have very high sustained virologic response to HCV (SVR), has led to a marked improvement in the treatment of HCV since 2014 (*16*). The evolution of HCV and its countermeasures over the past 30 years in Japan in terms of basic medical, clinical and epidemiological aspects is very impressive (Figure 1).

Natural history of HCV simulated by Markov Model

The natural history of chronic HCV infection was clarified for the first time in 2003 using a Markov model based on clinical cohort data composed of a group of patients who were found to be infected at the time of blood donation and were followed up for a long time at the liver disease hospitals in the 1990s (*19*). Using medical records of a total 942 HCV carriers among blood donors from 1990 to 1999, the natural history of HCV infection was simulated by the Markov Model. The hypothetical cohort demonstrated that among 40 year old males who were diagnosed as asymptomatic HCV carriers, 2.62% of them remain unchanged in their liver disease state but 48.4% developed into chronic hepatitis (CH), 14.6% into LC and 34.4% into HCC at 30 years after initial diagnosis and without any treatment. In contrast to males, the rates were 1.85%, 45.4%, 32.8% and 20.0% respectively in females of the same age group (*19*).

Based on the cumulative probabilities for developing

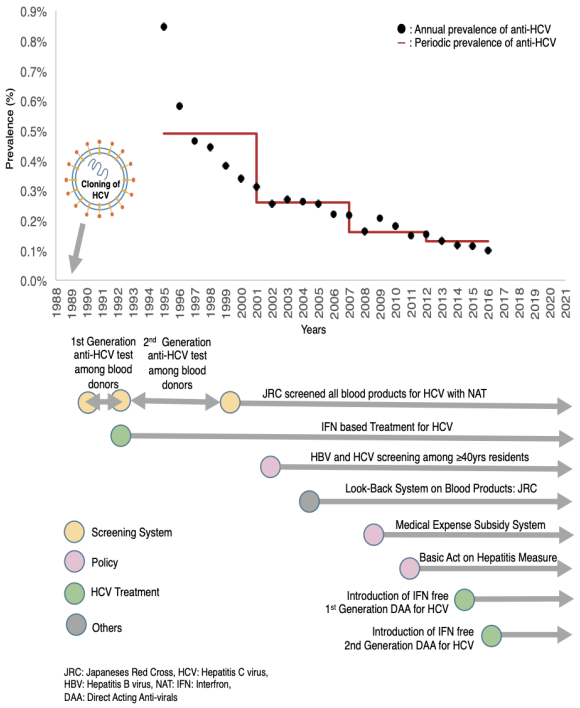

Figure 1. HCV prevalence trend among first time blood donors and its corresponding countermeasure in Japan. In the figure, the red line shows the prevalence of anti-HCV among first time blood donors since 1995. The decreasing trend was illustrated by line and each countermeasure was stated with corresponding arrow indicating the implemented year.

LC and HCC, 43.8% of 40 year old male initially diagnosed as CH remains unchanged as CH, but 15.0% developed into LC and 41.1% into HCC when they were 70 years old. Meanwhile, the rates were 38.9%, 32.7% and 22.0% respectively in females of the same age group (*19*) (Figure 2).

Based on the aforementioned results, it was clarified that the liver disease state progresses in those chronically infected with HCV even if the person is asymptomatic. Moreover, the turnover rate to HCC is increased with age. On the other hand, it is important to find a person who is chronically infected with HCV at an early stage before symptoms appear (necessity of hepatitis virus screening) and provide effective treatment to prevent the onset of carcinogenesis, and most importantly to treat HCC at its dominant age of carcinogenesis. This is part of the evidence that led to the introduction of hepatitis virus testing for all Japanese residents aged 40 and over.

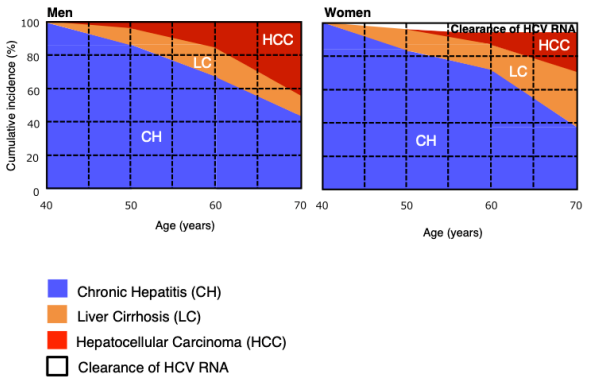

Figure 2. Natural course of HCV infection in hypothetical cohorts aged 40 years until they reach 70 years of age. It shows the transition probabilities and the natural course of HCV infection in those who were diagnosed with HCV induced chronic hepatitis at the age of 40 and then turned into 70 years old. The starting point is defined at 40 years old who were first diagnosed as chronic hepatitis.

Prevalence of HCV in Japan

A study of anti-HCV prevalence among blood donors during 1995-2000 included 3,485,648 first time blood donors in Japan and the prevalence was reported to be 0.49%. Females had higher prevalence than males (0.48% *vs.* 0.50%) (*20*). Anti-HCV positive rate is high in the west regions (Chugoku, Shikoku, Kinki and Kyushu regions) ranging from 0.6-0.7% and lower in the east regions (Tohoku, Kanto and Chubu regions) ranging from 0.3 to 0.4% except Hokkaido (0.6%) (*20*).

The prevalence also differed by age and sex, females had higher prevalence than males until 35 years old but the reciprocal was found after 35 years old having lower prevalence in females (*21*). Anti-HCV positive rate of the elderly is extremely high at 1.28-3.38%, and the same tendency is shown in all regions. In Japan, 89-93% of anti-HCV positive people are over 40 years old in 2000.

The Epidemiological Research Group on the Burden of Viral Hepatitis and Measures for its Elimination (VH-Epi) conducted the study about HCV among first time blood donors in collaboration with the Japanese Red Cross Society (*20,22,23*). The overall anti-HCV prevalence among first-time blood donors was 0.49% (95% CI: 0.48-0.50%) during 1995-2000 (*20*), 0.26% during 2001-2006 (*23*) and 0.16% during 2007-2011 (*22*). The prevalence was found to be less than 1% in all age groups of both sexes (*22*) while it was as low as 0.13% (95% CI: 0.13-0.14%) in the 2012-2016 population (Figure 3) (*24*). Moreover, the prevalence among first-time blood donors in all of Japan during 2012-2016 were divided into the eight main regions of Japan and shown in Figure 3. Age dependent prevalence was reported, with higher prevalence of HCV infection in older age groups and low prevalence in the generation born in the 1990s. Although prevalence among older generation during 2012-2016 was reportedly higher than young generation, it was found to be lower than the same age group of the previous study during 1995-2000. Although the data contained those who were born before 2000, no administrative or clinical cases of widespread infection were reported in the population born after 2000 and it is suggested that HCV infection rate among the general population born after 2000 remains low. To explore prevalence among those born after 2000, a further study is needed.

Incidence of HCV in Japan

New incident cases of HCV in Japan are obligated to report to the Infectious Disease Surveillance of National Institute of Infectious Disease as a Type 5 infectious disease so that such information can be obtained in Japan.

As HCV infection is somehow asymptomatic and subclinical, it is important to monitor the persistence of HCV infection in combination with surveillance through notification under the Infectious Disease Control Law. Additionally, the epidemiological survey on specific populations is also considered necessary to be conducted regularly.

Since the early 1990s, the VH-Epi has conducted and reported on several database-oriented surveys with the cooperation of JRC in order to clarify the new incidence of HCV regionally and on a nationwide scale, the results are shown as follows.

The incidence of HCV among 448,020 individuals who donated 2,676,738 blood units in Osaka during 1992-1997 was reported to be 3.8 per 100,000 person-years (*25*). The highest incidence rate of HCV was found in younger blood donors (16-24 years old: 8.89) compared to older blood donors (35-49 years old: 1.81). In Hiroshima, the incidence study on HCV among blood donors has been started since 1994 (*26*). This study included 218,797 individuals who donated 1,207,773 blood units at regional JRC Blood Center in Hiroshima

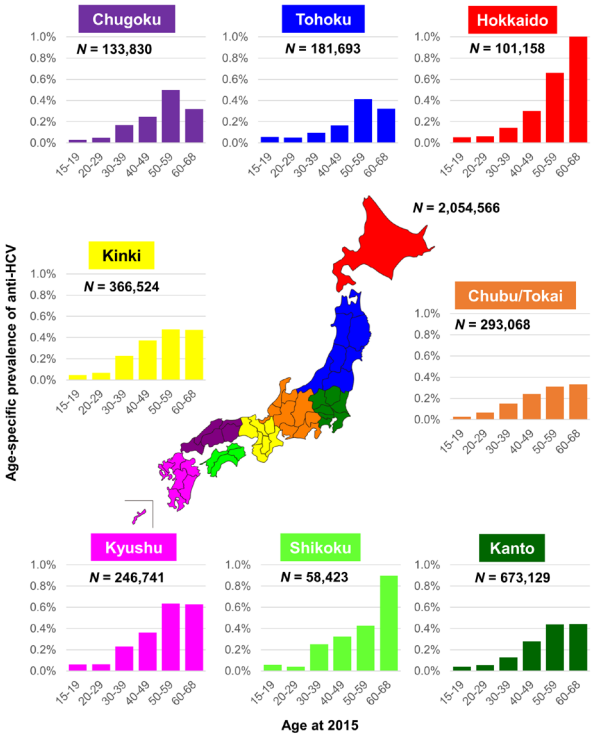

Figure 3. Age-specific prevalence of anti-HCV among first-time blood donors during 2012-2016. In this figure, Japan is geographically divided into eight main regions and the age specific prevalence of anti-HCV is shown for each region in the bar graph and each color in the map represents its corresponding region.

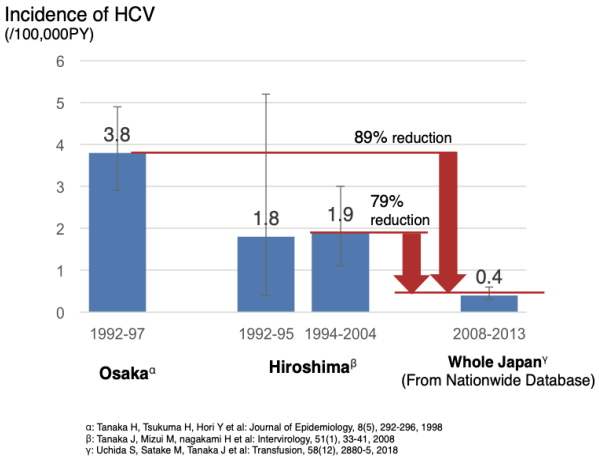

Figure 4. Trend of HCV Incidence among blood donors. This figure represents the incidence rate of anti-HCV among blood donors in Osaka (1992-19797), Hiroshima (1992-1995 and 1994-2004) and all of Japan (2008-2013). The reduction of the incident cases is indicated by the red arrow.

during 1994-2004 (*26*). HCV infection developed in 16 individuals in follow-up visits accounting for an incidence rate of 1.86 per 100,000 person-years (95% CI: 1.06-3.01) (Figure 4). The incidence rate was higher in females than males in the age group over 50 (*26*).

Using the national database of blood donors in Japan, the retrospective cohort study on HCV incidence was conducted in collaboration between the VH-Epi group and JRC to investigate new HCV RNA positivity (new HCV infection) during 2008-2013 (Figure 4) (*27*). The cohort included those who donated blood at least twice during the two-year period from October 2008 to September 2010, 2,341,338 (7,770,533 person-years) and were consecutively "HCV RNA negative and HCV antibody negative" at the first two donations (Figure 4). From the results, the rate of new HCV infections as a whole in Japan is estimated to be 0.40 per 100,000 person-years (95% CI: 0.27-0.57) (*27*), which is considered to be a very low rate and it is an 89% reduction from previous study in Osaka during 1992-1997 (*25*) and a 79% reduction from previous study in Hiroshima during 1994-2004 (*26*).

The incidence of post-transfusion hepatitis in Japan was high (> 50%) in the 1960s when the system was based on the sale of blood but fell sharply to 0.48% in 1992 with introduction of the blood donation system, the elimination of HBsAg-positive or anti-HCV positive blood, the introduction of 400 ml blood collection followed by the introduction of nucleic acid amplification testing. The number of cases of post-transfusion infections (HBV, HCV and HIV) since 2008 were also reported (*24*). The number of cases identified as post-transfusion infection after confirmation of donated blood samples were investigated retrospectively. After the NAT introduction, no cases of HCV infection have been found since 2009 (*24*). Therefore, transfusion associated HCV infection in Japan is considered to be almost under control.

Total number of chronic HCV infections in Japan

Since the introduction of anti-HCV screening system to all blood donors in 1990, the nationwide epidemiological study on HCV infection has been conducted in each period. Such prevalence studies are able to estimate the number of chronic HCV infections in each age group with known age specific anti-HCV or HCV RNA prevalence. The estimated number of chronic HCV infections aged 16-69 years old during 1995-2000 was 884,954 (95% CI: 725,082-1,044,826) in total, 0.46 million in males and 0.42 million in females (*20*). Based on the above mentioned results during 1995-2000, MHLW added additional data covering over 70 years old undiagnosed carriers and patients. Therefore, estimation of chronic HCV infection was expanded, and the total number was estimated to be 1,694,954-2,194,954 including patients engaged in care and undiagnosed carriers as of 2000. Later the medical claim recording system and the health information system were improved after installing the electronic data system in medical institutions and systematic use of International Classification of Disease (ICD) for electronic input of medical data, clinical diagnosis, and its associated

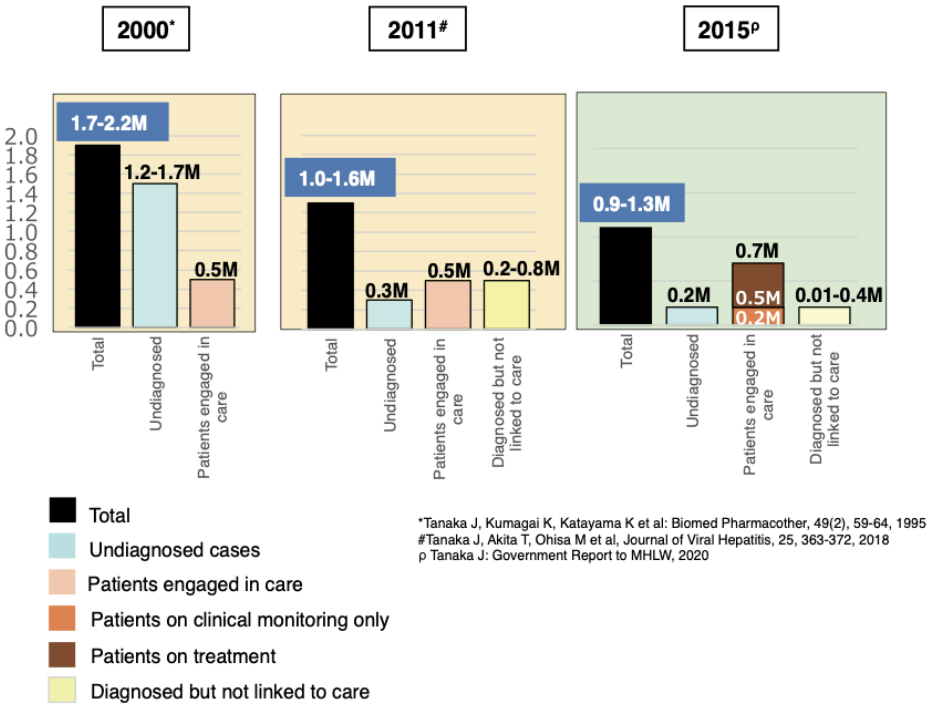

Figure 5. Trend of HCV carriers in Japan during 2000-2015. This figure simply presents the number of HCV carriers by their liver disease status in 2000 and 2011. Each colored bar represents each liver disease status, in order, Total number of HCV carriers, Undiagnosed HCV carriers, Patients taking medical care as in or outpatients at health facilities, and the un-consulted patients who never visit or were lost to follow-up after being diagnosed as HCV carriers. For 2015, the patients are shown in two subcategories: dark brown bar for those taking antiviral treatment and light brown bar for those not taking any antiviral treatment.

records. Considering HCV diagnosed cases but not linked to care, the estimated number of people with chronic HCV infection in the year 2011 was 983,879-1,583,879 (*22*). That number has obviously decreased during 2000-2011 and it is believed to be the impact of the introduction of interferon-based treatment (1992) and NAT to all blood donors (1999) and to all over 40 years old (2002), and installing the medical subsidy system (2008) in Japan. This configuration of the total number of chronic HCV infections allowed us to understand the current HCV burden in Japan. During 2000-2011, the number of HCV new infections was 33,460, the number of cases achieving HCV-RNA clearance was 200,000-300,000 and the number of deaths due to all causes among carriers was 230,750-411,075 (*16,22*) (Figure 5). Based on the analysis of the national database, the total number in 2015 decreased to 890,902-1,302,179, the undiagnosed cases decreased to 224,652, the number diagnosed but not linked to care was 13,061-424,338, those on treatment was 471,986 and those taking clinical monitoring only was 181,203 (*24*).

The VH-Epi is managing many public and national databases such as blood donor data, National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), infectious disease surveillance system of the National Institute of Infectious Diseases, other national data (demographic, statistics, patient surveys, report on regional public health services and health promotion service, and issued record of application for government subsidized medical expense of hepatitis treatment), *etc.* Based on the abovementioned databases, which cover all of Japan, the VH-Epi, have been conducting complementary verification work with the data obtained from large-scale surveys, *etc.* (survey on the consultation rate after diagnosis, hepatitis virus screening receiving rate survey, pregnant woman survey, serum epidemiological survey in highly invasive areas), and have calculated the number of people chronically infected with hepatitis viruses including HCV in Japan over time.

Moreover, the total number of people chronically infected with HCV in Japan was effectively utilized not only by the government but also by companies as baseline data for planning hepatitis countermeasures and treatment strategies.

Contribution of HCV to HCC in Japan

Malignant neoplasms (cancer) have been the major leading cause of death in Japan since 1981, accounting for 27.3% of all deaths (*28*). In 2019, the cancer related mortality was 304.2 per 100,000 population attributing 376,425 deaths and reportedly an increase of 2841 deaths compared to the previous year. The second leading cause was heart disease (15.0%), followed by senility (8.8%), cerebrovascular disease (7.7%) and pneumonia (6.9%). When aspiration pneumonia was removed from the pneumonia category since 2017, the deaths due to

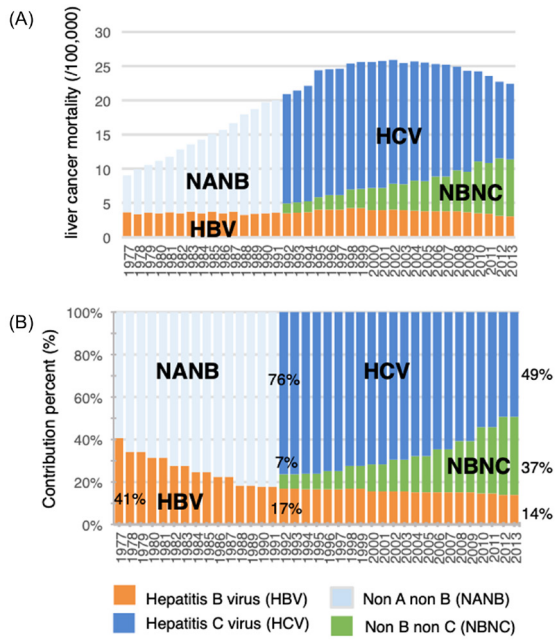

Figure 6. Contribution of HBV, HCV and others to HCC related deaths in Japan. This figure describes the contribution of HBV, HCV and others to HCC related deaths in Japan. The orange bar represents HBV, the green bar HCV, the light blue bar non-A non-B and the dark blue bar non B non C.

pneumonia was downgraded from third to fifth. Out of 376,425 malignant neoplasms, 20.0% originated from lung, 13.7% from colon, 11.4% from stomach, 9.7% from pancreas and 6.7% from liver (5th place for male and 7th place for female).

The VH-Epi has consistently used the same method and the same database to show the proportion of etiological factors contributing to liver cancer mortality since 1980 using the demographic data and the results of the Japan Liver Cancer Study Group. The trends in primary hepatocellular carcinoma (malignant neoplasms of the liver and intrahepatic bile ducts) in Japan are shown in Figure 6. The HCC mortality rate peaked in 2002 and has been decreasing slightly since 2000 for men and since 2010 for women (HCC deaths: 34,637 in 2002 and 25,264 in 2019). Figure 6 shows the causes of HCC by etiological virus. From the late 1970s to 2010, the mortality rate of HCC caused by persistent HBV infection remained almost constant at 3 to 4 per 100,000, but from 2010 to 2013, it showed a slight downward trend (Figure 6A). The proportion of HCV-induced HCC occurrence was 76% in 1992, but this proportion has gradually decreased and was estimated to be 49% in 2013 (Figure 6B). Instead, the proportion of death due to HCC from non-hepatitis B and non-hepatitis C has risen sharply in recent years. The "Basic Plan for the Promotion of Cancer Control" uses the "age-standardized mortality rate under 75 years" (ASR < 75) as an evaluation index for cancer deaths, and it was also calculated for death due to HCC. The number of deaths due to HCC under the age of 75 years has decreased, and those aged 75 years and over tend to account for half of all liver cancer deaths. Next, based on "under-75 age-adjusted mortality rate" for the period 2002-2017, the projection of HCC related mortality was estimated using the same generalized linear model by the National Cancer Centre, it was reported to be 2.7 and 1.9 per 100,000 population in 2025 and 2030, respectively (*24*). From these results, it is suggested that 60% of deaths due to HCC will occur in the people aged 75 and over in the near future and it indicates that the demand for liver cancer treatment for the elderly will increase. Therefore, it is necessary to consider providing liver cancer treatment to the elderly.

HCV infection among hemodialysis patients

Hemodialysis patients are prone to be infected with blood born infection including HCV infection. The reason behind is not only due to frequent long-term invasive therapeutic procedure but also due to the underlying impaired immune system. In 1990, the anti-HCV prevalence among hemodialysis patients was reportedly high at 23.5% and the blood transfusion history had no association to anti-HCV positivity (*21*). A study from 1999 to 2003 on HCV infection among hemodialysis patients in Hiroshima showed that the HCV RNA positive rate was 15.7% in 1999 and then decreased to 12.9% in 2003 (*29*). The prevalence decreased over 5 years after comprehensive installment of effective infection control measures in hemodialysis centers. The annual incidence of HCV infection was 0.33% *i.e.*, 3 in 1,000 hemodialysis patients were newly infected with HCV infection in a year. A recent study showed that the decreasing trend of both anti-HCV and HCV RNA positivity was found by their dialysis started year (*12*). For those who started dialysis after 2002, anti-HCV prevalence was 9.5% and HCV RNA positivity was 7%. The study also revealed that HCV RNA positivity is the predictive factor for poor prognosis of hemodialysis patients.

The Japanese Society of Dialysis Therapy (JSDT) has also conducted a survey on all 4026 of its institutional members (*30*). Although anti-HCV positive rate among the maintenance dialysis patients (approximately 120,000 patients in 2017) is reported at 5.18%, the rate is already high (3.37%) at the time of new dialysis introduction. Compared to the anti-HCV positive rate of 9.8% obtained from the same survey in 2007 (*31*), the rate has decreased by half over the past 10 years. By the latest 2018 annual report on dialysis patients with viral hepatitis, the prevalence of anti-HCV was 4.7% (*32*) and the positivity of HCV RNA among anti-HCV positives was 37% which was markedly lower than previous report (67% in 2007) (*31*). Moreover, the new treatment guideline for HCV infection especially for dialysis patients infected with HCV has been modified as the 2019 update (*33*) in which the Japan Society of Hepatology (JSH) in joint care with JSDT first recommends DAAs to dialysis

patients. In the future, it will be important to promote awareness of HCV-related guidelines to increase collaboration between nephrologists/dialysis specialists and hepatologists, referral rates to specialists and the uptake of antiviral therapy in order to combat HCV infection in dialysis facilities.

Conclusion

Japan has a vigorous effort on countermeasures against viral hepatitis, from four main aspects. First, the screening system, which was first introduced by JRC among blood donors and later expanded to the over 40 years old general population in all regions after development of anti-HCV measurement and NAT robustly disrupt the transmission cascade, reduce the incident and prevalent cases. Second, widespread screening at the regional and national level provides early diagnosis of asymptomatic carriers, early referral to liver disease specialty hospitals, installment of base specialty hospitals in all prefectures and introduction of highly effective DAAs mightily reduces the total number and contrary increases in number those on treatment, which distinctly reduces HCC occurrence and HCV related deaths. Third, the national policy plays a critical role, the medical subsidy system and the Basic Act on Hepatitis Measure are the very effective tools for promoting care and treatment of HCV and reducing its burden, and consequently accelerating universal health coverage. Last but not least, the cooperation between patients and medical associations is crucial to provide outstanding health care service and to attain the utmost control over HCV. Understanding the epidemiological changes in HCV is important in assigning, modifying, and designating effective response systems. Selective or national action plans, strategic approaches, and cooperation between government sectors have a positive impact on HCV prevention and control. A dramatic decrease in total number of HCV carriers, increase in number of people treated with highly effective DAA, and subsequent high SVR indicates Japan might achieve WHO's target of HCV elimination by 2030.

Acknowledgements

A part of this study was presented and published at American Association for the Study of Liver Diseases (AASLD) Special Conference on Hepatitis C in USA (New York) in 2014, the 51st International Liver Congress 2016 (EASL) in Spain Barcelona in 2016, Asian Pacific Association for the Study of Liver (APASL) 2016 in Tokyo, Japan in 2016, The Liver Meeting in USA (Washington) in 2016 and at the 24th International Symposium on Hepatitis C virus and Related Viruses (HCV2017) in USA (Massachusetts) in 2017. The authors thank many of the collaborative researchers and colleagues of the Epidemiological Research Group on the Burden of Viral Hepatitis and Measures for its Elimination (VH-Epi) under MHLW of Japan), Shigeki Uchida: Central Blood Institute of Japanese Red Cross Society; Hideki Aizaki: National Institute of Infectious Diseases; Kenji Ikeda: Toranomon Hospital; Tomiko Koyama: Iwate Health Service Association; Kazumi Yamasaki: National Hospital Organization Nagasaki Medical Center; Takashi Kumada: Ogaki Municipal Hospital; Keisuke Hino: Kawasaki Medical School; Takuji Torimura: Kurume University; Yoshihiko Tani: Osaka Red Cross Blood Center; Keiko Katayama, Masayuki Ohisa and Aya Sugiyama: Hiroshima University; and Kan Kikuchi: Shimoochiai Clinic, Tokyo, Japan for their great research work and reports. We express our sincere and great gratitude to Professor Emeritus Hiroshi Yoshizawa for his endless support.

Funding: This review article sums up the results of studies partly granted by the Ministry of Health, Labour and Welfare of Japan (H22-kanen-ippan-012, H25-kanen-ippan-010, H28-kansei-ippan-001 and 19HC1001).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Feinstone SM, Kapikian AZ, Purcell RH, Alter HJ, Holland PV. Transfusion-associated hepatitis not due to viral hepatitis type A or B. N Engl J Med. 1975; 292:767-770.
2. Bukh J. The history of hepatitis C virus (HCV): Basic research reveals unique features in phylogeny, evolution and the viral life cycle with new perspectives for epidemic control. J Hepatol. 2016; 65:S2-S21.
3. World Health Organization (WHO). HCV Fact Sheet. 2020. *https://www.who.int/news-room/fact-sheets/detail/hepatitis-c* (accessed May 22, 2021).
4. Goossens N, Hoshida Y. Hepatitis C virus-induced hepatocellular carcinoma. Clin Mol Hepatol. 2015; 21:105-14.
5. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science. 1989; 244:359-362.
6. Dubuisson J, Cosset FL. Virology and cell biology of the hepatitis C virus life cycle: An update. J Hepatol. 2014; 61:S3-S13.
7. Nakano T, Lau GM, Lau GM, Sugiyama M, Mizokami M. An updated analysis of hepatitis C virus genotypes and subtypes based on the complete coding region. Liver Int. 2012; 32:339-345.
8. Toyoda H, Kumada T, Takaguchi K, Shimada N, Tanaka J. Changes in hepatitis C virus genotype distribution in Japan. Epidemiol Infect. 2014; 142:2624-2628.
9. Chung H, Ueda T, Kudo M. Changing trends in hepatitis C infection over the past 50 years in Japan. Intervirology. 2010; 53:39-43.
10. Mizokami M, Tanaka Y, Miyakawa Y. Spread times of hepatitis C virus estimated by the molecular clock differ

among Japan, the United States and Egypt in reflection of their distinct socioeconomic backgrounds. Intervirology. 2006; 49:28-36.
11. Aikawa T, Tsuda F, Horie K, Ohnishi H, Okamoto H. Distribution of hepatitis C virus (HCV) genotype in HCV-infected patients in the Mito area of Japan stratified by the assumed transmission route and year of infection. Kanzo. 2017; 58:307-309. (in Japanese)
12. Ko K, Nagashima S, Yamamoto C, Takahashi K, Matsuo J, Ohisa M, Akita T, Matyakubov J, Mirzaev U, Katayama K, Masaki T, Tanaka J. Eighteen-year follow-up cohort study on hepatitis B and C virus infections related long-term prognosis among hemodialysis patients in Hiroshima. J Med Virol. 2020; 92:3436-3447.
13. Moriya T, Koyama T, Tanaka J, Mishiro S, Yoshizawa H. Epidemiology of hepatitis C virus in Japan. Intervirology. 1999; 42:153-158.
14. Yoshizawa H. Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. Oncology. 2002; 62 Suppl 1:8-17.
15. Yoshizawa H. Current status of hepatocellular carcinoma in Japan 2002. Chapter 4. Trends of hepatitis virus carriers. Hepatol Res. 2002; 24:S28-S39.
16. Tanaka J, Akita T, Ko K, Miura Y, Satake M. Countermeasures against viral hepatitis B and C in Japan: An epidemiological point of view. Hepatol Res. 2019; 49:990-1002.
17. Japanese Red Cross Society. Blood Service 2018. *https://www.jrc.or.jp/english/pdf/Blood_Services_2018_web.pdf* (accessed on May 22, 2021).
18. Oza N, Isoda H, Ono T, Kanto T. Current activities and future directions of comprehensive hepatitis control measures in Japan: The supportive role of the Hepatitis Information Center in building a solid foundation. Hepatol Res. 2017; 47:487-496.
19. Tanaka J, Kumada H, Ikeda K, Chayama K, Mizui M, Hino K, Katayama K, Kumagai J, Komiya Y, Miyakawa Y, Yoshizawa H. Natural histories of hepatitis C virus infection in men and women simulated by the Markov model. J Med Virol. 2003; 70:378-386.
20. Tanaka J, Kumagai J, Katayama K, Komiya Y, Mizui M, Yamanaka R, Suzuki K, Miyakawa Y, Yoshizawa H. Sex- and age-specific carriers of hepatitis B and C viruses in Japan estimated by the prevalence in the 3,485,648 first-time blood donors during 1995-2000. Intervirology. 2004; 47:32-40.
21. Yamaguchi K, Kiyokawa H, Machida J, Obayashi A, Nojiri N, Ueda S, Takatsuki K. Seroepidemiology of hepatitis C virus infection in Japan and HCV infection in haemodialysis patients. FEMS Microbiol Rev. 1994; 14:253-258.
22. Tanaka J, Akita T, Ohisa M, Sakamune K, Ko K, Uchida S, Satake M. Trends in the total numbers of HBV and HCV carriers in Japan from 2000 to 2011. J Viral Hepat. 2018; 25:363-372.
23. Tanaka J, Koyama T, Mizui M, Uchida S, Katayama K, Matsuo J, Akita T, Nakashima A, Miyakawa Y, Yoshizawa H. Total numbers of undiagnosed carriers of hepatitis C and B viruses in Japan estimated by age- and area-specific prevalence on the national scale. Intervirology. 2011; 54:185-195.
24. Tanaka J. Ministry of Health, Labour and Welfare of Japan Report on the Epidemiological Research on the Burden of Viral Hepatitis and Measures for its Elimination. p 225-237, 2020. *https://mhlw-grants.niph.go.jp/project/28011/1* (accessed May 12, 2021). (in Japanese)
25. Tanaka H, Tsukuma H, Hori Y, Nakade T, Yamano H, Kinoshita N, Oshima A, Shibata H. The risk of hepatitis C virus infection among blood donors in Osaka, Japan. J Epidemiol. 1998; 8:292-296.
26. Tanaka J, Mizui M, Nagakami H, Katayama K, Tabuchi A, Komiya Y, Miyakawa Y, Yoshizawa H. Incidence Rates of Hepatitis B and C Virus Infections among Blood Donors in Hiroshima, Japan, during 10 Years from 1994 to 2004. Intervirology. 2008; 51:33-41.
27. Uchida S, Satake M, Kurisu A, Sugiyama A, Ko K, Akita T, Tanaka J. Incidence rates of hepatitis C virus infection among blood donors in Japan: a nationwide retrospective cohort study. Transfusion. 2018; 58:2880-2885.
28. National Cancer Center Japan. Center for cancer control and information services. *https://www.ncc.go.jp/en/cis/Publication_Reports/index.html* (accessed on May 22, 2021).
29. Kumagai J, Komiya Y, Tanaka J, Katayama K, Tatsukawa Y, Yorioka N, Miyakawa Y, Yoshizawa H. Hepatitis C virus infection in 2,744 hemodialysis patients followed regularly at nine centers in Hiroshima during November 1999 through February 2003. J Med Virol. 2005; 76:498-502.
30. Kikuchi K. Ministry of Health, Labour and Welfare of Japan Report-Study on hepatitis virus infection status, testing, and treatment in dialysis facilities under Health and Labour Science Research Grant of the Epidemiological Research on the Burden of Viral Hepatitis and Measures for its Elimination. p 93-97, 2009. *https://mhlw-grants.niph.go.jp/project/27360/1* (accessed May 12, 2021). (in Japanese)
31. Nakai S. The history of Japanese Society for Dialysis Therapy Registry. J Jpn Soc Dial Ther. 2010; 43:119-152. (in Japanese)
32. Nitta K, Nakai S, Masakane I, *et al.* 2018 annual dialysis data report of the JSDT Renal Data Registry: patients with hepatitis. Renal Replacement Therapy. 2021; 7:22.
33. Asahina Y; Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology. JSH Guidelines for the Management of Hepatitis C Virus Infection, 2019 Update; Protective Effect of Antiviral Therapy against Hepatocarcinogenesis. Hepatol Res. 2020; 50:775-790.

Received June 8, 2021; Revised June 26, 2021; Accepted July 26, 2021.

Released online in J-STAGE as advance publication August 13, 2021.

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Global Health & Medicine. 2021; 3(5):270-275.
REVIEW
DOI: 10.35772/ghm.2021.01080

Prevalence, diagnosis, and treatment of hepatitis C in Mainland China

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Abstract: Infection with the hepatitis C virus (HCV) is a major cause of liver disease and hepatocellular carcinoma in China. Rapid economic development has had an enormous impact on the epidemiology and treatment of hepatitis C. The prevalence of anti-HCV antibodies in Mainland China is approximately 0.91%, and use of injected drugs has become the main route of HCV transmission in China. Reimbursement for 3 direct-acting antivirals (DAAs) has been approved by the National Medical Insurance scheme in China, which ensures the accessibility of treatment for an HCV infection. To improve the awareness of treatments for hepatitis C among medical personnel and the rate of in-hospital screening for HCV, the Chinese Medical Association has formulated guidelines for the diagnosis and treatment of hepatitis C and a process of in-hospital screening for hepatitis C in China. These efforts have standardized the screening, diagnosis, treatment, and management of hepatitis C. Based on the international strategy for micro-elimination of hepatitis C, China has also screened and treated groups at risk of hepatitis C infection, and this has reduced the number of the infected. The current review describes the status of and issues with the prevalence, diagnosis, and treatment of hepatitis C in Mainland China as part of the global effort to eliminate viral hepatitis by 2030.

***Keywords*:** prevalence, diagnosis, treatment, hepatitis C, Mainland China

Introduction

In 2016, the World Health Organization (WHO) proposed a new global goal to eliminate viral hepatitis by 2030 (*1*). Compared to 2015, the incidence of hepatitis C decreased by 80% and its mortality decreased by 65%, and 90% of patients with hepatitis C were diagnosed and 80% of eligible patients were treated (*1,2*). The Chinese Government and healthcare system are tirelessly working to achieve the goal of eliminating hepatitis C as soon as possible. There are approximately 10 million patients infected with the hepatitis C virus (HCV) in China, and they account for more than 14% of the global population infected with HCV (*3*). Nearly one-fifth of the total deaths from hepatitis C-related cirrhosis and hepatocellular carcinoma occur in China every year (*1*).

Current data on hepatitis C in China indicate that the number of patients with hepatitis C-related cirrhosis or liver cancer and deaths from those conditions will increase over the next 12 years (*3*). This will increase the disease burden for patients, society, and the medical system. The current status of hepatitis C in China needs to be promptly ascertained in order to reduce the burden of HCV infection and achieve the goal of eliminating hepatitis C by 2030.

Discussed here are the status of and issues with the epidemiology, diagnosis, and treatment of and screening for hepatitis C in Mainland China.

Epidemiological changes

Chronic hepatitis C is a substantial medical burden worldwide. China has one of the world's largest populations with hepatitis C. In China, there are about 200,000 new cases of hepatitis C and 360,000 liver cancer deaths every year in which liver cancer-associated with hepatitis C accounts for 37.48%. There are at least 133,000 deaths caused by hepatitis C (*3-5*).

Over the past 30 years, the prevalence of anti-HCV antibodies has changed in Mainland China (Figure 1). A study conducted in 1992 found that the prevalence of anti-HCV antibodies was 3.2% (*6*). China subsequently took effective measures to prevent the spread of HCV infection, blood donation was changed from paid to voluntary, and disinfection standards and hospital infection control standards were implemented (*7,8*). The prevalence of anti-HCV antibodies in China had dropped to 0.43% by 2006 (*9*). However, the prevalence of anti-HCV antibodies (0.58%) increased from 2011 to 2015, which may be related to the enhancement of hepatitis C screening and the variety of routes of HCV infection in recent years (*10*). A recent meta-analysis reported that the

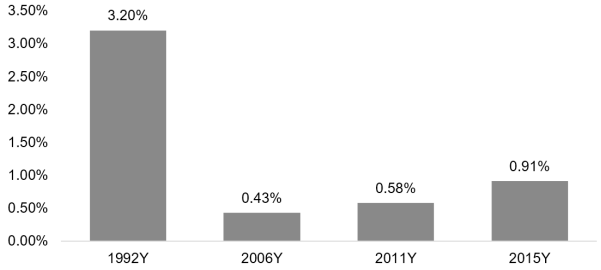

Figure 1. Changes in levels of anti-HCV antibodies in Mainland China.

prevalence of anti-HCV antibodies in Mainland China is 0.91% [95% confidence interval (CI) 0.81-1.03%] (*10*). The prevalence of anti-HCV antibodies differed significantly in different regions, ranging from 0.32% to 6.51%, and the rate of detection was relatively low in East China and South China (*9,10*). The prevalence of anti-HCV antibodies in rural areas seems to be higher than that in urban areas, which may be related to poor medical conditions and less health awareness (*11*). As age increased, the rate of detection of anti-HCV antibodies increased from 0.16% to 3.95% (*10,12*).

There are eight HCV genotypes (GT1-8) reported around the world, and GT1-6 is found in China (*13,14*). GT1b and GT2a are the main genotypes of HCV in China, accounting for 62.78% (95% CI: 59.54-66.02%) and 17.39% (95% CI: 15.67-19.11%), respectively. The prevalence of HCV-GT differs markedly among regions. In northern and central China, GT1b and GT2a still are the main subtypes (*15,16*). However, the genotypes distribution in southern China is transitioning from GT1b to GT3 and GT6; about half of the population infected with HCV in southern China have the GT1b genotype, and more than 40% of the population have GT3 or GT6 (*14,17*). These marked changes may be related to population mobility and use of addictive intravenous drugs as a route of transmission. In recent years, the proportion of co-infection with multiple HCV subtypes in China has gradually increased, and these subtypes are mainly GT1b, GT2a, and GT6a (*14,18*). The most common is co-infection with GT1b/2a, which accounts for 81.8%, followed by co-infection with GT6a/2a and GT6a/1a (*14,19*). Co-infection with multiple HCV subtypes is mainly found in patients who repeatedly received blood products, shared needles with intravenous drug users, or who often underwent hemodialysis (*14,20*).

Changes in the routes of HCV transmission

Due to lack of supervision of the safety of blood products in the past, the main route of HCV infection in China was through blood transfusions (*20*). In 1993, the Chinese Government formulated a policy to screen blood donors and it enacted related laws to screen all blood donors for anti-HCV antibodies. Since 2015, China began to screen blood donors who were anti-HCV antibody-negative for HCV RNA. In addition, the methods of recruiting blood donors have gradually changed (*21*). Apart from these, the standards for disinfection, nosocomial infection control standards, and hepatitis C prevention and control guidelines have been formulated and put into practice. These measures significantly reduced the spread of HCV infection. Since then, HCV infection by blood transfusion has rarely occurred. The main high-risk population has gradually become patients who inject drugs (PWID), patients undergoing hemodialysis (HD), and patients co-infected with the human immunodeficiency virus (HIV), or patients infected with the hepatitis B virus (HBV) (*22*).

At present, use of injected drugs has become the main route of HCV transmission in China. Infection with HCV through unsafe injections accounts for 30-49% of all infections, and the figure is as high as 60-90% in some provinces (*10,22*). In Hubei, Yunnan, Guangxi, Hunan, and Xinjiang, the prevalence of HCV was the most serious among PWIDs (*22*). In a study of more than 2,000 PWIDs in Yunnan Province, 77% of the participants were infected with HCV (*23*). Due to needle sharing, the prevalence of HCV among injected drug users in China is higher than that among general drug users, including those who take drugs oral or *via* inhalation (80.0%) and those who voluntarily or compulsorily recover or receive methadone maintenance treatment) (48.7%) (*22,24*). The prevalence of HCV is about 5.21-8.25%, and the figure is as high as 30.2-38.1% in some dialysis units (*22,25*).

High-risk sexual behavior is also one of the main routes for HCV transmission among patients infected with HIV. Several studies have indicated that the incidence of HCV infection among people infected with HIV in China ranges from 8% to 18% (*26,27*). In addition, sharing of razors in households, unsafe ear piercings, and tattoos may also lead to HCV infection. Mother-to-child transmission is also a common route of HCV infection. According to one study, pregnant women on the Chinese Mainland tested positive for anti-HCV antibodies at a rate of 0.235%, the incidence of HCV transmitted to newborns by HCV-positive mothers is about 2% (*28*). A high HCV RNA load and HIV infection can increase the risk of transmission.

Status of diagnosis and detection

Studies have indicated that the rate of diagnosis of hepatitis C in China is only 2.1% (*8,29*). Early screening and diagnosis are always the biggest obstacles to eliminating infection with HCV. At present, the methods of detecting HCV infection in China include serological detection (detection of anti-HCV antibodies or the HCV core antigen) and detection of nucleic acids (HCV RNA) (*30*). Hospitals and communities mainly screen for HCV infection *via* serum anti-HCV antibodies. Patients who are positive for anti-HCV antibodies are commonly tested for HCV RNA to determine whether they are currently infectious or not. Due to its low specificity and

sensitivity, HCV core antigen detection is not widely used (*31*).

However, some researchers have recently proposed an assessment involving the simultaneous detection of the HCV core antigen and HCV non-structural proteins. Compared to serum anti HCV antibody detection and HCV-RNA detection, detection of multiple HCV antigens has a specificity of 98.9% and a sensitivity of 100% (*32*). A recent study has reported an immunoassay to detect the HCV core protein in antibody-negative samples during the early stage of HCV infection (*32*). This method is well-suited to screening blood products in blood banks for HCV and monitoring the HCV viral load after liver transplantation, and it is especially useful at screening when detection of HCV RNA is difficult.

The 2019 Chinese guidelines for prevention and treatment of hepatitis C state that the HCV core antigen is a marker of HCV replication and could replace HCV RNA in the diagnosis of an acute/chronic HCV infection. HCV core antigen detection could be used when detection of HCV RNA is not feasible (*8*).

Changes in treatment: From PR to DAA

Although 25% of China's 10 million patients with chronic hepatitis C need urgent treatment, less than 1.3% receive treatment (*33*). Prior to 2017, treatment for hepatitis C mainly involved interferon and ribavirin (PEG/RBV) for 24 or 48 weeks based on the genotype (*34*). Treatment is expensive, its efficacy is only 60-70%, some patients had adverse reactions, and the treatment takes a long time (*35*). Many patients often discontinue treatment for economic reasons. Since 2017, China's health authorities have made substantial progress in the prevention and treatment of hepatitis C. Several direct-acting antivirals (DAAs) have been approved for marketing in China. After oral administration for 8–16 weeks, a sustained virological response (SVR) has been achieved in more than 90% of patients infected with any genotype of HCV, adverse reactions are rare, and patient tolerance and compliance are better (*36*).

In 2019, the Chinese Medical Association updated its guidelines on hepatitis C to keep pace with international standards (*8*). The guidelines indicate that DAAs could replace the conventional regimen of interferon combined with ribavirin and that DAAs become the first-line therapy for hepatitis C, further standardizing the treatment of hepatitis C in China. Three DAAs for hepatitis C were subsequently included in the list of medications reimbursed by medical insurance, with an average price reduction of more than 85% (*37*). This changed the situation for patients who discontinued treatment because of its expense. Two of the medications, elbasvir/grazoprevir and ledipasvir/sofosbuvir, are for patients with GT1b hepatitis C. A third medication is sofosbuvir/velpatasvir (SOF/VEL). The simplified regimen of SOF/VEL for 12 weeks could meet the clinical needs of most patients infected with HCV, including patients with chronic kidney disease, decompensated cirrhosis, and previous treatment failure. SOF/VEL is highly efficacious in and well tolerated by patients with any of the six HCV genotypes (GT1-6) and in different stages of liver fibrosis in China. There is no need to detect the HCV genotype or the stage of fibrosis before treatment, and no dynamic monitoring is required during therapy (*8*). Clinical use is convenient and feasible, further reducing medical expenses and potentially improving the rate of compliance in rural areas.

In addition, the first-line salvage therapy recommended by the HCV guidelines is Vosevi tablets (sofosbuvir, velpatasvir, and voxilaprevir tablets) (*38*). This medication was also approved for reimbursement by medical insurance in December 2019, providing treatment options to patients with hepatitis C in whom previous DAA treatment failed. Clinical studies have indicated that Vosevi had an overall cure rate of 97% in patients who failed to respond to DAA treatment, regardless of the state of liver cirrhosis and the DAAs that they had previously received. In addition, China has also independently developed some DAAs. Phase II-III clinical trials of the DAAs Ganovo (danoprevir or ASC08) and ravidasvir (a next-generation NS5A inhibitor of all genotypes) were completed in June 2018. Ravidasvir and danoprevir are the first oral interferon-free regimen developed in China. The regimen achieved an SVR of 99% at 12 weeks in non-cirrhotic GT1 patients receiving initial treatment and an SVR of 100% in patients with NS5A resistance mutations at the baseline. In July 2020, China approved the 2 drugs for use in combination with other drugs in non-cirrhotic GT1 patients (*39*). The approval of domestic DAAs in China could reduce medical costs and make drugs more accessible to patients infected with HCV. These efforts have improved the diagnosis and treatment of hepatitis C in China and they represent a step towards achieving the global goal of "eliminating viral hepatitis by 2030".

Improved screening

As DAAs have become more available, the treatment of hepatitis C in China has become more feasible. The key lies in screening for the infected. A study analyzed the detection and prevalence of anti--HCV antibodies in inpatients at 8 tertiary hospitals in different regions of China from January to December 2016 (*40*). Results indicated that the rate of detection of anti-HCV antibodies was no higher than 50% and average positivity was 0.88%; results also indicated that 90.14% of anti-HCV antibody-positive patients were over 40 years old. Due to a lack of consultation and referral for diagnosis and treatment, anti-HCV antibody-positive patients often have no chance to receive early treatment. A 2016 to 2018 study of patients infected with HCV at

76 hospitals in China found that the rate of detection of anti-HCV antibodies was 48.4%, while the rate of detection of HCV RNA was 34.9%; the missed diagnosis rate was as high as 65.1%, resulting in only 12.2% of the population receiving antiviral treatment (*41*).

Clinicians in Non-infectious Liver Diseases have a limited awareness of hepatitis C, and especially the need for hepatitis C screening and standards for diagnosis, treatment, and management of hepatitis C. Moreover, patients with obvious clinical manifestations of chronic viral hepatitis and a high risk of infection with HCV lack awareness of active testing (*42*). Thus, the Chinese Medical Association formulated its "process of in-hospital screening for hepatitis C in China" in 2021 (*43*). The process recommends creation of a multidisciplinary team (MDT) and it recommends that clinical departments, the laboratory, and infection control at medical facilities enhance the referral and treatment of anti-HCV antibody-positive patients and promote the screening/diagnosis and antiviral treatment of patients with chronic hepatitis C (Figure 2).

Recently, the European Association for the Study of the Liver (ESAL) proposed a more pragmatic strategy – "Conquering Hepatitis C *via* Micro-Elimination (CHIME)" (*44*). This approach breaks down the goal of eliminating hepatitis C into providing interventions for specific groups (such as high-risk groups), including marginalized groups (such as PWIDs). As an example, screening high-risk groups is more effective than screening the general population. Efficacious DAAs can also be prioritized for treatment of these high-risk groups, which may reduce the spread of the disease to the general population.

Given its population and socio-economic conditions, China is also optimizing the micro elimination strategy in different regions. At present, potential target populations for the HCV micro elimination strategy in China are PWIDs, patients undergoing HD, patients co-infected with HIV, women of childbearing age, pregnant women, and children. In early 2018, an assistance program to identify and treat hepatitis C initiated by the Primary Healthcare Foundation of China was rolled out to the entire country (*45*). The program provides free medication for patients with the lowest standard of living and half-price medication for low-income patients. These initiatives are moving in the right direction and are helping to improve the management of hepatitis C (Figure 3).

Recently, AI and information technology and efforts to identify patients *via* their medical data have gradually been used in China. Although action is being taken, problems with the management of HCV, such as a lack of general awareness of hepatitis C, a low screening rate, and poor ties to medical care, have not been completely resolved in China. In the future, the current prevention and control strategies need to be further optimized and coordination among public health departments, Centers for Disease Control, and tertiary medical facilities needs to be enhanced. Promoting more cost-effective screening and treatment of HCV infection in the population could

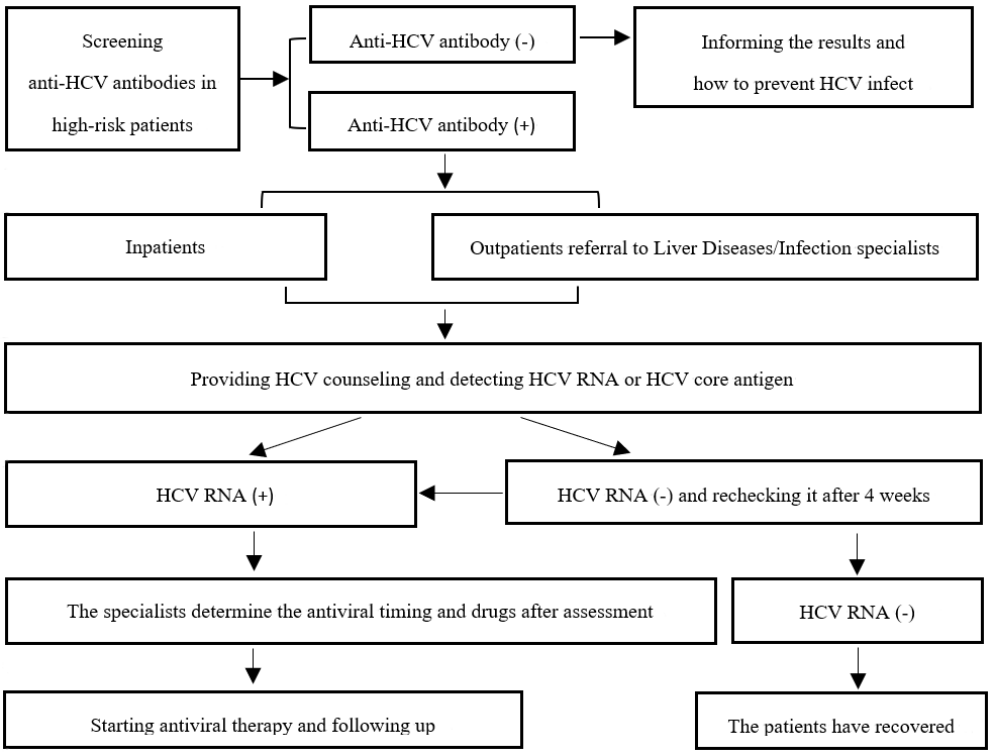

Figure 2. Flow chart for the process of in-hospital screening for hepatitis C in China. *Abbreviations*: HCV, hepatitis C virus; (+), positive; (-), negative.

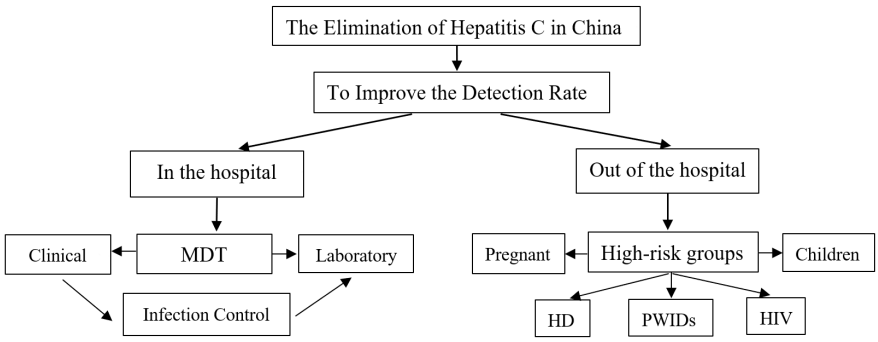

Figure 3. The elimination of hepatitis C in China. *Abbreviations:* MDT, multidisciplinary team; HD, hemodialysis; PWID, patients who inject drugs; HIV, human immunodeficiency virus.

lead to the successful elimination of hepatitis C in China by 2030.

Funding: This work was supported by the project for research in medical innovation under the Shanghai 2020 Action Plan for Scientific and Technological Innovation and the Shanghai Clinical Research Center for Infectious Diseases (HIV/AIDS) (20MC1920100).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. World Health Organization. Global Hepatitis Report, 2017-New hepatitis data highlight need for urgent global response. 2017. *https://www.who.int/news/item/21-04-2017-new-hepatitis-data-highlight-need-for-urgent-global-response* (accessed September 12, 2021).
2. Revill PA, Chisari FV, Block JM, *et al*. A global scientific strategy to cure hepatitis B. Lancet Gastroenterol Hepatol. 2019; 4:545-558.
3. Chinese Center for Disease Control and Prevention. The status of notifiable infectious diseases in China in 2020. *http://www.nhc.gov.cn/jkj/s3578/202103/f1a448b7df7d4760976fea6d55834966.shtml* (accessed September 12, 2021). (in Chinese)
4. World Health Organization. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. *https://www.who.int/publications/i/item/9789241550345* (accessed September 12, 2021).
5. Irshad M, Mankotia DS, Irshad K. An insight into the diagnosis and pathogenesis of hepatitis C virus infection. World J Gastroenterol. 2013; 19:7896-7909.
6. Zhang M, Sun XD, Mark SD, Chen W, Wong L, Dawsey SM, Qiao YL, Fraumeni JF Jr, Taylor PR, O'Brien TR. Hepatitis C virus infection, Linxian, China. Emerg Infect Dis. 2005; 11:17-21.
7. Chinese Society of Hepatology, Chinese Medical Association, Wei L; Chinese Society of Infectious Diseases, Chinese Medical Association, Hou JL. Guidelines for the prevention and treatment for hepatitis C: A 2015 update. Zhonghua Gan Zang Bing Za Zhi. 2015; 23:906-923. (in Chinese)
8. Chinese Society of Hepatology; Chinese Society of Infectious Diseases, Chinese Medical Association. Guidelines for the prevention and treatment of hepatitis C (2019 version). Zhonghua Gan Zang Bing Za Zhi. 2019; 27:962-979. (in Chinese)
9. Chen YS, Li L, Cui FQ, Xing WG, Wang L, Jia ZY, Zhou MG, Gong XH, Wang FZ, Zheng H, Luo HM, Bi SL, Wang N, Yang WZ, Liang XF. A sero-epidemiological study on hepatitis C in China. Zhonghua Liu Xing Bing Xue Za Zhi. 2011; 32:888-891. (in Chinese)
10. Gao Y, Yang J, Sun F, Zhan S, Fang Z, Liu X, Zhuang H. Prevalence of anti-HCV antibody among the general population in Mainland China between 1991 and 2015: A systematic review and meta-analysis. Open Forum Infect Dis. 2019; 6:ofz040.
11. Zhang Q, Qi W, Wang X, Zhang Y, Xu Y, Qin S, Zhao P, Guo H, Jiao J, Zhou C, Ji S, Wang J. Epidemiology of hepatitis B and hepatitis C infections and benefits of programs for hepatitis prevention in Northeastern China: A cross-sectional study. Clin Infect Dis. 2016; 62:305-312.
12. Maaroufi A, Vince A, Himatt SM, *et al*. Historical epidemiology of hepatitis C virus in select countries-Volume 4. J Viral Hepat. 2017; 24 Suppl 2:8-24.
13. Borgia SM, Hedskog C, Parhy B, Hyland RH, Stamm LM, Brainard DM, Subramanian MG, McHutchison JG, Mo H, Svarovskaia E, Shafran SD. Identification of a novel hepatitis C virus genotype from Punjab, India: Expanding classification of hepatitis C virus into 8 genotypes. J Infect Dis. 2018; 218:1722-1729.
14. Zhang Y, Chen LM, He M. Hepatitis C Virus in mainland China with an emphasis on genotype and subtype distribution. Virol J. 2017; 14:41.
15. Dong ZX, Zhou HJ, Wang JH, Xiang XG, Zhuang Y, Guo SM, Gui HL, Zhao GD, Tang WL, Wang H, Xie Q. Distribution of hepatitis C virus genotypes in Chinese patients with chronic hepatitis C: Correlation with patients' characteristics and clinical parameters. J Dig Dis. 2012; 13:564-570.
16. Chen Y, Yu C, Yin X, Guo X, Wu S, Hou J. Hepatitis C virus genotypes and subtypes circulating in Mainland China. Emerg Microbes Infect. 2017; 6:e95.
17. Chen YD, Liu MY, Yu WL, Li JQ, Peng M, Dai Q, Liu X, Zhou ZQ. Hepatitis C virus infections and genotypes in China. Hepatobiliary Pancreat Dis Int. 2002; 1:194-201.
18. Xu R, Wang M, Qiu Y. Hepatitis C virus (HCV) infection with different genotypes in China. Chinese J Viral Diseases. 2015; 5:11-16. (in Chinese)
19. Wang J, Tang S. HCV genotyping among HCV patients with different transmission routs. China Public Health. 2013; 29:809-811. (in Chinese)
20. Chen F, Sun D, Guo Y, Guo W, Ding Z, Li P, Li J, Ge L, Li N, Li D, Wang L, Wang Z. Correction: Spatiotemporal

scan and age-period-cohort analysis of hepatitis C virus in Henan, China: 2005-2012. PLoS One. 2015; 10:e0136333.
21. Gao X, Cui Q, Shi X, *et al*. Prevalence and trend of hepatitis C virus infection among blood donors in Chinese mainland: a systematic review and meta-analysis. BMC Infect Dis. 2011 Apr 9;11:88.
22. Li M, Zhuang H, Wei L. How would China achieve WHO's target of eliminating HCV by 2030? Expert Rev Anti Infect Ther. 2019; 17:763-773.
23. Zhou YH, Yao ZH, Liu FL, Li H, Jiang L, Zhu JW, Zheng YT. High prevalence of HIV, HCV, HBV and co-infection and associated risk factors among injecting drug users in Yunnan Province, China. PLoS One. 2012; 7:e42937.
24. Zhuang H. Report on the status of hepatitis C infection in China and prevention and treatment strategies (Zhuang H, Wei L, Yang XZ, eds.). People's Medical Publishing House, Beijing, China, 2017; pp.1-4. (in Chinese)
25. Sun J, Yu R, Zhu B, Wu J, Larsen S, Zhao W. Hepatitis C infection and related factors in hemodialysis patients in China: Systematic review and meta-analysis. Ren Fail. 2009; 31:610-620.
26. Xie J, Han Y, Qiu Z, Li Y, Li Y, Song X, Wang H, Thio CL, Li T. Prevalence of hepatitis B and C viruses in HIV-positive patients in China: A cross-sectional study. J Int AIDS Soc. 2016; 19:20659.
27. Zhang F, Zhu H, Wu Y, Dou Z, Zhang Y, Kleinman N, Bulterys M, Wu Z, Ma Y, Zhao D, Liu X, Fang H, Liu J, Cai WP, Shang H. HIV, hepatitis B virus, and hepatitis C virus co-infection in patients in the China National Free Antiretroviral Treatment Program, 2010-12: A retrospective observational cohort study. Lancet Infect Dis. 2014; 14:1065-1072.
28. Ma J, Cao WP, Wang M, Qiao XW, Li JS, Ren XW, Liu XN. Meta-analysis on the positive rate of hepatitis C antibody among pregnant females in China from 2008 to 2018 Chinese J Evidence-based Med. 2021; 21:394-400. (in Chinese)
29. Huang M, Xie Q. Hepatitis C screening is very important, standardized treatment is the key. Journal of Liver Doctor. 2015; 01:16-17. (in Chinese)
30. Warkad SD, Song KS, Pal D, Nimse SB. Developments in the HCV screening technologies based on the detection of antigens and antibodies. Sensors (Basel). 2019; 19:4257.
31. Kuo YH, Chang KC, Wang JH, Tsai PS, Hung SF, Hung CH, Chen CH, Lu SN. Is hepatitis C virus core antigen an adequate marker for community screening? J Clin Microbiol. 2012; 50:1989-1993.
32. Hu KQ, Cui W, Rouster SD, Sherman KE. Hepatitis C virus antigens enzyme immunoassay for one-step diagnosis of hepatitis C virus coinfection in human immunodeficiency virus infected individuals. World J Hepatol. 2019; 11:442-449.
33. Pawlotsky JM. New hepatitis C therapies: The toolbox, strategies, and challenges. Gastroenterology. 2014; 146:1176-1192.
34. World Health Organization. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. *https://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf* (accessed September 12, 2021).
35. Fridriksson B, Bergmann OM, Olafsson S. Treatment of hepatitis C with peginterferon and ribavirin in Iceland from 2002-2012. Laeknabladid. 2017; 103:125-128. (in Icelandic)
36. Younossi ZM, Tanaka A, Eguchi Y, Lim YS, Yu ML, Kawada N, Dan YY, Brooks-Rooney C, Negro F, Mondelli MU. The impact of hepatitis C virus outside the liver: Evidence from Asia. Liver Int. 2017; 37:159-172.
37. State Council, China. National Healthcare Security Administration: Notice on inclusion of drugs negotiated in 2019 under the scope of category B of the National Catalogue of Medicines for Basic Medical Insurance, Work Injury Insurance, and Maternity Insurance. *http://www.gov.cn/xinwen/2019-11/28/content_5456662.htm* (accessed September 12, 2021). (in Chinese)
38. Gilead Sciences. China National Medical Products Administration Approves Vosevi® (sofosbuvir, velpatasvir, and voxilaprevir) for people with chronic hepatitis C infection who require re-treatment. *https://www.gilead.com/news-and-press/press-room/press-releases/2019/12/china-national-medical-products-administration-approves-vosevi-sofosbuvir-velpatasvir-and-voxilaprevir-for-people-with-chronic-hepatitis-c-infecti* (accessed September 12, 2021).
39. National Medical Products Administration. State Food and Drug Administration approves the listing of ravidavir hydrochloride tablets. *https://www.nmpa.gov.cn/yaopin/ypjgdt/20200731143324140.html* (accessed September 12, 2021). (in Chinese)
40. Liu L, Xu H, Hu Y, *et al*. Hepatitis C screening in hospitals: Find the missing patients. Virol J. 2019; 16:47.
41. Feng XF, Ding GW, Yu HL, Pan L, Gao Y, Tang Y, Mao YR, Pang L. Current status of diagnosis and treatment of hepatitis C in medical institutions. Chinese J AIDS & STD. 2020; 26:247-249. (in Chinese)
42. Chen YX, Wu CH. Establishment and implementation of hepatitis C screening and referral channels in the hospitals. Chinese J Hepatol. 2020; 28:820-823. (in Chinese)
43. China Liver Health, Chinese Society of Hepatology, Chinese Medical Association, Chinese Society of Laboratory Medicine, Chinese Medical Association, Hospital Infection Management Committee, Chinese Hospital Association. In-hospital process for viral hepatitis C screening and management in China (Draft). J Clin Hepatobiliary Diseases. 2021, 37:1534-1539. (in Chinese)
44. Lazarus JV, Safreed-Harmon K, Thursz MR, Dillon JF, El-Sayed MH, Elsharkawy AM, Hatzakis A, Jadoul M, Prestileo T, Razavi H, Rockstroh JK, Wiktor SZ, Colombo M. The micro-elimination approach to eliminating hepatitis C: Strategic and operational considerations. Semin Liver Dis. 2018; 38:181-192.
45. Sina News Center. Efforts to eliminate hepatitis in 2030: Patients in low-income households can now apply for free medication. *http://news.sina.com.cn/c/2018-07-26/doc-ihfvkitx0242256.shtml* (accessed September 12, 2021). (in Chinese)

Received June 27, 2021; Revised September 30, 2021; Accepted October 8, 2021.

Released online in J-STAGE as advance publication October 14, 2021.

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Global Health & Medicine. 2021; 3(5):276-282.
REVIEW
DOI: 10.35772/ghm.2021.01075

Achieving WHO target of HCV control in Hong Kong: challenges and strategies

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Abstract: With the introduction of effective directly acting antiviral agents (DAAs) therapy, control and elimination of hepatitis C virus (HCV) infection is becoming a feasible goal. In Hong Kong, HCV prevalence in general population is 0.3%-0.5% over the past decades. However, like other high-income areas/countries, high prevalence of HCV infection has been found in several population groups, such as people who inject drugs (PWID), patients undergoing dialysis, and human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS) patients. Based on the epidemiological study using data retrieved from the Hong Kong HCV Registry from January 2005 to March 2017, the estimated territory-wide diagnosis rate and treatment rate of HCV infection were only 50.9% and 12.4%, respectively. Although these rates was comparable to many developed countries/areas, the performances remained substantially below 90% and 80%, the 2030 targets proposed by World Health Organization (WHO). In recognition of the challenges, the Hong Kong Government set up the Steering Committee on Prevention and Control of Viral Hepatitis (SCVH) which formulated the *Hong Kong Viral Hepatitis Action Plan 2020-202*4. The *Action Plan* adopts four key strategies, as described in the WHO framework for global action, namely, awareness, surveillance, prevention and treatment. With the effective implementation of the *Action Plan*, especially in targeted screening of high-risk populations and more generalized use of the highly efficacious DAAs for all diagnosed HCV subjects, the goals of reducing HCV transmission and HCV-related morbidity and mortality can be achieved in Hong Kong by 2030.

***Keywords*:** HCV, prevention, treatment, elimination, Hong Kong

Introduction

Hepatitis C virus (HCV) is a small, enveloped, single stranded RNA virus identified in 1989 and is transmitted mainly through exposure to contaminated blood or blood products (*1,2*). As one of the major causes of liver-related morbidity and mortality, including liver cirrhosis and hepatocellular carcinoma (HCC), chronic HCV infection is becoming an important public health burden, with around 71 million infections worldwide and at least 400,000 deaths per year (*3-5*). Currently, there is still no effective vaccine for the prevention of HCV infection (*6*).

Over the past dozen years, the mainstay treatment for patients with HCV infection was the combination of weekly subcutaneous injections of pegylated interferon (PegIFN) and daily oral ribavirin (RBV). This treatment required 24-72 weeks and was accompanied by a wide variety of side effects and less than 60% of patients can achieve the sustained virologic response (SVR) (*7-9*). The development of directly acting antiviral (DAA) agents has revolutionised HCV treatment since 2014. Compared to the PegIFN/RBV regimen, DAA therapy is of shorter duration (8-24 weeks) and achieves over 90% SVR rate. It is also well tolerated and suitable for patients with former contraindications to PegIFN/RBV therapy, such as patients with decompensated cirrhosis or significant comorbidities (*10-12*). The pan-oral, IFN-free DAAs regimens with or without RBV have recently been recommended as the first-line therapy for HCV infection in clinical practice guidelines endorsed by different academic societies (*13-16*).

Meanwhile, in the light of these more efficacious treatment options, the World Health Organization (WHO) proposed to eliminate HCV as a public health threat, targeting a diagnosis rate of 90% of total infections, a 90% decrease in new infections and a 65% decrease in liver-related mortality by 2030 as compared with the baseline in 2015 (*17*). To realize these targets, several significant barriers should be overcome, including knowledge and awareness of viral hepatitis, identification of undiagnosed individuals, linkage to

continued care, and prevention of the occurrence of new cases or re-infection.

In this review, we summarize the current status of HCV epidemiology, diagnosis and treatment in Hong Kong, and outline the strategies formulated by the Hong Kong government for achieving the WHO goal of eliminating viral hepatitis as a major public health threat by 2030.

Epidemiology of HCV infection in Hong Kong

Prevalence of HCV

In contrast with high prevalence of hepatitis B virus (HBV) infection in Hong Kong, HCV infection is an uncommon occurrence among the local general population. One study of 382 individuals who attended a health exhibition in 1988 found that the prevalence of anti-HCV positivity was 0.5% (*18*). A community-based, territory-wide epidemiological study recruited 10,256 participants from February 2015 to July 2016, and found that overall anti-HCV positivity was 0.5% and the prevalence of viraemic HCV infection was 0.3% (*19*). Meanwhile, data from new blood donors in Hong Kong Red Cross Blood Transfusion Service, a major source of HCV epidemiological information, showed that HCV prevalence in adolescents and young adults ranged between 0.03% and 0.11% since the implementation of anti-HCV screening in 1991 (Figure 1). Among 29,332 new blood donors screened in 2019, anti-HCV was more commonly detected in subjects aged over 40 years as compared to those aged below 40 years (0.19% *vs.* 0.04%), and males were more commonly infected than females (0.10% *vs.* 0.05%) (*20*).

Before 1990s, HCV was infected mainly through transfusion with contaminated blood or blood products. With the introduction and implementation of anti-HCV screening for blood donations since 1991, the risk of transfusion-transmitted HCV infections has decreased to a very low level in Hong Kong (*21*). Transfusion-transmitted HCV infections are mainly found in patients requiring frequent blood or blood product transfusions, such as haemophilia patients. In high-income areas/countries, most HCV transmission has been found among PWID (*22*). From local studies published in the early 1990s, it was shown that anti-HCV was more commonly found in PWID (66.8%) and haemodialysis patients (4.6%) (*18*). An HCV seroprevalence study conducted in 2006 in methadone clinics, showed a 85% prevalence rate of anti-HCV seropositivity in this community (*23*). More recent studies involving PWID recruited at their gathering places also gave a similar figure of anti-HCV prevalence of 81.7% among 622 subjects in 2011 and 76.4% among 664 subjects in 2014, respectively (*24,25*). Among these subjects, injection duration, current or recent injections, sharing of injecting needles and concomitant use of other drugs, such as midazolam, were identified as the independent factors associated with HCV infection. In the New Life New Liver Project conducted between 2009 and 2018, 73.4% of 365 subjects participating in a targeted screening and assessment program for ex-PWID, were found to be anti-HCV positive (*26*).

HIV/AIDS patients are another population disproportionately affected by HCV infection in Hong Kong. Among 4416 new HIV/AIDS patients attending the Integrated Treatment Centre of Centre for Health Protection from 2000 to 2019, 385 (8.7%) tested positive for anti-HCV, and the prevalence rate appeared to be higher in male than female patients (9.4% *vs.* 4.1%) (*20*). HIV/HCV coinfection was found in 1.5-6.0% of HIV/AIDS patients infected through sexual contact, as compared with 97% of those patients infected through drug injection. Among those heterosexual HIV-infected

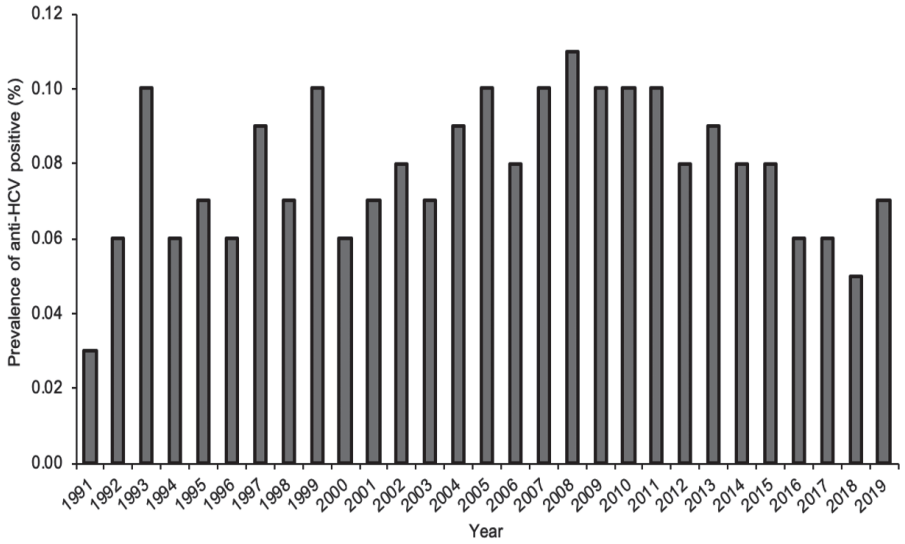

Figure 1. Prevalence of anti-HCV positive in new blood donors from 1991 to 2019 in Hong Kong (Date source: Hong Kong Red Cross Blood Transfusion Service, Hong Kong Special Administrative Region, China).

male patients without history of intravenous drug use, only 2.5% were anti-HCV positive (*20*).

HCV Genotypes

HCV is an enveloped, positive-strand RNA virus with extensive genetic heterogeneity, and has been classified into 7 major genotypes and over 75 subtypes with broad distribution in different geographical distributions (*27*). In contrast to western countries/regions where HCV genotype 1a is the most prevalent, HCV infections in Hong Kong are predominately caused by genotype 1b and 6a (*28*). In an early study involving 212 viraemic blood donors from 1991 to 1994, genotype 1b and 6 were detected in 58.8% and 27.0%, respectively (*29*). In a recent comprehensive population-based epidemiological study, the prevalent HCV genotype was genotype 1 (48.8%), followed by genotype 6 (33.6%), genotype 3 (10.8%) and genotype 2 (3.2%) among 2699 anti-HCV positive patients from all public hospitals in Hong Kong between January 2005 and March 2017 (*30*). While in HIV/HCV co-infected patients, genotype 3 is the most common (27.2%), followed by genotype 1a (14.8%), genotype 1b (11.1%) and genotype 6 (11.1%) (*30*).

Current challenges and strategies in controlling HCV infection in Hong Kong

Although much has been done to prevent and control HCV infection and keep the prevalence rate low over the past decades in Hong Kong, a higher number of acute HCV infections had been reported annually in the past ten years as compared with the decade before (Figure 2) (*20*). Hong Kong is an international city with high population mobility, and people may get HCV infection in other countries/areas where effective screening and control of HCV infection might not have been implemented and achieved (*21*). Certain misconceptions of HCV infection are also widespread in the local community, such as the disease cannot be cured, or the disease is relatively benign because most of the patients with HCV infection are asymptomatic in the early phase. A retrospective analysis of untreated HCV-infected patients from 2000 to 2009 found that 31.9% of 138 patients declined treatment due to patients' preference (*31*). Based on the recent epidemiological study using data retrieved from the Hong Kong HCV Registry which covers up 94% of all secondary and tertiary care services in Hong Kong, a total of 11,309 patients who tested positive for anti-HCV were identified from January 2005 to March 2017 (*30*). Among these patients, only 2201 were found to have received antiviral treatment. Given a population of 7.4 million people and assuming a prevalence of 0.3% HCV infection with a viremic rate of 80% in Hong Kong, the estimated territory-wide diagnosis rate and treatment rate were only 50.9% and 12.4%, respectively. Although these rates were comparable to many developed countries/areas, the performance remained substantially below the 2030 targets of 90% and 80%, proposed by WHO.

Based on the hepatitis elimination initiative of the WHO, it is critical to identify HCV infected individuals to start antiviral therapy, avoid further transmission and the occurrence of new cases (*4*). Traditionally, HCV screening starts with testing the antibodies against HCV (anti-HCV) with immunoassay and then viral load quantitation using a polymerase chain reaction-based assay for subjects with positive anti-HCV results. This two-step process requires multiple visits and may take several days or weeks, leading to delayed diagnosis and increased risk of losing the patient to follow-up treatment (*32*). With the development of point-of-care

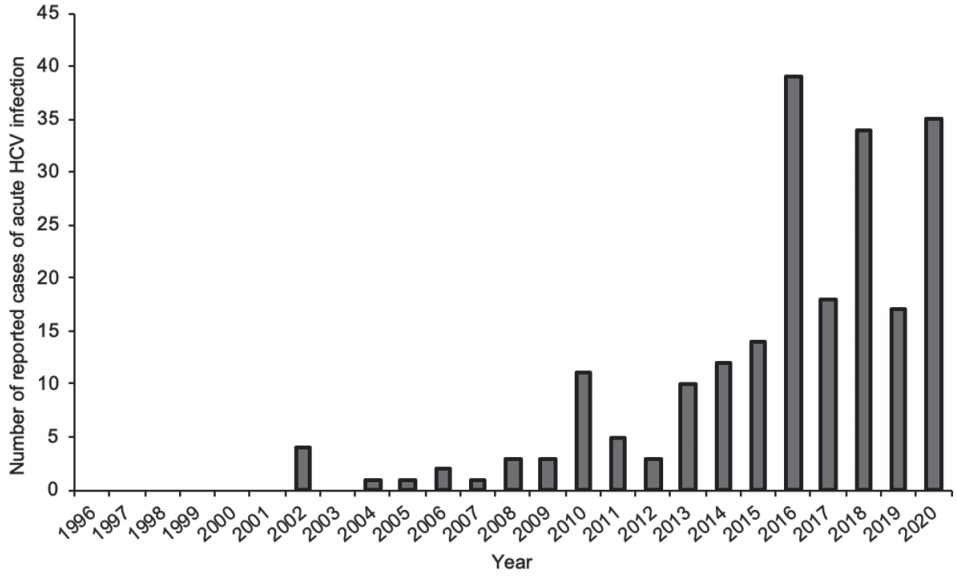

Figure 2. Number of reported cases of acute HCV infection from 1996 to 2020 in Hong Kong (Date source: Centre for Health Protection, Department of Health, Hong Kong Special Administrative Region, China).

(POC) and rapid diagnostic tests (RDT) which can offer results in minutes, rapid screening, confirmation of diagnosis and treatment initiation in the same clinic visit are possible nowadays.

Before 2014, PegIFN/RBV therapy was the mainstay treatment of patients with HCV infection. However, many patients with HCV infection declined the treatment due to the long treatment duration and associated adverse effects. It was noted that of 1,533 patients in consideration for PegIFN/RBV therapy, 16.1% refused this regimen while 17.2% did not get the treatment due to contraindication (*30*). With the development of DAAs, the treatment paradigm for HCV infection has been revolutionised since 2014. In comparison with traditional IFN-based therapy, DAAs are associated with high SVR (> 90%), shorter treatment duration (8-24 weeks), and much fewer side-effects. However, the high price of DAA therapy may prohibit its widespread use (*33-35*). In Hong Kong, due to a limited health-care budget and lack of comprehensive insurance coverage schemes, DAAs are not universally prescribed for every patient with HCV infection. Risk stratification is the strategy adopted by the Hospital Authority to prioritize those patients with advanced liver fibrosis (F3) or cirrhosis (F4), to receive subsidized DAA treatment.

In recognition of these service gaps, the Hong Kong Government announced in the 2017 Policy Address setting up a steering committee to formulate strategies to prevent and control viral hepatitis effectively. After reviewing local and international trends and new developments in the prevention and control of viral hepatitis, the committee formulated the *Hong Kong Viral Hepatitis Action Plan 2020-2024* in October 2020, providing a detailed strategic process for controlling HCV infection and reducing the public health burden in Hong Kong (*36*). The *Action Plan* adopts four key strategies, as described in the WHO framework for global action, namely, awareness, surveillance, prevention and treatment, to eliminate HCV infection in Hong Kong (Table 1).

Awareness

Lack of knowledge and awareness about HCV infection probably contributes to continued HCV transmission and missed prevention, early diagnosis and medical care opportunities (*37*). As described in the *Action Plan*, VHCO has been promoting public awareness through various channels, including, telephone hotline, internet, printed materials, health talks for the public, *etc.* A website (*www.hepatitis.gov.hk*) has been revamped to provide essential and up-to-date information on viral hepatitis by VHCO in early 2020. Roving exhibitions on viral hepatitis with different yearly themes of the awareness campaign are held on World Hepatitis Day each year. Meanwhile, professional training programs with the knowledge-attitude-practice (KAP) assessment for healthcare workers of different specialties are conducted in phases. Education on safe injection and safer sex practices for prevention of HCV infection is being integrated with the HIV prevention program, while standardized training and education materials on HCV infection for service providers of PWID is also developed. More importantly, the awareness campaign should emphasize that HCV is not a benign disease, which can potentially lead to liver cancer and liver failure, but the disease is curable nowadays.

Surveillance

As indicated by the *Action Plan*, the present surveillance system has some limitations, including under-reporting, seroprevalence data limited to specific subgroups, and artificial variation in incidence. A set of local indicators for monitoring and evaluation of HCV elimination strategies, including the prevalence of chronic HCV infection, people living with HCV diagnosed, treatment initiation and cure for patients with HCV infection, incidence of HCV infection, and deaths attributable to HCV infection, have been adopted to enhance the current surveillance system. Meanwhile, the Population Health Survey (PHS), a territory-wide survey with

Table 1. The action plan for eliminating HCV epidemic in Hong Kong

Key strategies	Contents
Awareness	- Awareness campaign for the general population - Professional training for healthcare workers - Education targeting at-risk populations, patients and their service providers - Building a supportive environment
Surveillance	- Ongoing surveillance from notification system for acute and chronic HCV infection - Development of local indicators for monitoring and evaluation of the HCV elimination strategies
Prevention	- Reduction of risk and disease burden in vulnerable populations - Prevention of healthcare-related transmission of HCV
Treatment	- Promotion of HCV testing in people who inject drugs - Micro-elimination of HCV in targeted populations - Expansion of access to DAAs for HCV

two components, namely household questionnaire survey and health examination, is being conducted during 2020-2021. It will cover the land-based non-institutional population aged 15 or above for the household questionnaire survey and a subsample of respondents aged between 15 and 84 for health examination. It will provide a representative and detailed analysis of the latest prevalence of chronic HCV infection in the general population, as well as the proportion of patients with chronic HCV infection who have been diagnosed, treated and cured. Clinical data from Health Authority will be the main data source for treatment initiation and cure for HCV patients as the majority of local populations are receiving outpatient and inpatient services for viral hepatitis in public hospitals of the Health Authority. Hopefully, this will significantly improve the 12% HCV treatment rate among diagnosed subjects reported in the territory-wide population-based study of chronic HCV infections in 2018 (*30*).

Prevention

Due to lack of a safe and effective vaccine, controlling practices known to spread HCV and curing patients with HCV infection should be taken as the prevention measures. In Hong Kong, the current blood safety strategies based on voluntary blood donations and quality-assured screening program can prevent transmission of HCV effectively. Patients potentially infected with HCV through contaminated blood or blood procedures before the implementation of anti-HCV screening for blood donors in 1991 are being traced, investigated and treated by Health Authority. Meanwhile, infection control training on Standard Precautions, such as aseptic technique, proper sharps handling and management of needlestick injury or mucosal contact, is being provided to healthcare workers on a regular basis, with an aim to reduce their chance of acquiring or passing on infections of HCV, through occupational exposure. On the other hand, condom programming and a harm reduction approach are needed to be intensified due to the emergence of sexually acquired HCV infection in HIV-positive MSM. The possibility that sexually acquired HCV crosses to HIV-negative MSM should also be scrutinized.

Treatment

Curing chronic HCV infection has been demonstrated to have an immense benefit not only for the patients but also society (*38-40*). With the gradual expansion of DAA therapy from patients with advanced fibrosis or cirrhosis who were contraindicated or intolerant to conventional PegIFN/RBV therapy to all HCV patients regardless of their disease severity in the fourth quarter of 2021 stated in the *Action Plan*, the remaining obstacles to treatment are identification of undiagnosed HCV patients and linkage to continued care and treatment. Universal screening for anti-HCV is not cost-effective due to the low prevalence of HCV infection in Hong Kong. However, several population groups with high prevalence of HCV infection, such as patients undergoing dialysis and HIV-positive patients, will be targeted for screening and treatment to achieve micro-elimination in these well-defined populations. PWID is another priority population for enhancing prevention, testing, linkage to care, treatment and follow-up care. A policy initiative to promote HCV screening and treatment in PWID, who are attending methadone clinics or are under custody of Correctional Services Department, has been established. Perhaps, point-of-care and rapid diagnostic tests can be offered to PWID attending methadone clinics along with educational information about HCV transmission through contaminated injection equipment. Currently, there are around 5,200 people registered with methadone clinics with an average 3,900 daily attendance. A pilot program involving selected methadone clinics is being carried out to test the feasibility and assess the acceptance of HCV testing among PWID. The information gained from the pilot program can also help better characterize the barriers to HCV testing and care, and devise strategies to overcome them.

The implementation of the above *Action Plan* will be monitored and evaluated regularly through different targets and indicators to drive progress towards the WHO 2030 goals of eliminating HCV infection in Hong Kong.

Conclusions

In Hong Kong, the estimated HCV prevalence in general population is 0.3%-0.5%, prevailing in several specific populations, including PWID, patients undergoing dialysis and HIV/AIDS patients. However, our territory-wide diagnosis rate and treatment rate are still substantially below the 2030 WHO targets of viral hepatitis elimination. To realize the elimination target, four key strategies including awareness, surveillance, prevention and treatment have been adopted in the *Hong Kong Viral Hepatitis Action Plan 2020-2024*. With the implementation of the *Action Plan*, especially in targeted screening approaches on high-risk populations and more generalized use of the highly efficacious DAAs for all diagnosed HCV subjects, the goals of reducing HCV transmission and HCV-related morbidity and mortality to the WHO targets can be achieved in Hong Kong by 2030.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science. 1989; 244:359-362.
2. Houghton M. Discovery of the hepatitis C virus. Liver Int. 2009; 29 Suppl 1:82-88.
3. Stanaway JD, Flaxman AD, Naghavi M, *et al.* The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet. 2016; 388:1081-1088.
4. World Health Organization. Global Hepatitis Report 2017. *https://www.who.int/publications-detail-redirect/global-hepatitis-report-2017* (accessed May 30, 2021).
5. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2017; 2:161-176.
6. Roger S, Ducancelle A, Le Guillou-Guillemette H, Gaudy C, Lunel F. HCV virology and diagnosis. Clin Res Hepatol Gastroenterol. 2021; 45:101626.
7. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, Goodman ZD, Ling MH, Cort S, Albrecht JK. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med. 1998; 339:1485-1492.
8. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002; 347:975-982.
9. Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. Gut. 2006; 55:1350-1359.
10. Schinazi R, Halfon P, Marcellin P, Asselah T. HCV direct-acting antiviral agents: the best interferon-free combinations. Liver Int. 2014; 34 Suppl 1:69-78.
11. Ji D, Chen GF, Wang C, Wang YD, Shao Q, Li B, Zhao J, You SL, Hu JH, Liu JL, Niu XX, Chen J, Lu L, Wu V, Lau G. Twelve-week ribavirin-free direct-acting antivirals for treatment-experienced Chinese with HCV genotype 1b infection including cirrhotic patients. Hepatol Int. 2016; 10:789-798.
12. Martinello M, Hajarizadeh B, Grebely J, Dore GJ, Matthews GV. Management of acute HCV infection in the era of direct-acting antiviral therapy. Nat Rev Gastroenterol Hepatol. 2018; 15:412-424.
13. Omata M, Kanda T, Wei L, *et al.* APASL consensus statements and recommendation on treatment of hepatitis C. Hepatol Int. 2016; 10:702-726.
14. Kanda T, Lau GK, Wei L, *et al.* APASL clinical practice recommendation: how to treat HCV-infected patients with renal impairment? Hepatol Int. 2019; 13:103-109.
15. Ghany MG, Morgan TR; AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Hepatology. 2020; 71:686-721.
16. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: Final update of the series. J Hepatol. 2020; 73:1170-1218.
17. World Health Organization. Combating hepatitis B and C to reach elimination by 2030. Published on May 2016. *https://apps.who.int/iris/bitstream/handle/10665/206453/WHO_HIV_2016.04_eng.pdf%3bjsessionid%3d4BD913237991690DE2A6A6FDE7DFD5A8%3fsequence%3d1.* (accessed May 5, 2021).
18. Chan GC, Lim W, Yeoh EK. Prevalence of hepatitis C infection in Hong Kong. J Gastroenterol Hepatol. 1992; 7:117-120.
19. Liu KSH, Seto WK, Lau EHY, Wong DK, Lam YF, Cheung KS, Mak LY, Ko KL, To WP, Law MWK, Wu JT, Lai CL, Yuen MF. A territorywide prevalence study on blood-borne and enteric viral hepatitis in Hong Kong. J Infect Dis. 2019; 219:1924-1933.
20. Viral Hepatitis Control Office, Department of Health, the Government of the Hong Kong Special Administrative Region. Surveillance of viral hepatitis in Hong Kong - 2019 Report. *https://www.hepatitis.gov.hk/tc_chi/document_cabinet/files/hepsurv19.pdf* (accessed May 5, 2021).
21. Wong NS, Lee CK, Ng SC, Wong HK, Chan DPC, Lee SS. Prevalence of hepatitis C infection and its associated factors in healthy adults without identifiable route of transmission. J Viral Hepat. 2018; 25:161-170.
22. Cooke GS, Andrieux-Meyer I, Applegate TL, *et al.* Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol. 2019; 4:135-184.
23. Lee KC, Lim WW, Lee SS. High prevalence of HCV in a cohort of injectors on methadone substitution treatment. J Clin Virol. 2008; 41:297-300.
24. Wong NS, Chan PC, Lee SS, Lee SL, Lee CK. A multilevel approach for assessing the variability of hepatitis C prevalence in injection drug users by their gathering places. Int J Infect Dis. 2013; 17:e193-198.
25. Chan DP, Lee KC, Lee SS, Tan TY. Community-based molecular epidemiology study of hepatitis C virus infection in injection drug users. Hong Kong Med J. 2017; 23 Suppl 5:27-30.
26. Wong GL, Chan HL, Loo CK, Hui YT, Fung JY, Cheung D, Chung C, Chim AM, Wong VW; Hong Kong Association for the Study of Liver Diseases (HKASLD). Change in treatment paradigm in people who previously injected drugs with chronic hepatitis C in the era of direct-acting antiviral therapy. J Gastroenterol Hepatol. 2019; 34:1641-1647.
27. Bukh J. The history of hepatitis C virus (HCV): Basic research reveals unique features in phylogeny, evolution and the viral life cycle with new perspectives for epidemic control. J Hepatol. 2016; 65:S2-S21.
28. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, Barnes E. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2015; 61:77-87.
29. Prescott LE, Simmonds P, Lai CL, Chan NK, Pike I, Yap PL, Lin CK. Detection and clinical features of hepatitis C virus type 6 infections in blood donors from Hong Kong. J Med Virol. 1996; 50:168-175.
30. Hui YT, Wong GLH, Fung JYY, *et al.* Territory-wide population-based study of chronic hepatitis C infection and implications for hepatitis elimination in Hong Kong. Liver Int. 2018; 38:1911-1919.
31. Yan KK, Wong GL, Wong VW, Chan HL. Rate and factors affecting treatment uptake of patients with chronic hepatitis C in a tertiary referral hospital. Dig Dis Sci. 2010; 55:3541-3547.

32. Patel AA, Bui A, Prohl E, Bhattacharya D, Wang S, Branch AD, Perumalswami PV. Innovations in hepatitis C screening and treatment. Hepatol Commun. 2020; 5:371-386.
33. Chen GF, Wei L, Chen J, *et al.* Will sofosbuvir/ledipasvir (harvoni) be cost-effective and affordable for Chinese patients infected with hepatitis C virus? An economic analysis using real-world data. PLoS One. 2016; 1:e0155934.
34. Lau G. Shortening HCV therapy: science meets public health. Lancet Gastroenterol Hepatol. 2017; 2:771-772.
35. Thomas DL. Global elimination of chronic hepatitis. N Engl J Med. 2019; 380:2041-2050.
36. The Government of the Hong Kong Special Administrative Region. Hong Kong Viral Hepatitis Action Plan: 2020-2024. *https://www.hepatitis.gov.hk/doc/action_plan/Action%20Plan_Full%20Version_PDF_en.pdf* (accessed May 5, 2021).
37. McLeod A, Cullen BL, Hutchinson SJ, Roy KM, Dillon JF, Stewart EA, Goldberg DJ. Limited impact of awareness-raising campaigns on hepatitis C testing practices among general practitioners. J Viral Hepat. 2017; 24:944-954.
38. Butt AA, Yan P, Shaikh OS, Lo Re V 3rd, Abou-Samra AB, Sherman KE. Treatment of HCV reduces viral hepatitis-associated liver-related mortality in patients: An ERCHIVES study. J Hepatol. 2020; 73:277-284.
39. Butt AA, Yan P, Aslam S, Shaikh OS, Abou-Samra AB. Hepatitis C virus (HCV) treatment with directly acting agents reduces the risk of incident diabetes: Results from electronically retrieved cohort of HCV infected veterans (ERCHIVES). Clin Infect Dis. 2020; 70:1153-1160.
40. Evon DM, Kim HP, Edwards A, Carda-Auten J, Reeve BB, Golin CE, Fried MW. "If I get cured, my whole quality of life will change": Patients' anticipated and actualized benefits following cure from chronic hepatitis C. Dig Dis Sci. 2021. doi: 10.1007/s10620-021-06829-2.

Received June 18, 2021; Revised July 26, 2021; Accepted August 3, 2021.

Released online in J-STAGE as advance publication August 13, 2021.

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Global Health & Medicine. 2021; 3(5):283-287.
REVIEW
DOI: 10.35772/ghm.2021.01049

HCV elimination in Hong Kong – Non-government organisation (NGO) activities

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Abstract: World Health Organization (WHO) calls for global hepatitis strategy to eliminate viral hepatitis by 2030. Yet many high-income countries were unable to achieve HCV elimination by 2030. Apart from the tremendous efforts and resources from the governments, many non-government organizations (NGOs) have been working very hard to contribute to HCV elimination. In Hong Kong, the Center for Liver Health of The Chinese University of Hong Kong (CUHK) has been working very closely with various NGOs to educate and screen subjects who previously use intravenous drugs. In this review article, we discussed in details the New Life New Liver Program, and the barriers to HCV elimination, with special highlight the role of NGOs in overcoming the barriers.

***Keywords*:** DAA, hepatitis elimination, IVDU, treatment uptake

Introduction

Chronic hepatitis C virus (HCV) infection has been one of the leading causes of chronic liver disease worldwide, resulting in various hepatic events, including cirrhosis and hepatocellular carcinoma (HCC), as well as extrahepatic complications (*1*). Its prevalence was 1.0% in 2015, equating 71 million individuals infected with HCV worldwide, with 475,000 deaths as a result (*2,3*). In Hong Kong, 0.3-0.5% of the 7.4 million population were chronically infected with HCV (*4*). Similar to the rest of the world, genotype 1 contributed to around 60% of HCV infection in the locality (*2,5*).

HCV infection is transmitted by direct exposure to blood. Intravenous drug use (IVDU) has remained a continuing reservoir of the HCV epidemic worldwide (*6*). Local data showed that the prevalence of HCV infection was up to 46% in patients with IVDU (*7*); 5% of patients with human immunodeficiency virus (HIV) infection have HCV/HIV co-infection (*8*). World Health Organization (WHO) calls for global hepatitis strategy to eliminate viral hepatitis by 2030, with 90% reduction in incident cases of viral hepatitis B and C, and 65% reduction in mortality. To achieve these, 80% of treatment-eligible patients should be treated (*9*). A recent analysis illustrated that 80% of high-income countries were unable to achieve HCV elimination by 2030, with 67% of them being off track by at least 20 years (*10*). Applying the same analysis model, Hong Kong is not expected to achieve the goal by 2050 due to suboptimal diagnosis and treatment rates (*4*).

Case identification and timely treatment of HCV patients are of paramount importance. Apart from increased effort from the healthcare sector and the government, improving social awareness to the disease is crucial. Non-government organizations (NGOs) set a channel for the general population and the at-risk groups to learn more about HCV infection, and hence may be game-changing to the current situation.

Overview of NGOs which serve HCV patients

Over the years, medical services provided by the government and the healthcare sectors have undoubtedly reduced the local prevalence of chronic HCV infection. Apart from that, there are also a number of NGOs in Hong Kong which put plentiful efforts in sealing the service gap by awareness enhancement and public education on HCV (*11*).

The Center for Liver Health of The Chinese University of Hong Kong (CUHK) is one of the largest centers in Hong Kong which is dedicated against hepatitis including HCV. The Center provides the public updated knowledge and information on liver diseases, as well as a range of tests to identify viral hepatitis and its complications. Caritas Lok Heep Club is another prestigious organization which serves many drug abusers in Hong Kong. Sharing the same goal, CUHK and Caritas Lok Heep Club have launched the New Life New Liver programme in 2009 which targets

the ex-IVDU (the population who is at the highest risk of HCV infection), focusing the effort to prevent the transmission of hepatitis, preserve the patient's liver function by early screening and provide counselling and referral to specialist clinics for timely treatment (see below) (*12,13*).

With the monumental effort of the two pioneer centers, the programme gradually evolves into a collaboration between CUHK and many other NGOs which help ex-IVDUs in rehabilitation. These NGOs provide substance abuse counselling and a variety of rehabilitation treatment programmes. Examples include Operation Daw, The Society of rehabilitation and crime prevention, Hong Kong; and The Society for the aid and Rehabilitation of Drugs abuses. Some of the NGOs also provide religion guidance and support on top of the above mentioned services, for example, Rehabilitation Centres of the Christian Zheng Sheng Association. Evangelical Lutheran Church Social Service, Ling Oi Centre, Pui Hong Self Help Association, Barnabas Charitable Service Association Limited, St Stephen's Society, DACARS Limited and Glorious Praise Fellowship (Hong Kong) Limited (*14-16*).

New Life New Liver Program

Background

People who inject drugs (PWID) are one of the most important special populations in eliminating HCV infection. It is because the prevalence of HCV infection is often high in PWID, and it is often challenging to reach these people out, link them to care, and keep them in the long-term care and complication screening (*7*). Most PWID are not aware of the knowledge of HCV infection and its treatment. As chronic HCV infection is often asymptomatic, HCV-infected PWID rarely seek medical attention or screen for viral hepatitis. PWID may first present to medical care with complication of liver of cirrhosis or hepatocellular carcinoma (HCC). To help this important special population, a joint effort of healthcare professionals and NGOs with experienced social workers is pivotal.

Objectives

The New Life New Liver Programme is a special programme focusing on ex-PWID in Hong Kong. This activity was started in 2009, initially as a collaborative effort of Caritas Lok Heep Club and Center for Liver Health of The Chinese University of Hong Kong (CUHK) (*13*). It subsequently evolves into a collaboration between CUHK and many other NGOs dealing with rehabilitation of ex-PWID. This is a targeted screening and assessment program for ex-PWID. We accepted referrals from social workers who have confirmed abstinence from intravenous drug use for at least one year. After the education talk, point-of-care anti-HCV testing was performed using the HCV Rapid Card (Bio Focus Company, Ui-Wang, Korea). The objectives of this program are listed in Table 1.

Table 1. Objectives of New Life New Liver programme

Icon	Objective
	Provide education on HCV infection and its complications.
	Screen for HCV infection and other liver diseases (*e.g.* HBV, HIV).
	Refer for antiviral treatment for those who are HCV infected.
	Support the social and psychological aspects of patients before, during and after antiviral treatment.
	Promote the avoidance of drug abuse to the public.

HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Workflow

In the New Life New Liver program, different types of personnel are working together in a multidisciplinary team for patients – hepatologists, psychiatrists, psychologists, social workers, project coordinators and laboratory technicians. The program is divided into three parts. First, we provide educational talk on HCV infection, complications and treatments to PWID and their family members. We allow ample time for the participants to raise any questions after the talk. Most of the PWID are concerned about the side effects of treatment, especially in the old days when peginterferon-alpha and ribavirin was the only reimbursed antiviral treatment (*17*). Second, risk assessment of HCV infection including blood tests and transient elastography examination for liver stiffness measurement is arranged within three months from this educational session (*18*). Because of the referral policy of Hospital Authority, Hong Kong, we refer HCV patients to their own regional hospitals (according to residential address) for long-term follow-up and social worker support in the respective NGOs.

Programme in pre-DAA era

From 2009 to 2012, we screened 234 ex-PWID; 130 (56%) subjects were anti-HCV positive. The number needed to screen to detect one patient with positive anti-HCV was 1.8 (95% confidence interval, 1.6-2.0). However, only 69 (53%) HCV patients attended subsequent follow-up at regional hospitals, and 26 (20%) received peginterferon-based antiviral therapy (*17*). Such treatment uptake rate revealed the barriers

at different steps of the care cascade for HCV patients. The most significant dropout occurred after the comprehensive liver assessment to first follow-up visit (dropout rate 37.8%) and treatment uptake (dropout rate 37.7%). The low treatment uptake rate was mainly because of mild liver disease, contraindications to peginterferon and psychosocial reasons (*17*). We learned from this initial phase of programme that further improvements in the referral system and treatment regimens were need to improve treatment uptake,

Programme in DAA era

We performed the second round of analysis in June 2018, by that time a few DAAs had been available in Hong Kong (*4,19*). Up to this analysis, 362 ex-PWID received HCV rapid test; 268 (73.4%) were found to be anti-HCV positive, with 234 (87.3%) attended the assessment session (mean age 52 years, 90.2% male, 45.5% genotype 1b, 41.1% genotype 6a, median liver stiffness 5.9 kPa); 187 (69.8%) attended follow-up visits at regional hospitals. Treatment uptake rates of PegIFN/RBV and DAA treatment in the pre- *vs*. post-DAA era were 22.3% *vs*. 48.5% and 0% *vs*. 15.6% respectively (*7*).

Barriers to eliminate HCV

After serving PWID for more than a decade, we identified a few key barriers at different steps of the care cascade (Figure 1). Education to various parties and stakeholders, including healthcare practitioners, patients and public is the key components in many steps. NGOs are particularly crucial in engaging newly diagnosed patients, *e.g*. from some screening programmes, and linking them to care. Social workers may facilitate the clinic visit by companying them and helping them to register.

Role of NGOs in DAA era

Since the introduction of DAA therapy, global elimination of HCV has been the ultimate goal. NGOs in Hong Kong play an integral role in educating the general public on the advantages of DAA, which has revolutionized the treatment of HCV. Compared to the traditional treatment regimens of weekly subcutaneously injectable peginterferon with oral ribavirin once or twice daily, current DAAs have much fewer side effects, much shorter treatment duration (8 to 12 weeks), higher rates of sustained virological response (SVR) universally to essentially all HCV genotypes, and a higher genetic barrier to resistance (*20*).

In the 9-year screening program done on Ex-PWID we described previously, we had already seen an improvement in treatment uptake rate since Hong

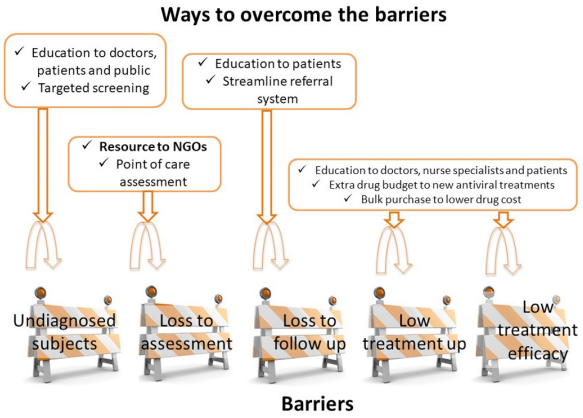

Figure 1. Barriers to HCV elimination, with special highlight the role of non-government organizations (NGOs) in overcoming the barriers (modified from Wong *et al*., *Ref. 7*)

Kong's shift into the DAA era, with a rise in treatment uptake in pre-DAA *vs*. post-DAA era; from 22.3% up to 48.5% in the traditional treatment group (PegIFN/RBV), and from 0% up to 15.6% in the DAA treatment group (*7*). The treatment landscape for HIV and HCV co-infection groups has also changed drastically since the introduction of DAA regimes, with higher rates of SVR and reduced drug-drug interaction observed (*21*).

However, a large percentage of HCV patients in Hong Kong still remain undiagnosed and untreated (*4*). Bridging the treatment gap remains a major challenge. Increasingly, we rely upon the help of NGOs in disseminating the news of these improved and more efficacious antiviral agents to the community, and in raising awareness of the importance of early initiation of HCV treatment. Late presentation for treatment can lead to advanced stages of disease, increased hospital admission and financial burden, and risk of increased viral transmission rates especially in high-risk communities (*22*).

NGO workers reach out to the underprivileged and at-risk groups in the society, by distributing books, brochures and holding educational talks about HCV in the community (*7*). They can support those who have screened positive to attend clinic follow-ups and help improve medication adherence by establishing rapport with vulnerable groups. Striving forward, we must liaise more closely with NGOs to develop a more streamline referral system to hospitals and hepatology units to avoid loss to follow-up. More than ever, NGOs remain the key players in our movement to reduce the disease burden of this now very treatable disease and join the global effort to HCV elimination.

Conclusions and Perspective

HCV infection remains a significant global health threat. Nevertheless, different measures and parties are working hand in hand to fight the battle. Among these, NGO plays an undeniable role in raising social

awareness to the disease and this ultimately leads to improved diagnosis and treatment rates. The New Life New Liver program provides a comprehensive pathway, from education and screening to disease assessment and referral for treatment, for ex-IVDU. The program would be hopefully improving the current inadequacy on control of HCV transmission and treatment, especially in this risk group which accommodates a significant proportion of HCV-infected individuals around the world.

"Treatment as prevention" is an important advocate in tackling HCV transmission. By eradicating HCV infection in patients at risk of transmitting HCV to others, the chain of propagation of HCV transmission would be interrupted. The point-of-care service of the New Life New Liver program, aiming at timely diagnosis and assessment of HCV infection, would likely increase the treatment uptake, serving as prevention for further transmission. With the more available pan-genotypic DAA and the loosening on treatment reimbursement policy in our locality, and the support from different stakeholders, the WHO 2030 viral hepatitis elimination target is not beyond reach.

Funding: None.

Conflict of Interest: Grace Wong has served as an advisory committee member for Gilead Sciences and Janssen. She has also served as a speaker for Abbott, Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen, and Roche. Other authors have no conflicts of interest to disclose.

References

1. Negro F, Forton D, Craxì A, Sulkowski MS, Feld JJ, Manns MP. Extrahepatic morbidity and mortality of chronic hepatitis C. Gastroenterology. 2015; 149:1345-1360.
2. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2017; 2:161-176.
3. World Health Organization. Global hepatitis report 2017. *https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/* (accessed April 20, 2021).
4. Hui YT, Wong GLH, Fung JYY, *et al*. Territory-wide population-based study of chronic hepatitis C infection and implications for hepatitis elimination in Hong Kong. Liver Int. 2018; 38:1911-1919.
5. The Government of the Hong Kong Special Administrative Region. Hong Kong viral hepatitis action plan 2020 - 2024. October 2020. *https://www.hepatitis.gov.hk/doc/action_plan/Action%20Plan_Full%20Version_PDF_en.pdf* (accessed April 20, 2021).
6. Degenhardt L, Peacock A, Colledge S, *et al*. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. Lancet Glob Health. 2017; 5:e1192-e1207.
7. Wong GL, Chan HL, Loo CK, Hui YT, Fung JY, Cheung D, Chung C, Chim AM, Wong VW; Hong Kong Association for the Study of Liver Diseases (HKASLD). Change in treatment paradigm in people who previously injected drugs with chronic hepatitis C in the era of direct-acting antiviral therapy. J Gastroenterol Hepatol. 2019; 34:1641-1647.
8. Centre for Health Protection. Surveillance of Viral Hepatitis in Hong Kong - 2017 Update Report. *https://www.chp.gov.hk/files/pdf/viral_hepatitis_report.pdf* (accessed April 20, 2021).
9. World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. *https://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en* (accessed April 20, 2021).
10. Razavi H, Sanchez Gonzalez Y, Yuen C, Cornberg M. Global timing of hepatitis C virus elimination in high-income countries. Liver Int. 2020; 40:522-529.
11. Center for Health Protection, Department of Health. Surveillance of Viral Hepatitis in Hong Kong 2018. *https://www.chp.gov.hk/files/pdf/viral_hep_sur_report_2018.pdf* (accessed April 20, 2021).
12. Caritas Lok Heep Club. Drug treatment and rehabilitation, Our services. *https://www.caritaslokheepclub.org.hk/en/drug-treatment-and-rehabilitation/services* (accessed April 20, 2021).
13. Center for Liver Health. New Life New Liver Programme-Details of Action Plan *https://livercenter.com.hk/article/%E6%98%8E%E8%82%9D%E8%A1%8C%E5%8B%95%E8%A8%88%E5%8A%83%E8%A9%B3%E6%83%85* (accessed April 20, 2021). (in Chinese)
14. Operation Dawn Limited (Gospel Drug Rehab). Operation Dawn Annual Report 2019-2020. *https://opdawn.org.hk/zh_hk/wp-content/uploads/2020/12/Annual-Report-2020-draft2b-1.pdf* (accessed April 20, 2021). (in Chinese)
15. St Stephen Society. What we do, Hong Kong. *http://www.ststephenssociety.com/en/hongkong.php* (accessed April 20, 2021).
16. The Society of Rehabilitation and Crime Prevention, Hong Kong. Social Rehabilitation and Crime Prevention Service 2019-2020. *https://sracp.org.hk/en/socialservice.html* (accessed April 20, 2021).
17. Wong VW, Wong GL, Chim AM, *et al*. Targeted hepatitis C screening among ex-injection drug users in the community. J Gastroenterol Hepatol. 2014; 29:116-120.
18. Wong GL. Non-invasive assessments for liver fibrosis: The crystal ball we long for. J Gastroenterol Hepatol. 2018; 33:1009-1015.
19. Chan HL, Tsang OT, Hui YT, *et al*. Real-life efficacy and safety of paritaprevir/ritonavir, ombitasvir, and dasabuvir in chronic hepatitis C patients in Hong Kong. J Gastroenterol Hepatol. 2017; 32:1230-1233.
20. Banerjee D, Reddy KR. Review article: safety and tolerability of direct-acting anti-viral agents in the new era of hepatitis C therapy. Aliment Pharmacol Ther. 2016; 43:674-696.
21. Lin M, Kramer J, White D, Cao Y, Tavakoli-Tabasi S, Madu S, Smith D, Asch SM, El-Serag HB, Kanwal F. Barriers to hepatitis C treatment in the era of direct-acting anti-viral agents. Aliment Pharmacol Ther. 2017; 46:992-1000.
22. He T, Lopez-Olivo MA, Hur C, Chhatwal J. Systematic review: cost-effectiveness of direct-acting antivirals

for treatment of hepatitis C genotypes 2-6. Aliment Pharmacol Ther. 2017; 46:711-721.

Received April 23, 2021; Revised May 17, 2021; Accepted May 19, 2021.

Released online in J-STAGE as advance publication May 27, 2021.

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Global Health & Medicine. 2021; 3(5):288-292.
DOI: 10.35772/ghm.2021.01057

REVIEW

Inclusion of hepatitis C virus testing in National Health Screening to accelerate HCV elimination in South Korea

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Abstract: In 2015, the World Health Organization (WHO) has set the goal of eliminating hepatitis C by reducing incidence of chronic viral hepatitis and related mortality by 2030 with the interim target of achieving 30% prevalence reduction by 2020. While The global prevalence of hepatitis C is known to be around 1.6%, the prevalence of hepatitis C in South Korea is 0.5-0.6% based on hepatitis C virus (HCV) antibody-positive rate. Although HCV antibody test has been included in the Annual National Health and Nutrition Survey in South Korea since 2012, a national initiative to eliminate hepatitis C was initiated by small clinic-related hepatitis C outbreaks in 2015-2016. These outbreaks caused by inappropriate use of syringes in 2015-2016 prompted the revision of hepatitis C reporting and control strategies in Korea following long-term discussion on including the HCV antibody test in the National Health Screening at a certain age. Since June 3, 2017, all hepatitis C cases should be reported to the Korea Disease Control Agency (KDCA). A pilot study for early detection of hepatitis C was conducted for the 56 years old population from September 1 to October 31 in 2020 by temporarily including HCV Ab in the National Health Screening followed by HCV RNA testing for HCV antibody positive cases. The final decision to include HCV antibody test in National Health Screening will be made based on results of the pilot study in 2020. To eliminate hepatitis B & C by 2030 in South Korea, the KDCA established a comprehensive viral hepatitis control and management system in 2020 with the interim goal of achieving an antibody positive rate of 0.3% and treatment rate of 90% by 2025.

***Keywords*:** hepatitis C elimination, National Health and Nutrition Survey, hepatitis C virus antibody, hepatitis C virus RNA, treatment

Introduction

Viral hepatitis caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) is the major cause of chronic liver disease in Korea. Hepatitis C remains a public health problem with low awareness resulting in low detection and treatment rate. WHO set the global target of eliminating hepatitis C by 2030 and adopted the WHO Global Health Sector Strategy on Viral Hepatitis 2016-2021 which provides a roadmap for eliminating hepatitis B and C with 5 strategic directions in 2016 (*1*). Global hepatitis C elimination: an investment framework also provides an investment framework for global hepatitis C elimination to accelerate domestic and international financing and political commitment (*2*).

Dore and Bajis described some country examples of HCV elimination efforts in a recent paper (*3*). One example is Egypt that is an exemplar country demonstrating how national HCV screening and treatment strategy can contribute to HCV elimination (*4*). From October 2018 to April 2018, 5,800-8,000 teams consisting of a physician, nurse and a data-entry person were involved in screening of a 49.6 million population (around 80% of whole population in Egypt) (*4*). It is important to note that political will is a key success factor of the massive HCV screening and treatment program in Egypt (*3*). Dore and Bajis also emphasized that a potential impediment to HCV elimination is how to access highly maginalized people such as people who inject drugs and that innovative strategies are required to access those hard-to-reach populations (*3*) A strategy utilizing pharmacy known as pharmacist-led care proposed by Radley *et al*. to deliver an HCV care pathway made testing and treatment accessible for patients and maintained a high treatment success rate (*5*).

In this review, the current situation of hepatitis C in Korea, small clinic-related hepatitis C outbreaks in 2015-2016 and national viral hepatitis C elimination strategy and action plan will be described.

Hepatitis C prevalence and current situation in Korea

Hepatitis C was classified as a designated infectious disease based on sentinel surveillance in 2000. It is

estimated that there are around 300,000 hepatitis C cases in Korea (0.57%) as of 2020 (*6*). Among those estimated cases, only around 1/3-1/4 is being treated under the current national health insurance system as described by Jeong *et al*. (*7*).

Figure 1 shows annual reported cases of hepatitis C from 2011 to 2020. Since the reporting of hepatitis C cases changed from sentinel surveillance to mandatory reporting of all cases from June 3, 2017, annually reported HCV cases were dramatically reduced from 2017. Figure 2 shows the age distribution of reported hepatitis C cases in Korea. The analysis of age distribution shows that more than 94% of reported cases are > 40 years old (*6*).

Small clinic-related hepatitis C outbreaks in Korea

During 2015-2016, healthcare-associated outbreaks of HCV were detected in Korea. Epidemiological investigation revealed that reuse of needles or syringes was related to outbreaks. Briefly, samples from 1,721 patients who attended one clinic were tested for HCV antibody and HCV RNA followed by sequencing and 96 samples were positive for HCV Immunoglobulin(Ig) G. Among 96 HCV IgG positive samples, 70 were positive for HCV RNA. Interestingly, HCV genotype 1a sequences were detected from most cases. As genotype 1a is very rare in Korea, it was concluded that IV injection at this clinic was a source of HCV infection (*8*). From HCV RNA testing of additional environmental samples such as multi-dose vials and medical apparatus from this clinic, HCV RNA was also detected indicating HCV transmission occurred in the medication room due to reuse of syringes and contaminated multi-dose vials (*8*). Investigation of another HCV outbreak in an orthopedic clinic in 2015 also confirmed that medical

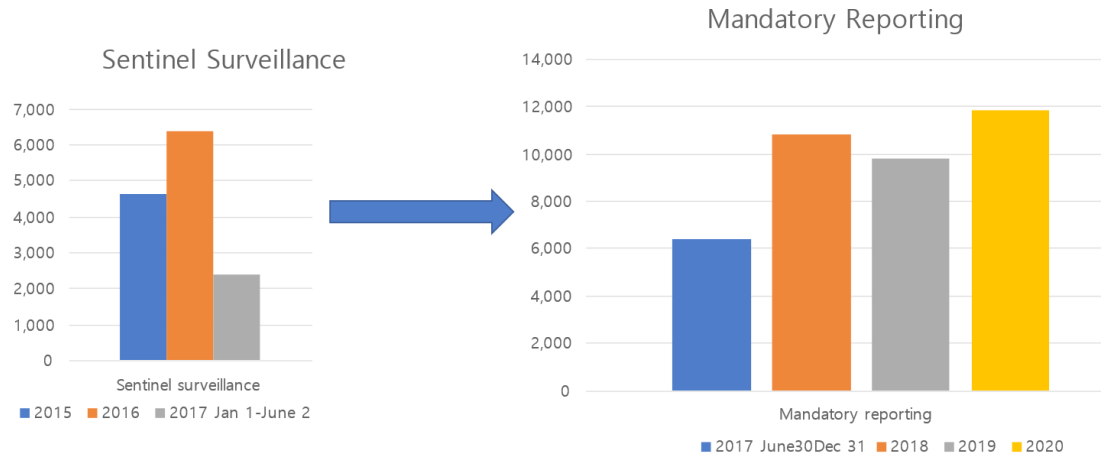

Figure 1. Annually reported hepatitis C cases in Korea, 2011-2020. *Data source*: Reference 14, Infectious Disease Portal, KDCA.

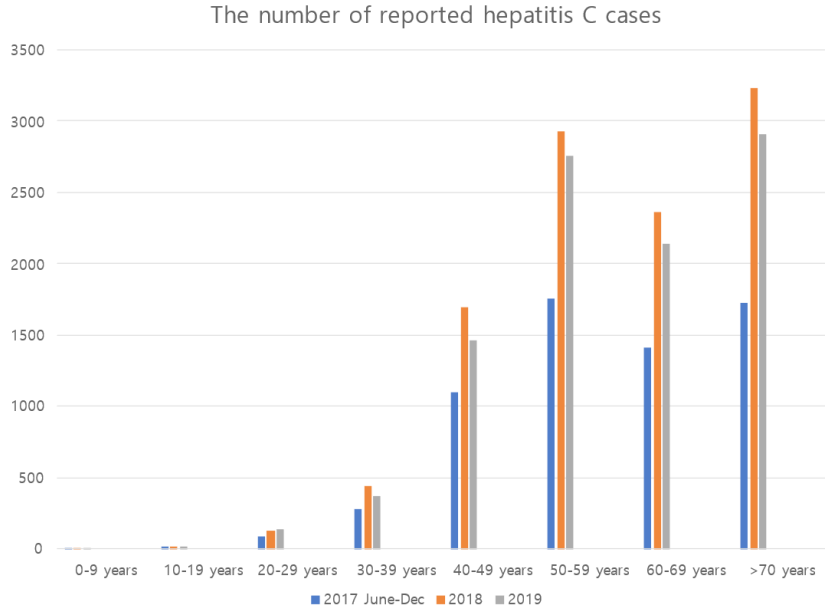

Figure 2. Age distribution of reported hepatitis C cases in Korea (2017 June-2019). *Data source*: Reference 6.

procedures within the clinic were the source of HCV transmission.

These outbreaks prompted the change of hepatitis C surveillance from sentinel surveillance to mandatory reporting in 2017.

National viral hepatitis C elimination strategy and action plan

Availability of effective direct-acting antiviral agents (DAA) for treating hepatitis C allows global elimination efforts feasible. If cases are detected and treated early, hepatitis C- related morbidity and mortality can be significantly reduced. A review by Shahid *et al*. describes that the advancement and implementation of state-of-the-art diagnostic platforms in low-to-middle income countries as well as high income countries allowed identification of millions of undiagnosed hepatitis C-infected individuals (*9*). With the availability and the national health insurance coverage of DAA that can cure HCV infection, Jeong *et al*. (*7*) stressed the importance of HCV screening test in conjunction with national health examination as a cost-effective strategy for HCV elimination and eradication. A preprint submitted by Tatara *et al*. re-iterates the importance of reaching out to a hard-to-reach population emphasizing that re-treatment with DAA would be needed to achieve hepatitis C elimination especially among individuals who inject drugs (*10*).

The Korea Disease Control Agency (KDCA) is the national public health institute with responsibilities for management and control of human diseases that include infectious diseases. It establishes and implements national polices on infectious diseases including viral hepatitis. KDCA set a vision of eliminating hepatitis B and C by 2030 with an integrated viral hepatitis control and management system.

For prevention of HCV transmission, reuse of disposable syringes and medical supplies are strictly prohibited and relevant guidelines were revised and distributed (*10*). KDCA is also planning to strengthen research on epidemiology, disease burden, treatment strategies as well as prevention and control policies to control viral hepatitis. Improving the proportion of timely reporting of hepatitis C among all reported cases was included as one criterion for the hepatitis C control program. Implementation of the Integrated Viral Hepatitis Control and Management System shown in Figure 3 and national 5- year plan for integrated management and control of viral hepatitis shown in Figure 4 by KDCA will accelerate the process to achieve hepatitis C elimination by 2030 (*11,12*).

For early detection and treatment of hepatitis C cases, KDCA is planning to introduce HCV antibody testing as a life cycle-based screening in the National Health Screening and to expand the insurance benefit for treatment of hepatitis C. Life cycle-based HCV screening strategy to include HCV antibody testing at the certain age of the National Health Screening was proposed by the Korean Association for Study of the Liver.

During liver week 2020, the Korean Association for Study of the Liver (KASL) proposed 4 strategies to eliminate hepatitis C: *i*) establishing designated division for viral hepatitis in the Korea Disease Control Agency, *ii*) increasing hepatitis C research fund, *iii*) conducting a study on reviewing cost-effectiveness of introducing HCV antibody testing in National Health Screening as a life cycle approach, and *iv*) integrated control of chronic viral hepatitis B and C. KASL announced the vision, strategies and goal of eliminating hepatitis C by 2030 by improving awareness from 30% to 90%, increasing hepatitis C laboratory testing rate from < 10% to 90% and case treatment rate from 60% to 90% by 2028 (*13*).

KDCA and KASL are collaborating to conduct a pilot study for early detection of hepatitis C among

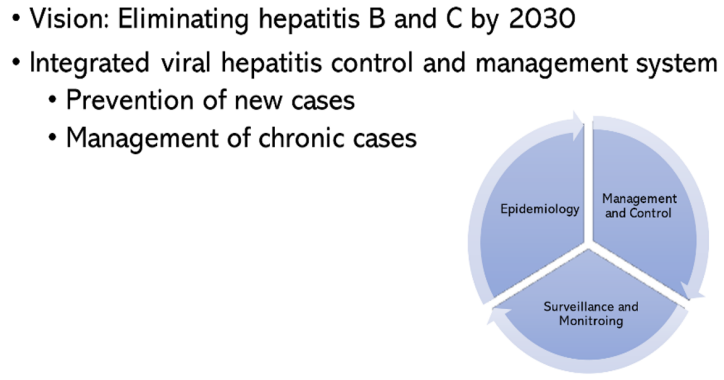

Figure 3. Integrated Viral Hepatitis Control and Management System. Integrated Viral Hepatitis Control System of Epidemiology, Management and Control and Surveillance and Monitoring to prevent new cases and to manage chronic cases. *Data source*: Reference 12.

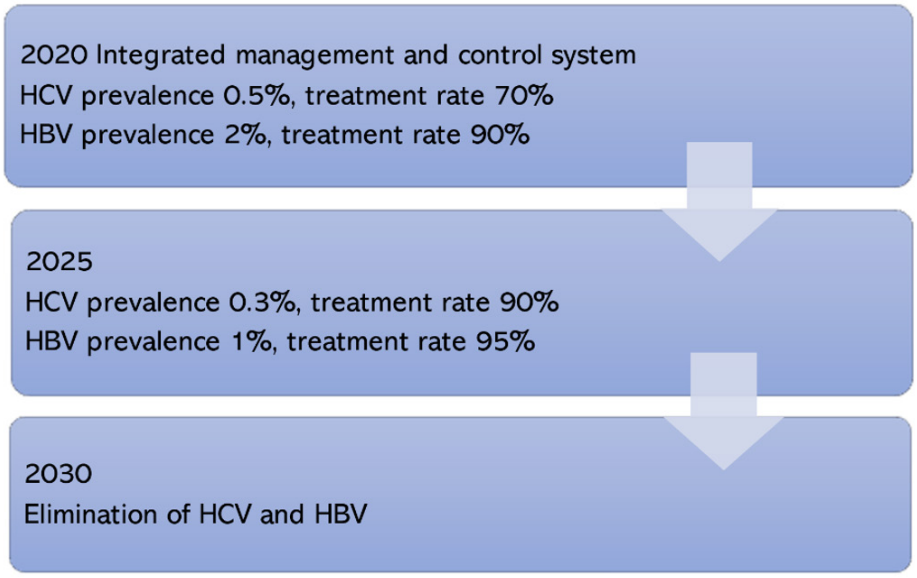

Figure 4. National target to control and eliminate viral hepatitis B and C by 2025 and 2030. National targets to control and eliminate viral hepatitis B and C by 2025 and 2030 are proposed. *Data source*: Reference 12.

56 years-old population in Korea from September to October 2020 by temporarily including anti-HCV antibody testing followed by HCV RNA testing in the National Health Screening (*6*). This pilot study is to confirm the prevalence and risk factors of hepatitis C and cost-effectiveness of including anti-HCV testing and HCV RNA testing in the National Health Survey. The results of the study will be utilized for the government's decision to include HCV antibody test in the National Health Screening and design of additional studies. The national strategy may also address strategic preparation for possible unification with North Korea in the future (*6*).

WHO Global Health Sector Strategy on Viral Hepatitis 2016-2021 emphasizes the importance of implementing evidence-based national hepatitis plans and priority actions such as establishing a national governance structure and coordination mechanism (*1*). It is urgently needed to set up an integrated governance structure for eliminating viral hepatitis in KDCA, to finalize and implement the comprehensive national hepatitis plan and to monitor progress of the national hepatitis plan in partnership with KASL.

Conclusion

To achieve the goal of elimination of hepatitis C and hepatitis B by 2030, KDCA's leadership in pursuing the goal and close partnership between KDCA and KASL would be essential. Partnering with WHO, Coalition for Global Hepatitis Elimination (CGHE) and other international public and private partners will facilitate the efforts to eliminate hepatitis C in Korea.

Funding: None.

Conflict of Interest: The author has no conflicts of interest to disclose.

References

1. World Health Organization. Global Health Sector Strategy on Viral Hepatitis 2016-2021. *http://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf;jsessionid=9A17B3F9C66A7A152BD4D5368FBB2524?sequence=1* (accessed May 16, 2021).
2. Pedrana A, Howell J, Scott N, *et al*. Global hepatitis C elimination: an investment framework. Lancet Gastroenterol Hepatol. 2020; 5:927-939.
3. Dore GJ, Bajis S. Hepatitis C virus elimination: laying the foundation for achieving 2030 targets. Nat Rev Gastroenterol Hepatol. 2021; 18:91-92.
4. Waked I, Esmat G, Elsharkawy A, *et al*. Screening and treatment program to eliminate hepatitis C in Egypt. N Engl J Med. 2020; 382:1166-1174.
5. Radley A, de Bruin M, Inglis SK, Donnan PT, Hapca A, Barclay ST, Fraser A, Dillon JF. Clinical effectiveness of pharmacist-led versus conventionally delivered antiviral treatment for hepatitis C virus in patients receiving opioid substitution therapy: a pragmatic, cluster-randomised trial. Lancet Gasteroenterol Hepatol. 2020; 5:809-818.
6. Ministry of Health and Welfare of the Republic of Korea. Press Release "Launching a pilot study on early detection of hepatitis C cases" *http://www.mohw.go.kr/react/al/sal0301vw.jsp?PAR_MENU_ID=04&MENU_ID=0403&page=1&CONT_SEQ=359673* (accessed May 16, 2021). (in Korean)
7. Jeong SH, Jang ES, Choi HY, Kim KA, Chung W, Ki M. Current status of hepatitis C virus infection and countermeasures in South Korea. Epidemiol Health. 2017; 39: e2017017.
8. Chung YS, Choi JY, Han MG, Park KR, Park SJ, Lee H, Jee Y, Kang C. A large healthcare-associated outbreak of hepatitis C virus genotype 1a in a clinic in Korea. J Clin Virol. 2018; 106:53-57.

9. Shahid I, Alzahrani AR, Al-Ghamdi SS, Alanazi IM, Rehman S, Hassan S. Hepatitis C diagnosis: simplified solutions, predictive barriers, and future promises. Diagnostics (Basel). 2021; 11:1253.
10. Tatara E, Gutfraind A, Collier NT, Echevarria D, Cotler SJ, Major M, Ozik J, Dahari H, Boodram B. Re-treatment with direct-acting antivirals policy is needed to eliminate Hepatitis C among persons who inject drugs. bioRxiv. 2021. doi: https://doi.org/10.1101/653196.
11. 2020 National Hepatitis C Control Guideline by KDCA. *http://www.kdca.go.kr/npt/biz/npp/portal/nppPblctDtaView.do?pblctDtaSeAt=8&pblctDtaSn=2081* (accessed May 16, 2021). (in Korean)
12. Kim Y. Current status and countermeasures for hepatitis B and D in Korea. *https://www.kasl.org/pdf/2016_fall/%ea%b9%80%ec%9c%a4%ec%a4%802.pdf* (assessed May 16, 2021). (in Korean)
13. Korean Association for the Study of the Liver. Press release "Elimination of hepatitis C by 2030". *https://www.kasl.org/bbs/index.html?code=report&category=&gubun=&page=1&number=4207&mode=view&keyfield=&key=* (assessed May 16, 2021).
14. Infectious Disease Portal. Korea Disease Control Agency. *http://www.kdca.go.kr/npt/biz/npp/ist/bass/bassDissStatsMain.do* (assessed May 16, 2021).

Received May 19, 2021; Revised October 2, 2021; Accepted October 11, 2021.

Released online in J-STAGE as advance publication October 16, 2021.

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Global Health & Medicine. 2021; 3(5):293-300.
DOI: 10.35772/ghm.2021.01064

REVIEW

Taiwan accelerates its efforts to eliminate hepatitis C

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Abstract: The estimated prevalence of anti-HCV was 3.3% (1.8-5.5%) in the general population in Taiwan with several regional disparities. The reactive anti-HCV in different regions may vary between 0% and 65%. The National Hepatitis C Program (NHCP) office estimated approximately 623,323 persons reactive with anti-HCV based on several extensive region- and cohort-wide studies. Taiwan has accelerated its efforts to eliminate hepatitis C since 2018 by committing to achieve World Health Organization (WHO)'s 2030 goal of treating 80% of eligible patients by 2025. Many aggressive measures by the Ministry of Health and Welfare (MOHW) have been ongoing including several key success factors such as political commitment by the MOHW to finance this national program and improve National Health Insurance (NHI) reimbursement restrictions for treatment. Meanwhile, the Taiwan Centers for Disease Control (CDC) instituted harm reduction programs and the Health Promotion Administration (HPA) started to improve awareness and perform national screening programs. The NHCP office instituted monitoring, evaluation, micro-elimination and funding to linkage to care programs. In addition to sustainable financing, it is imperative to scale-up screening coverage through a precision public health approach to fill the gap of under-diagnosis. Hopefully, we can achieve early elimination by announcing the treatment target of 250000 CHC patients by 2025.

***Keywords*:** HCV elimination, Taiwan's effort, National Hepatitis C Program

Introduction

Hepatitis C virus (HCV) infection is a major cause of liver cirrhosis and hepatocellular carcinoma (HCC) affecting approximately 70-80 million chronic hepatitis C (CHC) patients globally and 0.7 million die of its complication annually (*1*). HCV infection remains a public health issue with an estimated prevalence of 3.3% (1.8-5.5%) in the general population and there are several regional disparities in terms of prevalence of hepatitis C in Taiwan. Therefore, the percentage of anti-HCV seropositivity in different regions may vary between 0% and 65%. Moreover, great disparities of anti-HCV seropositivity population between different cohorts were also noted. Compared to younger cohorts, older cohorts displayed higher prevalence in anti-HCV seropositivity (*2,3*).

Major transmission of HCV is through an iatrogenic route in the early years. The risk of iatrogenic exposure has diminished nowadays, and the HCV endemic has turned into sporadic phase. Nationwide, a large-scale and population-representative anti-HCV screening program is missing at present, and the reactive anti-HCV population in Taiwan extrapolated by division of epidemiology research, National Hepatitis C Program (NHCP) office is approximately 423,283 to 745,109 persons (median: 623,323 persons) based on several extensive region- and cohort-wide anti-HCV seropositivity studies in 2016. Furthermore, according to previous community screening results, patients with CHC and seropositive for HCV RNA accounted for about 65% of the reactive anti-HCV population. In this case, there are an estimated 275,134 to 484,321 patients with CHC and viremia (median: 405,160 patients) in Taiwan (*3-6*). The median prevalence of 405,160 is thereby adopted for convenience as the estimate of patients with CHC that requires proper treatment in Taiwan.

World Health Organization (WHO) launched an ultimate goal at the 69th World Health Assembly (WHA) in May 2016 to eliminate viral hepatitis as a public health threat by 2030. To achieve such a goal, the execution plan can be divided into three strategies: reduction of new chronic hepatitis B/hepatitis C infection by 90%, reduction of dying from hepatitis B/hepatitis C by 65% and proper treatment for 80% of patients with chronic hepatitis B/hepatitis C (*7*). In addition, to effectively stop viral hepatitis transmission

and allow patients with viral hepatitis receiving safe, affordable and effective care and treatment, WHO also recommends the international society implementing universal health coverage, providing a continuum of hepatitis services and introducing a public health approach. To respond to the ultimate goal set by WHO, Ministry of Health and Welfare (MOHW), Taiwan convenes expert meetings and establishes policy guidelines to meet the national goal of treating 80% of eligible patients by 2025 with strong government support (*5,6,8,9*). Excluding 80,000 CHC patients already successfully treated with peginterferon plus ribavirin (PR) before the direct acting antiviral agents (DAA) era, it is doing this by treating 250,000 new CHC patients between 2017 and 2025 with DAA.

Treatment situations in Taiwan before 2017

Antiviral therapies for HCV infection have been reimbursed by the Taiwan National Health Insurance (NHI) since 2003 and provided around 20-30% treatment coverage with 95,000 treated patients up to 2017 (*10*). From 2003 to 2016, the interferon (IFN)-based with or without ribavirin therapy was the standard treatment for HCV infection, which achieved an overall sustained virologic response (SVR) rate of 76-84% in Taiwan (*11,12*). Although the SVR rates of IFN-based therapies in Asia were satisfactorily higher than those in the western countries (54%-63%) (*11,12*), the ineligibility and treatment-related adverse events (AEs) often raise safety concerns, especially in patients with prior treatment failure, higher age, low platelet count, certain comorbidities, or hepatic decompensation (*13*). These concerns may have partially contributed to the enormous gap observed between clinical efficacy and community effectiveness in HCV treatment (*3*), despite the high SVR rate and wide NHI coverage in Taiwan.

With introduction of novel DAA agents, which are IFN-free, all-oral, with higher efficacy, excellent safety profile, and shorter treatment duration, a paradigm shift of HCV treatment landscape is emerging. In Taiwan, DAAs have been reimbursed by NHI since 2017 and are currently available for HCV viremic patients regardless of liver fibrosis status and genotype.

Political commitment

Because of the heavy disease burden and even though Taiwan is not a member of WHO, Taiwan still took serious actions to follow the WHO guidelines on control of viral hepatitis (*14*). When the WHA adopted the global health sector strategy on viral hepatitis in 2016, it immediately caught the attention of the Taiwanese people and government, and efforts towards elimination of CHC were seriously considered. The NHCP office had been set up soon in December 2016 under the guidance of MOHW. The organization chart is shown in Figure 1. The first co-conveners were minister of health and welfare (Dr. Shih-Chung Chen) and academician Ding-Shinn Chen. There are six task force groups in the program including clinical medicine, organization coordination, dissemination, epidemiology, economic evaluation and foresight research, and industry cooperation. After 2 years, efforts from experts, public health officers, legislators, and government leaders have culminated in a consensus of reaching the WHO goals by 2025, 5 years earlier than the 2030 deadline set by WHO.

Finance a national program

Based on models similar to those used by Razavi's study (*15*), Chen *et al.* conclude that Taiwan will

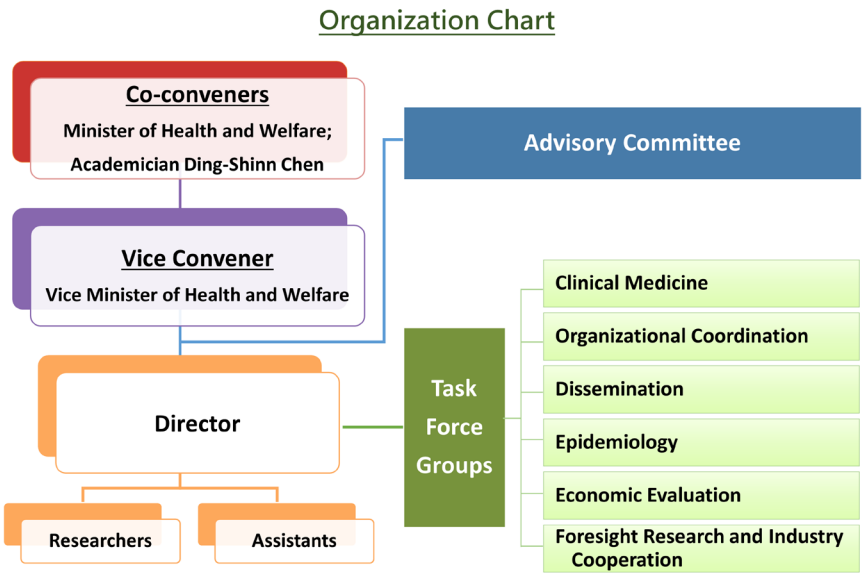


Figure 1. National Hepatitis C Program (NHCP) Office, Ministry of Health and Welfare since December 2016.

achieve WHO targets by increasing patients treated annually to 30,000 by 2025 (*16*). Political commitment by the MOHW is to finance this national program and remove NHI reimbursement restrictions for treatment. A nationwide program that reimbursed the DAAs for CHC patients with advanced hepatic fibrosis was launched on January 24, 2017 under the NHI, a mandatory single-payer scheme that provides universal high-quality health care for more than 99% of Taiwan residents (*17*). This program recruited CHC patients who received DAA therapy under the NHI's reimbursement criteria since January 24, 2017 until now. A special budget supporting the DAAs treatment was arranged for nearly 120,000 patients in 2017-2020, corresponding to 30% treatment coverage with two billion New Taiwan Dollar (NTD) in 2017, 4.8 billion NTD in 2018, 5.6 billion NTD in 2019, and 8.4 billion in 2020. Including 80,000 successfully treated patients with PR, the overall coverage rate of treatment was 50% by 2020. Briefly, only patients with advanced fibrosis, F3 and F4 were covered due to the limited budget during 2017-2018. At the beginning, prior PR failure experience was required for reimbursement, and this was no longer needed after May 15, 2017. As the NHI gradually expanded different DAA regimens, the HCV genotypes that were covered by reimbursed DAAs increased in number. Two DAAs targeting HCV genotypes 1a and 1b, daclatasvir/asunaprevir and ombitasvir/paritaprevir/ritonavir±ribavirin, were reimbursed first. Elbasvir/grazoprevir±ribavirin for treating genotypes 1a, 1b and 4 were reimbursed as of August 1, 2017. Ledipasvir/sofosbuvir±ribavirin for genotypes 1a, 1b, 4, 5 and 6 and sofosvuvir±ribavirin for genotype 2 were reimbursed as of January 1, 2018. Two pan-genotypic DAAs glecaprevir/pibrentasvir, and sofosvuvir/velpatasvir, that covered genotypes 1-6, was reimbursed by the NHI beginning August 1, 2018 and June 1, 2019, respectively. Furthermore, treatment restrictions based on fibrosis stage were removed in 2019. The number of patients treated annually has vastly increased, rising from 9,500 patients in 2017 to 46,000 in 2019. In addition, a registry platform including all patients who applied for the NHI-reimbursed DAAs was established. The registry included patients' demographic characteristics, DAAs regimens, baseline information about HCV RNA viral load, genotype, liver fibrosis status and RNA viral load at the end of DAA therapy and 12 weeks after therapy.

Taiwan Hepatitis C Policy Guideline 2018-2025

For effective policy communication and coordination, MOHW announced the "Taiwan Hepatitis C Policy Guideline 2018-2025" (*6*) and identified three policy directions to achieve the goal for 2025, which includes: *i*) Therapy spear-heading prevention: to prevent new infection by reducing the number of infectious, namely CHC patients, *via* affordable and available treatment; *ii*) Screening support therapy: to launch screening activity to identify around 120,000 CHC patients since about half of the CHC patients are not diagnosed; *iii*) Prevention securing outcomes: to block transmission routes to prevent new-infections and re-infections, as well as to block other liver-disease risk factors such as alcohol.

There are several main challenges to move forward to these three policy directions, such as sustainable financing, effective and efficient screening, continuum of care, and improving accessibility. Therefore, the policy guidelines have highlighted three core strategies, including:

i) Precision public health: to launch public health interventions such as smart screening in terms of effectiveness and efficiency. The policy guidelines aim for different prevention and control strategies for four target populations (including highly hepatitis C prevalent area, mountains and offshore islands, special population and general areas) based on the concept of precision public health (Figure 2):

(a) Highly hepatitis C prevalent area: Define highly

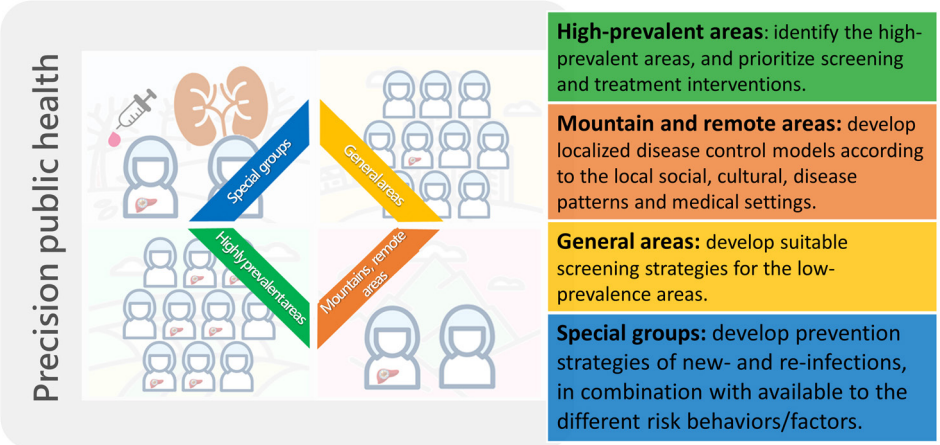


Figure 2. Precision public health.

hepatitis C prevalent area and prioritize intervention (active screening and treatment) for target population.
(b) Mountains and offshore islands: Prioritize the establishment of accessible hepatitis C prevention and control models depending on local customs (*e.g.* drinking habit, loss of young and middle-aged labor force, *etc.*) to facilitate local treatment services.
(c) Special population: Refers to high-risk HCV infection population, including patients undergoing dialysis, community/incarceration drug addicts (through IV injections) and subjects conducting unprotected sexual intercourse (male-to-male or with sex workers). The key hepatitis C prevention and control focuses on the development of strategies preventing HCV infection and re-infection, and measures in combination with available routine inspection/intervention.
(d) General areas: For lower hepatitis C prevalent areas (general areas), a suitable screening program should be built based on the concept of cost-effectiveness. For example, establishing an accessible and cost-effective screening program out of available health examination programs (with alternative indicators).

ii) Continuum of care: to link prevention, screening, diagnosis, treatment, and follow-up together *via* the support of case management system and information platform. Although this is a patient-centered policy guideline, because most patients with CHC lack disease awareness or fail to seek medical assistance actively, how to screen these patients and connect them to subsequent treatments to provide a patient-centered continuum of care is the key to success. In addition, except connection of screening, diagnosis and treatment, it is also required to establish a three-phase/five-tier-packaged healthcare program with health promotion and infection prevention as leading strategies and regular disease follow-up and integrative management as continuous measures. In addition to providing first-line, patient-centered continuum of care, an interdisciplinary hepatitis C prevention task force is also required in order to coordinate all services and businesses between central and local authorities, private institutions and non-governmental organizations (NGOs) (Figure 3) to promote a rolling plan and achieve a common goal on the basis of interdisciplinary teamwork.

iii) Localized care delivery: to increase access and improve equality, especially in remote areas with scarce medical resources. According to the hepatitis C epidemiology studies in Taiwan, highly hepatitis C prevalent areas are mainly located in regions with poor medical resources or an economically disadvantaged population, or in remote areas with poor public transport, suggesting that restricted access to medical resources becomes the primary hinderance of successful treatment for hepatitis C in these areas. To provide effective treatment for patients with CHC, a localized care delivery model (local screening, diagnosis, treatment and follow-ups) is required (Figure 4) in order to facilitate localized care delivery, increase accessibility to healthcare services, and promote right of equality to healthcare services.

Micro-elimination of special groups

Higher prevalence of HCV infection has been reported among certain populations (*18-21*) in Taiwan. The anti-HCV prevalence of 20-40% was reported in patients with end-stage renal disease (ESRD) under hemodialysis due to increased nosocomial infection risk (*18,19*). The majority of the people who inject drugs (PWID) were found to be seropositive for anti-HCV at a rate of 91.3%. Moreover, 57.1% of these patients were coinfected with HIV (*20*). In HIV-negative and HIV-positive men who have sex with men (MSM), the overall HCV seroprevalence rates were 0.4% and 5.5%, respectively (*21*). A national survey of HIV-positive patients found that the overall HCV seroprevalence among HIV-positive patients was decreasing, but remained high at 94.0% among PWID. By contrast, anti-HCV seropositivity was relatively low among HIV-positive homosexual men compared to HIV-positive

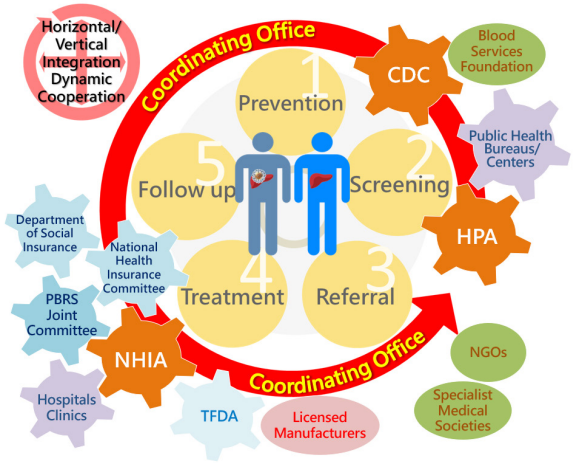


Figure 3. HCV elimination coordinating office.

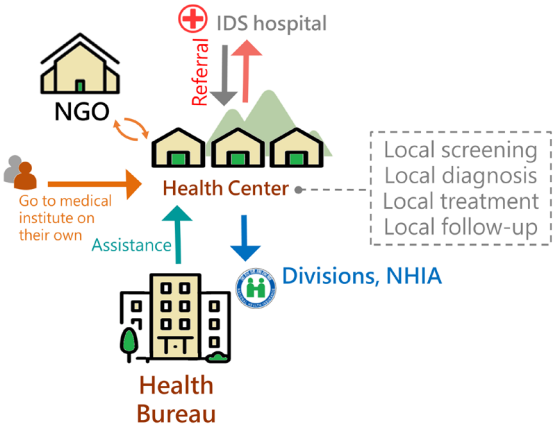


Figure 4. Localized care delivery.

heterosexuals, at 3.5% and 10.9%, respectively (*22*). In the era of DAA treatment, it can improve the adherence of patients, minimize the side effects and enhance the SVR rate, even in difficult-to-cure populations (*23*).

Micro-elimination approach, which focuses on treating smaller, targeted high-risk subpopulations, has been proposed as an effective means to tackle HCV (*24*). According to the Taiwan hepatitis C policy guidelines, we coordinate the prevention, health literacy, screening, diagnosis, treatment, follow-up, and patient management services, both vertically and horizontally. Also, we encourage the gastroenterologist to cooperate with nephrologist, psychiatrist and infectious disease physician to perform micro elimination in these high risk patients. The NHI agrees to expand prescription privilege to infectious disease physicians to treat dual HIV+HCV infected patients with DAA (*25*). Meanwhile, a new inter-disciplinary collaborative care model implemented by collaborating teams of dialysis practitioners and gastroenterologists working under auspices of Changhua Public Health Bureau have screened 3657 patients from 31 dialysis facilities and treated 173 HCV infected patients with a 96% SVR rate (*26*) in Changhua county. In addition, a large proportion of the prison population in Taiwan is composed of criminalized persons with injected substance use. In 2019, 27,893 incarcerated persons were convicted of substance use-related crimes, accounting for 49.5% of the total prison population. Injected substance use is prohibited in Taiwan's prison system. Those incarcerated patients had HCV infection before they entered prison. Yang *et al.* have performed a micro-elimination program for incarcerated persons in Taiwan. They invited 1402 incarcerated persons to perform an anti-HCV screening test, and 824 (59%) accepted. The prevalence of anti-HCV seropositivity was 33.5% (276/824) with a viremic rate of 69.2% (191/276). In total, 165 patients received glecaprevir/pibretasvir therapy and achieved a 100% SVR 12 rate (*27*).

Preventive measures for specific high-risk populations

For those high risk populations for HCV infection, we set several preventive strategies and measures to block the possible transmission routes.

i) For high-risk HCV infection populations [*e.g.* patients with HIV infection, patients undergoing dialysis, drug addicts (through IV injections), drug addicts residing in incarcerated or correctional facilities (through IV injections), unprotected sexual intercourse (male-to-male), unprotected sexual intercourse with sex workers], it is required to adopt core strategies along with available routine tests and interventional measures against new-and re-infections.

ii) Establish better knowledge, awareness and literacy about prevention of HCV transmission among high-risk populations, healthcare personnel, nursing staff, staff of community healthcare service departments, and tattoo or piercing artists.

iii) Audit the competence of long-term care or nursing care facilities in implementing infection control procedures.

iv) Audit the competence of tattoo artists or piercing artists in implementing infection control procedures.

v) Audit the competence of folk therapists (responsible for scraping, bleeding, cupping and acupuncture therapy) in implementing infection control procedures.

vi) Execute testing, management and therapeutic protocols for known HCV infected populations residing in incarcerated or correctional facilities.

Remove treatment restrictions

As previous mentioned that highly hepatitis C prevalent areas are mainly located in regions with poor medical resources or economically disadvantaged populations, or in remote areas with poor public transport, suggesting restricted access to medical resources. To improve accessible medical care for CHC patients in remote areas, the NHI agrees to set up a clinic in health centers of remote areas, which is named an outreach clinic. The physician from the medical center continues to support the health center to overcome the handicap of medical care accessibility in remote villages. The NHCP office continues to resolve several barriers in HCV elimination such as an adequate yearly budget, with no limitations on hepatic fibrosis status, no limitation for patients with persistent ant-HCV seropositivity for > 6 months, approval of timely pangenotypic regiments, reimbursement for DAAs in GT1 patients aged > 12 years and precision screening strategies. Extended localized care delivery to general practitioner (GP with specialist training in gastroenterological field) by resolving HCV RNA and genotyping prescription issues and reducing GP income tax by adjusting the cost of tax.

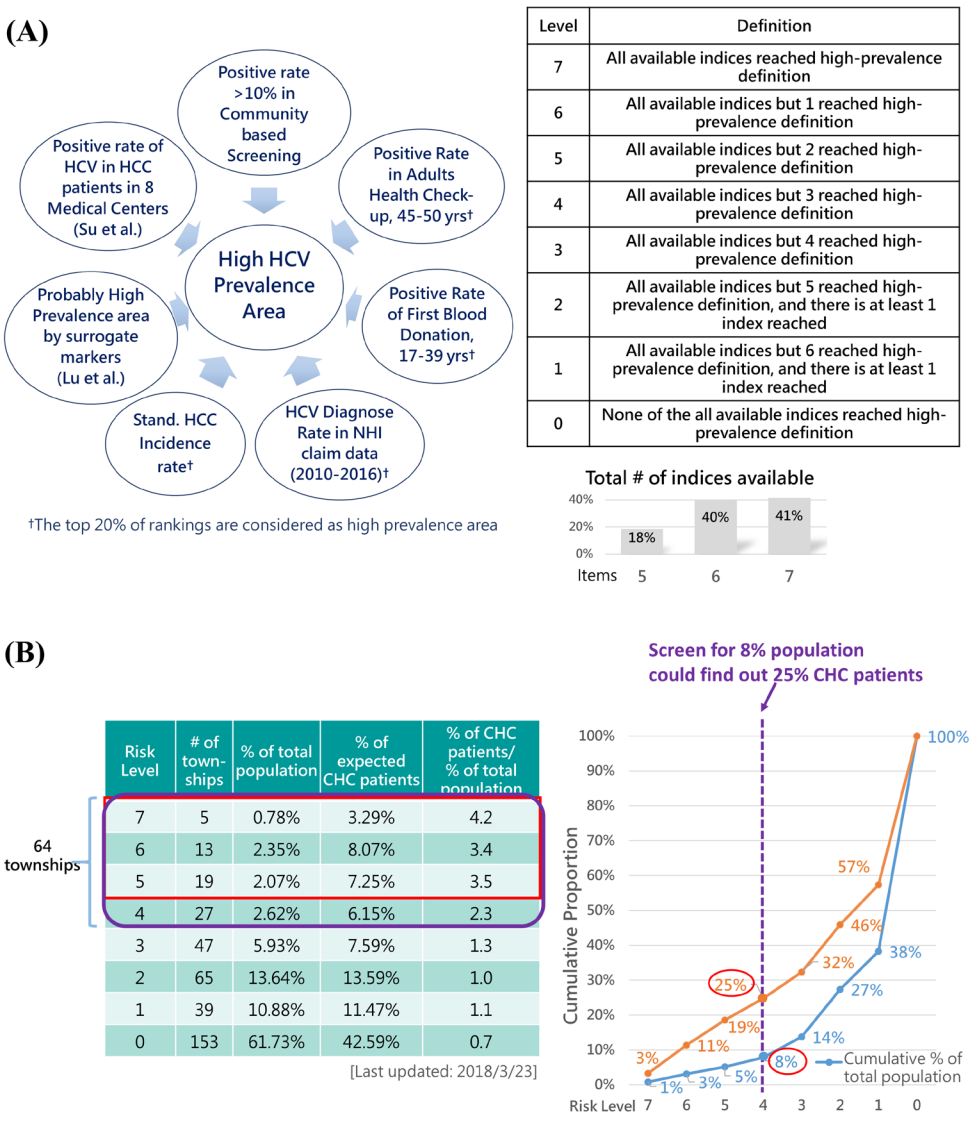
Implement awareness and national screening program

A nationwide, large-scale and population-representative anti-HCV screening program has been previously missing. In light of the experience from other high-income countries, such as United States, Japan, Australia, Germany, and Spain, the number of treated patients is decreasing as the pool of diagnosed and under-care patients is also decreasing (*7*). Meanwhile, there are about 120,000 CHC patients awaiting to be diagnosed in Taiwan, and screening is becoming challenging and critical on the road toward elimination. But, HCV prevalence has great geographic variation in Taiwan, as the cost-effectiveness of the screening program would also greatly vary across different populations. The screening cost per CHC patient

identified, which includes anti-HCV and HCV RNA testing, would increase rapidly while HCV prevalence is lowered. Therefore, it is vital that we develop tailored screening tools and delivery programs according to different population characteristics.

The first core strategy is precision public health. According to different risk areas, we set different public health interventions such as: *i*) In those high-prevalent areas: identify the high-prevalent areas and give them high priority for coordinated intervention; *ii*) In those mountain and remote areas: develop specific disease control models according to local social, cultural disease patterns and medical settings; *iii*) In those general areas: develop screening strategies specifically fitting low-prevalence areas; *iv*) In those special groups: develop prevention strategies for new- and re-infections according to different risk behaviors/factors.

How to identify the higher HCV prevalence areas, we use previous seven large epidemiologic studies and database form Taiwan as an index including HCV diagnosis rate in national health insurance administration claims data from 2010 to 2016 and stratify them into 7 levels. If the anti-HCV positive rate fulfilled all the available indices, it reached high prevalence definition level 7. If the anti-HCV positive rate fulfills all available indices but 1, it reaches high prevalence definition level 6. Overall, 40% and 41% fulfilled level 6 and 7 respectively (Figure 5A). We can estimate the percentage of hepatitis C patients in every area according to the risk level. Figure 5B shows that choosing risk level 4 or above can be considered for universal screening for HCV because of screening 8% of the population could find 25% of CHC patients. It could be very cost effective. The universal screening program for HCV has been set up by health promotion administration, MOHW on September 28, 2020 where adults older than 45 years can receive both the anti-HCV and HBsAg screening test once in their lifetime.



Level	Definition
7	All available indices reached high-prevalence definition
6	All available indices but 1 reached high-prevalence definition
5	All available indices but 2 reached high-prevalence definition
4	All available indices but 3 reached high-prevalence definition
3	All available indices but 4 reached high-prevalence definition
2	All available indices but 5 reached high-prevalence definition, and there is at least 1 index reached
1	All available indices but 6 reached high-prevalence definition, and there is at least 1 index reached
0	None of the all available indices reached high-prevalence definition

Risk Level	# of town-ships	% of total population	% of expected CHC patients	% of CHC patients/ % of total population
7	5	0.78%	3.29%	4.2
6	13	2.35%	8.07%	3.4
5	19	2.07%	7.25%	3.5
4	27	2.62%	6.15%	2.3
3	47	5.93%	7.59%	1.3
2	65	13.64%	13.59%	1.0
1	39	10.88%	11.47%	1.1
0	153	61.73%	42.59%	0.7

Figure 5. (A) Seven indices of higher HCV prevalence; (B) Estimated percentage of chronic hepatitis C patients by risk levels.

Conclusion and perspective

Taiwan has accelerated its efforts to eliminate hepatitis C since 2018 by committing to achieve WHO's 2030 goal of treating 80% of eligible patients by 2025. Obviously, Taiwan is on track to eliminate HCV by 2025 because of aggressive measures by the MOHW. These include several key success factors including political commitment by the MOHW to finance this national program and remove NHI reimbursement restrictions for treatment. In addition, the Taiwan Centers for Disease control instituted harm reduction programs and the NHCP office instituted monitoring, evaluation and micro-elimination. We are continuing to expand other measures noted as key success factors, including awareness and active screening programs, and funding linkage to care programs. In addition to sustainable financing, it is imperative to scale-up the screening coverage through a precision public health approach to fill the gap of under-diagnosis. Hopefully, we can bring the battle against HCV to the end and achieve early elimination by announcing the treatment target of 250000 CHC patients by 2025.

Funding: This work was supported in part from a grant of Ministry of Science and Technology, Taiwan (MOST109-2314-B-182A-063).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. World Health Organization. Global report on access to hepatitis C treatment: focus on overcoming barriers. Geneva. 2016. *https://www.who.int/publications/i/item/global-report-on-access-to-hepatitis-c-treatment---focus-on-overcoming-barriers* (accessed on June 1, 2021).
2. Bennett H, Waser N, Johnston K, Kao JH, Lim YS, Duan ZP, Lee YJ, Wei L, Chen CJ, Sievert W, Yuan Y, Li H. A review of the burden of hepatitis C infection in China, Japan, South Korea and Taiwan. Hepatol Int 2015; 9:378-390.
3. Yu ML, Yeh ML, Tsai PC, *et al.* Huge gap between clinical efficacy and community effectiveness in the treatment of chronic hepatitis C: a nationwide survey in Taiwan. Medicine (Baltimore). 2015; 94:e690.
4. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2017; 2:161-176.
5. Wu GH, Pwu RF, Chen SC, Chen DS. Taiwan is on track of accelerating hepatitis C elimination by 2025. Liver Int. 2020; 40:1506-1507.
6. Taiwan hepatitis C policy guidelines 2018-2025. Taipei City: Ministry of Health and Welfare, Executive Yuan Taiwan, 2019.
7. World Health Organization. Global health sectors strategy on viral hepatitis 2016-2021: towards ending viral hepatitis. Geneva 2016. *https://www.who.int/publications/i/item/WHO-HIV-2016.06* (accessed on June 1, 2021).
8. Wu GH, Pwu RF, Chen SC. Achieving hepatitis C elimination in Taiwan-Overcoming barriers by setting feasible strategies. J Formos Med Assoc. 2018; 117:1044-1045.
9. Chen DS. Taiwan commits to eliminating hepatitis C in 2025. Lancet Infect Dis. 2019; 19:466-467.
10. Wu GH, Pwu RF, Chen SC. Achieving hepatitis C elimination in Taiwan-Overcoming barriers by setting feasible strategies. J Formos Med Assoc. 2018; 117:1044-1045.
11. Kao JH. Hepatitis C virus infection in Taiwan: past, present and future. J Formos Med Assoc. 2016; 115:65-66.
12. Yu ML, Chuang WL. Treatment of chronic hepatitis C in Asia: when east meets west. J Gastroenterol Hepatol. 2009; 24:336-345.
13. Liu CH, Yu ML, Peng CY, Hsieh TY, Huang YH, Su WW, Cheng PN, Lin CL, Lo CC, Chen CY, Chen JJ, Ma Q, Brooks-Rooney C, Kao JH. Real-world anti-viral treatment decisions among chronic hepatitis C patients in Taiwan: the INITIATE study. J Formos Med Assoc. 2019; 118:1014-1023.
14. Chen DS. Fighting against viral hepatitis: lessons from Taiwan. Hepatology. 2011; 54:381-392.
15. Razavi H, Sanchez Gonzalez Y, Yuen C, Cornberg M. Global timing of hepatitis C virus elimination in high-income countries. Liver Int. 2020; 40:522-529.
16. Chen DS, Hamoudi W, Mustapha B, *et al.* Strategies to manage hepatitis C virus infection disease burden -Volume 4. J Viral Hepat. 2017; 24 supple 2: 44-63.
17. Wu TY, Majeed A, Kuo KN. An overview of the healthcare system in Taiwan. Lond J Prim Care (Abingdon). 2010; 3:115-119.
18. Chen DS, Kuo GC, Sung JL, Lai MY, Sheu JC, Chen PJ, Yang PM, Hsu HM, Chang MH, Chen CJ, Hahn LC, Choo QL, Wang TH, Houghton M. Hepatitis C virus infection in an area hyperendemic for hepatitis B and chronic liver disease: the Taiwan experience. J Infect Dis. 1990; 162:817-822.
19. Liu CH, Kao JH. Treatment of hepatitis C virus infection in patients with end-stage renal disease. J Gastroenterol Hepatol. 2011; 26:228-239.
20. Hsieh MH, Tsai JJ, Hsieh MY, Huang CF, Yeh ML, Yang JF, Chang K, Lin WR, Lin CY, Chen TC, Huang JF, Dai CY, Yu ML, Chuang WL. Hepatitis C virus infection among injection drug users with and without human immunodeficiency virus co-infection. PloS One. 2014; 9:e94791.
21. Tseng YT, Sun HY, Chang SY, Wu CH, Liu WC, Wu PY, Lu CL, Hsieh CY, Hung CC. Seroprevalence of hepatitis virus infection in men who have sex with men aged 18-40 years in Taiwan. J Formos Med Assoc. 2012; 111:431-438.
22. Li CW, Yang CJ, Sun HY, Tsai MS, Lin SP, Lin TY, Cheng CY, Lee YC, Huang YS, Liu CE, Lee YT, Tang HJ, Wang NC. Changing seroprevalence of hepatitis C virus infection among HIV-positive patients in Taiwan. PloS One. 2018; 13:e0194149.
23. Llaneras J, Riveiro-Barciela M, Lens S, *et al.* Effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in patients with chronic hepatitis C previously treated with DAAs. J Hepatol. 2019; 71:666-672.
24. Lazarus JV, Safreed-Harmon K, Thursz MR, Dillon JF, EI-Sayed MH, Elsharkawy AM, Hatzakis A, Jadoul M, Prestileo T, Razavi H, Rockstroh JK, Wiktor SZ, Colombo

M. The micro-elimination approach to eliminating hepatitis C: strategies and operational considerations. Semin Liver Dis. 2018; 38:181-192.
25. Liou BH, Sun HY, Yang CJ, *et al.* Real-world experience with coformulated ledipasvir and sofosbuvir for HIV-positive patients with HCV genotype 2 infection: a multicenter retrospective study. Infect Dis Ther. 2021; 10:827-838.
26. Hu TH, Su WW, Yang CC, *et al.* Elimination of hepatitis C virus in a dialysis population: a collaborative care model in Taiwan. Am J Kidney Dis. 2021; S0272-6386(21)00575-8.
27. Yang TH, Fang YJ, Hsu SJ, Lee JY, Chiu MC, Yu JJ, Kuo CC, Chen CH. Micro-elimination of chronic hepatitis C by universal screening plus direct acting antivirals for incarcerated persons in Taiwan. Open Forum Infect Dis. 2020; 7:ofaa301.

Received June 1, 2021; Revised June 10, 2021; Accepted June 30, 2021.

Released online in J-STAGE as advance publication July 5, 2021.

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Global Health & Medicine. 2021; 3(5):301-307. REVIEW
DOI: 10.35772/ghm.2021.01063

Nationwide awareness-raising program for viral hepatitis in Japan: the "*Shitte kan-en*" project

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Abstract: Chronic viral hepatitis is one of the most widespread infectious diseases in Japan. In the 2009 financial year, the Japanese government enacted the Basic Act on Hepatitis Measures, followed by the Basic Guidelines for Promotion of Control Measures for Hepatitis 2 years later. The guidelines emphasize the importance of provision and dissemination of accurate information on viral hepatitis and public awareness-raising. A subsidy program on hepatitis was therefore launched by the Ministry of Health, Labour and Welfare in 2011, called "*Shitte kan-en*" (in English, "Let's learn about hepatitis"), and involves popular Japanese actors and singers. The project started awareness-raising activities in the 2013 financial year, as the "National Campaign Project for Hepatitis Measures". It aims to communicate concise and accurate information about hepatitis and the necessity of testing for viral hepatitis. It also encourages citizens to take a positive approach to early detection and treatment. To date, the main initiatives of the project are as follows: *i*) celebrity visits to prefectural governors to draw attention to the condition, *ii*) educational events in cooperation with hepatologists in regional core hospitals, *iii*) support for partner companies' hepatitis awareness activities in workplaces, and *iv*) support for the activities of program promoters. Targeting approaches to particular groups is likely to be key to success for general awareness-raising. Evaluation of the effectiveness of this multifaceted approach is warranted to reduce the undiagnosed population and improve the link between testing and care for viral hepatitis in Japan.

***Keywords*:** Basic Act on Hepatitis Measures, Basic Guidelines on Hepatitis Measures, hepatitis, awareness-raising

Introduction

In Japan, viral hepatitis is one of the most widespread infectious diseases. In 2015, hepatitis B virus (HBV) affected an estimated 1.1-1.2 million and hepatitis C virus (HCV) 0.9-1.3 million (*1*). If untreated, viral hepatitis can progress to more severe diseases such as liver cirrhosis and liver cancer. According to Vital Statistics of Japan, in 2019, hepatocellular carcinoma was the fifth most frequent cause of cancer death in men and the seventh in women (*2*). Over 59.7% of people with liver cirrhosis in Japan have had HBV or HCV infections (*3*). Approximately 25,000 deaths each year in Japan are caused by liver cancer, and 67.5% of these are attributed to persistent HBV or HCV infection (*2,4*). Therefore, from the public health and hygiene perspective, implementing measures against hepatitis B and C is a critical matter in Japan. Early detection and treatment of patients with viral hepatitis is important. It is recommended that everyone undergoes hepatitis virus testing at least once in a lifetime and those with positive results should be treated by hepatologists.

To address these issues, the Japanese government enacted the Basic Act on Hepatitis Measures in January 2010, which reinforced the promotion of comprehensive measures against hepatitis (*5*). On the basis of this law, the government also published the Basic Guidelines for Promotion of Control Measures for Hepatitis in June 2011. The guidelines, revised in 2016 (*6*), explain the importance of disseminating accurate information to help all citizens understand hepatitis, and particularly how to prevent and treat it. Comprehensive measures against hepatitis including awareness-raising have therefore been implemented in line with these guidelines.

This review examines the purpose, targets and activities of the nationwide awareness-raising program for viral hepatitis in Japan, or the "*Shitte kan-en*" project (in English, "Let's learn about hepatitis"), and

involves popular Japanese actors and singers. The program name invokes the ideal attitude of people being willing to learn about hepatitis, including the necessity and importance of testing for viral hepatitis. The program is linked to the national campaign project for hepatitis measures and is positioned as one way to disseminate accurate information about the hepatitis virus and hepatitis as a liver disease. It is designed to improve attitudes towards hepatitis testing.

Basic Act on Hepatitis Measures and the Basic Guidelines on Hepatitis Measures

The purpose of this Act is to provide the basic principles for hepatitis measures, and clarify the responsibilities of the national government, local governments, medical insurers, citizens, physicians, and others. It also provides for the formulation of guidelines for the promotion of hepatitis and basic measures (*5*).

The basic principles for hepatitis measures are as follows: *i*) to promote specialized, interdisciplinary or comprehensive research on hepatitis, and to develop, disseminate, and exploit technological improvements for prevention, diagnosis, and treatment of hepatitis, and other research results; *ii*) to make hepatitis examinations equally accessible to all, regardless of their location ; *iii*) to make appropriate medical care for hepatitis equally accessible to any carrier of the hepatitis virus or hepatitis patient regardless of where they live; and *iv*) in implementing these measures, to respect the human rights of hepatitis patients and others, and ensure that no groups are discriminated against.

In formulating the Basic Guidelines on Hepatitis Measures, the Minister of Health, Labour and Welfare is required to consult the heads of the relevant administrative organs and the Council for Promotion of Hepatitis Measures. The Minister also has to review the Basic Guidelines on Hepatitis Measures at least once every 5 years, considering changes in hepatitis-related medical care and evaluating the effects of hepatitis measures. This review may lead to revisions to the guidelines (Figure 1).

The Ministry of Health, Labour and Welfare (MHLW) has been promoting comprehensive control measures for hepatitis since the 2008 financial year. These consist of five key strategies: *i*) environmental improvement to enhance hepatitis treatment; *ii*) facilitation of hepatitis virus testing; *iii*) preparation of a treatment/consultation system for hepatitis; *iv*) preparation and dissemination of accurate information to the public; and *v*) promotion of hepatitis-related research (*6*). The guideline includes a detailed policy for "preparation and dissemination of accurate information to the public" (*6*).

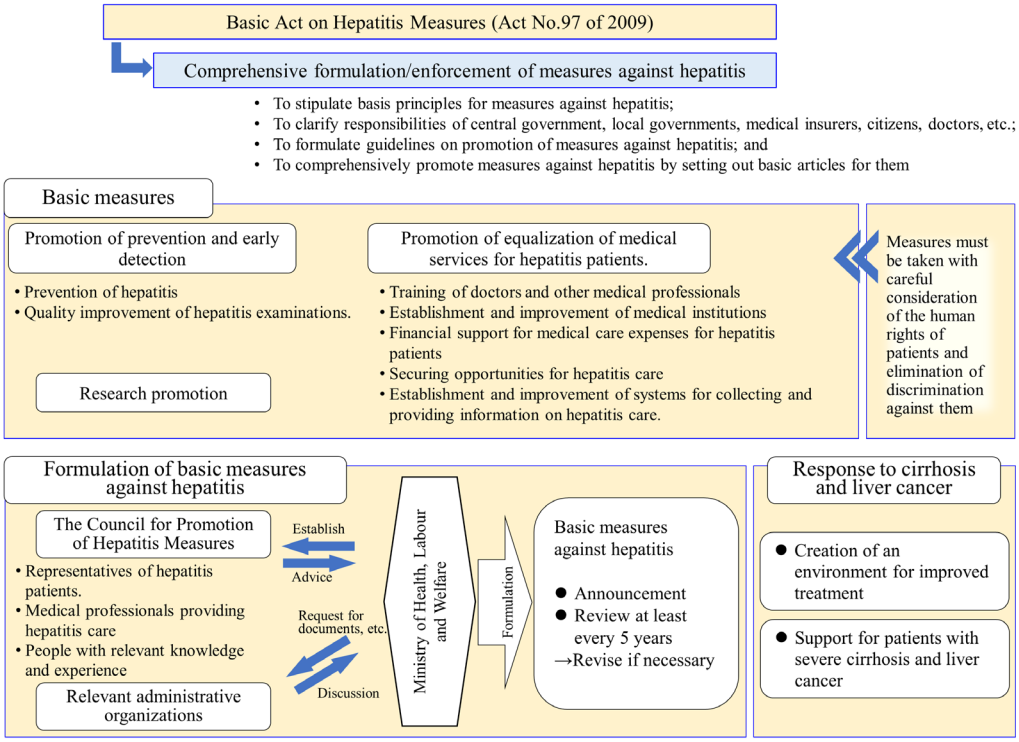

Figure 1. Overview of comprehensive hepatitis measures. Outline of the relationships between the Basic Act on Hepatitis Measures, the Basic Guidelines on Hepatitis Measures, and the Council for Promotion of Hepatitis Measures. The Basic Guidelines on Hepatitis Measures are based on the Basic Act on Hepatitis Measures and set out the requirement for comprehensive hepatitis measures. They emphasize basic measures including promotion of prevention and early detection of hepatitis, uniform accessibility of hepatitis-related medical care, and relevant research. The Minister of Health, Labour and Welfare of Japan is required to review the Basic Guidelines on Hepatitis Measures at least once every 5 years, taking into consideration changes in hepatitis-related medical care and evaluating the effects of hepatitis measures, and revise them when necessary.

What is the "*Shitte kan-en*" project?

Hepatitis is still under-recognized and misunderstood, often undiagnosed and untreated, despite the incredible toll it takes on health (*7*). In 2010, the WHO designated July 28 as "World Hepatitis Day", with the aim of preventing the spread of viral hepatitis on a global scale, eliminating stigma, discrimination and prejudice against patients and infected people, and promoting infection prevention (*8*). Japan has therefore designated July 28 as Japan Hepatitis Day and has been working on an awareness-raising program to promote understanding of the pathogenesis, prevention, and treatment of hepatitis. It also encourages medical examinations, in cooperation with national and local governments, medical organizations, employers' organizations and other stakeholders.

The national sampling survey conducted by the MHLW in the 2011 financial year has been analyzed in detail (*1*). It clarified the rate of hepatitis screening by metropolis and districts, and identified factors associated with hepatitis screening. The rate of screening was 57.7% for HBV and 48.1% for HCV. By 2017, the rates had risen to 71.0% and 61.6%. These results show that approximately 30%-40% of people have never taken a hepatitis virus test, although the testing rate seems to be increasing. In 2017, 20.1% of people who had taken a test for HBV, and 18.7% for HCV acknowledged being screened for hepatitis, although approximately 40% were not sure. The survey also showed that approximately 30% of people did not seek out medical attention even if their results were positive. Approximately 40% of the public were unaware of the government's measures to promote hepatitis awareness (*1,9*).

The "*Shitte kan-en*" project was launched as a subsidy program for hepatitis measures by the MHLW following publication of the basic guidelines for hepatitis measures in May 2011. The project uses popular Japanese athletes, actors and singers as delegates. By publicizing them undertaking various activities about hepatitis, the project is able to attract considerable public attention. The project started its awareness-raising activities in the 2013 financial year as the "National Campaign Project for Hepatitis Measures". It aimed to communicate information about hepatitis and the importance of testing, and to ensure that all citizens know about hepatitis and act proactively to enable early detection and treatment.

This project therefore involves the cooperation of many people, including local governments, medical professionals, patients with viral hepatitis, universities and academic societies, private companies, the media, public organizations, and the wider public. The "*Shitte kan-en*" project will serve as a catalyst to connect these groups (Figure 2) (*7*).

Specific measures in the "*Shitte kan-en*" project

Visits to the prefectural governors

The project has asked celebrities to act as ambassadors and special supporters. In Japan, the main work on

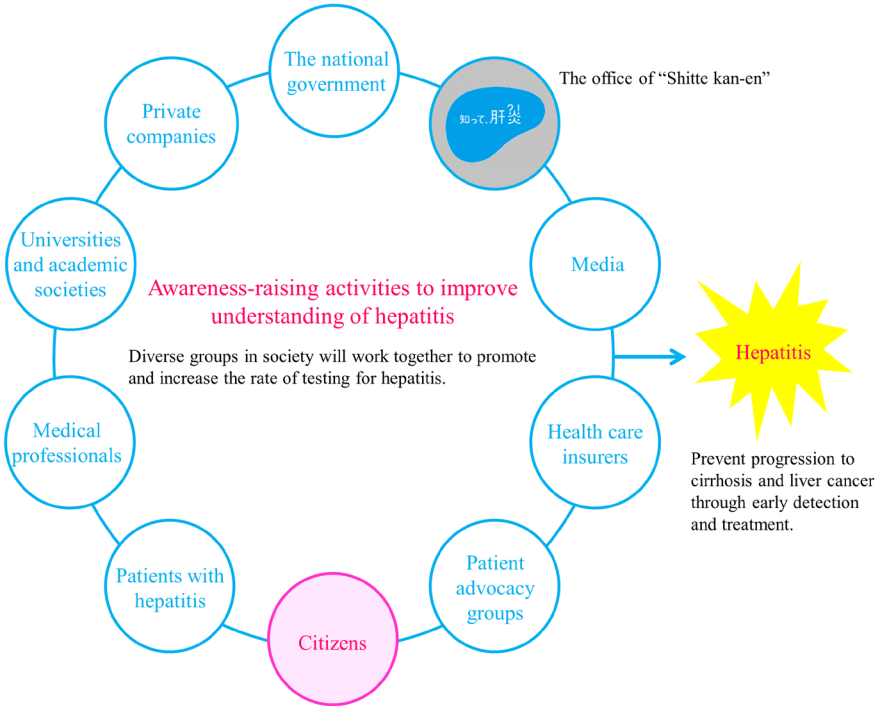

Figure 2. Preparation and dissemination of accurate information to the public for hepatitis. To improve understanding about hepatitis, and promote control measures at a national and local government level, all relevant parties need to work together and establish further collaboration.

hepatitis measures is at the prefectural government level. The ambassadors and special supporters have therefore visited the prefectural governors in every part of Japan to talk about the necessity of early diagnosis and treatment, and ask them to promote measures to encourage viral hepatitis screening. These visits drew considerable public attention. At the end of the 2020 financial year, the delegates had visited 38 of the 47 prefectures in Japan.

Educational events with regional core centers for the management of liver disease

Since 2007, the MHLW has required the prefectural governments to prepare linked regional core centers for the treatment of liver disease. There are currently 71 regional core centers nationwide. The roles of these centers fit into four main categories: *i*) the capacity to offer general medical information about liver disease; *ii*) the ability to collect and disseminate information about medical and related institutions; *iii*) the capacity to organize workshops and lectures for medical personnel and local residents, and offer consultations and provide support for liver disease; and *iv*) the capacity to hold meetings with specialized institutions to discuss matters concerning liver disease. To support these regional core centers, the Hepatitis Information Center was established as a division of the Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine (Ichikawa, Japan) in November 2008 (*10*).

The Hepatitis Information Center has conducted an annual survey about the activities of all regional core centers since 2010. The activities include liver disease seminars to give patients with hepatitis information about the pathology of hepatitis, the latest therapies, and points to note in daily life. In the 2017 financial year, seminars were held at 60 regional core centers. The most common type of educational activity was distribution of posters/leaflets, newspaper advertisements/articles, and events/symposiums. Other activities included dissemination of information through websites and social media, traveling liver disease seminars, and hepatitis testing (*11*).

Several hepatitis awareness events have also been organized by the "*Shitte kan-en*" project in cooperation with regional core centers. These are designed to provide information to the general public about hepatitis. To date, the project has worked with 29 regional core centers. At most events, hepatologists give lectures on hepatitis, and celebrities communicate the importance of hepatitis testing. The events aim to increase understanding and empathy for those with hepatitis.

The project has used an approach tailored to the targeted population, who are relatively active and healthy. The project starts with a lecture on the basics, such as the role of the liver. People are then given opportunities to learn about viral hepatitis transmission and prevention. Junior high and high school students may not have much opportunity to undergo hepatitis testing, but the aim is to convey the message to their families about the need for early detection and treatment. For people of working age, the project mainly provides information about where they can be tested for hepatitis, and subsidy programs offered by the government. Until 2020, most awareness-raising was *via* lectures open to all, including college, elementary, junior high, and high school students. Promotional leaflets were also distributed on the streets. These events were often held in open spaces, such as Civic Halls, college campuses, and public squares (plazas) (Table 1). Sometimes there was a demonstrational event where celebrities were tested for hepatitis or had an abdominal ultrasound examination in public. These events are appealing to the younger generation, and convey the message that hepatitis testing is quick and easy. A recorded video was distributed online and had been viewed more than one million times on YouTube by May, 2021.

In 2020, the impact of COVID-19 meant it was difficult to hold events with a lot of people, so "Movie for hepatitis awareness" was created. The purpose of this video is to inform young people (mainly junior high and high school students) about viral hepatitis using an educational approach. The video was recorded in a studio that resembled a school classroom, with hepatologists from three regional core centers as the teachers and celebrities as the students. The video was produced so that the viewers would feel as if they were taking a class together. Three 10-minute videos were created to keep viewers interested.

The first video is titled "Knowledge about viruses. Let's learn about viruses!". It provides general information about viruses including COVID-19, and the infection route of the hepatitis virus. The video contains two important messages. First, there are still patients with viral hepatitis who face discrimination and prejudice in Japan. Second, sharing accurate information about infectious diseases can help us to create a society where we can coexist without stigma and discrimination.

The second video is entitled "Progress in hepatitis treatment. It's amazing how far science has come". Since 2014, some new direct-acting antiviral agents have enabled high rates (> 90%) of sustained virological response in Japanese patients with HCV infection. For hepatitis B, nucleotide/nucleoside analogue therapies have suppressed viral replication in patients under treatment. This video conveys the importance of early detection of viral hepatitis to receive these treatments.

The third video is entitled "Take a hepatitis virus test at least once in your lifetime! Early detection is key". This video shows that hepatitis A and B are preventable by vaccination, and that there are many places where you can be tested for viral hepatitis. Examinations include blood tests and imaging, as well

Table 1. Educational events with regional core centers for the management of liver disease

Date	Region	Target group	Contents	Participating regional core center (Number)
July 31, 2016	Saga	All	· Hepatitis seminar	Saga
November 26, 2017	Ehime	College students	· Hepatitis seminar · Talk on hepatitis awareness with hepatologist and special supporter	Ehime
July 8, 2018	Tokyo	All	· Hepatitis seminar · Information on exercise and hepatitis · Talk on hepatitis awareness between hepatologist and special supporter	Kanto regions (*5*)
November 21, 2018	Toyama	Elementary school students	· Hepatitis seminar · Talk on hepatitis awareness between hepatologist and special supporter	Toyama
July 27, 2019	Yamaguchi	All	· Distribution of leaflets about hepatitis awareness	Chugoku and Shikoku regions (*10*)
October 23, 2019	Hokkaido	High school students	· Hepatitis seminar · Talk on hepatitis awareness between hepatologist and special supporters	Hokkaido
November 2, 2019	Tokyo	All	· Hepatitis seminar · Talk on hepatitis awareness between hepatologist and special supporter	Kanto regions (*4*)
December 1, 2019	Aomori	College students	· Hepatitis seminar · "*Shitte kan-en*" dance with participants	Aomori
January 14, 2020	Ibaraki	Elementary and junior high school students	· Hepatitis seminar · Talk on hepatitis awareness between hepatologist and special supporter	Ibaraki
March 1, 2021	Online	All	· Classes on hepatitis awareness	Tohoku, Niigata and Saitama (*3*)

as other methods for precise detection of viral hepatitis. The video also explains the importance of checking the results and visiting a medical institution if the result is positive. It concludes with celebrity supporters saying, "We would like to share these videos with more people, so that more people learn about hepatitis".

Support for partner companies' hepatitis awareness activities

The "*Shitte kan-en*" project is recruiting partner companies that support the aims of the project. Possible ways to participate include: *i*) distributing booklets about viral hepatitis to employees, sharing posters to raise awareness of hepatitis, and providing the URL of websites about hepatitis; *ii*) holding study groups and seminars on hepatitis; and *iii*) conducting questionnaires on hepatitis.

The project provides partner companies with reports on the status of activities on the "*Shitte kan-en*" project's website. It also provides support for internal awareness-raising activities, and on-site seminars. Where company annual health checkups do not include a viral hepatitis test, the project recommends employees take a viral hepatitis test provided by local governments or at testing facilities. By promoting these initiatives, the project aims to raise workplace awareness of the importance of early detection, diagnosis, and treatment of hepatitis, and hepatitis prevention. There are currently 195 companies and organizations participating in this project (as of May 2021).

Support for the activities of the "Shitte kan-en" promoters

"*Shitte kan-en*" promoters are hepatitis medical care coordinators (HMCCs) who support the project's activities in Japan, and who are responsible for disseminating information on the "*Shitte kan-en*" project in addition to their usual activities. The MHLW has aimed to strengthen regional hepatitis care networks through the Hepatitis Information Center. Local government and regional core medical centers have organized education programs, including a viral hepatitis lecture for medical workers to certify participants as an HMCC. By the end of March 2020,

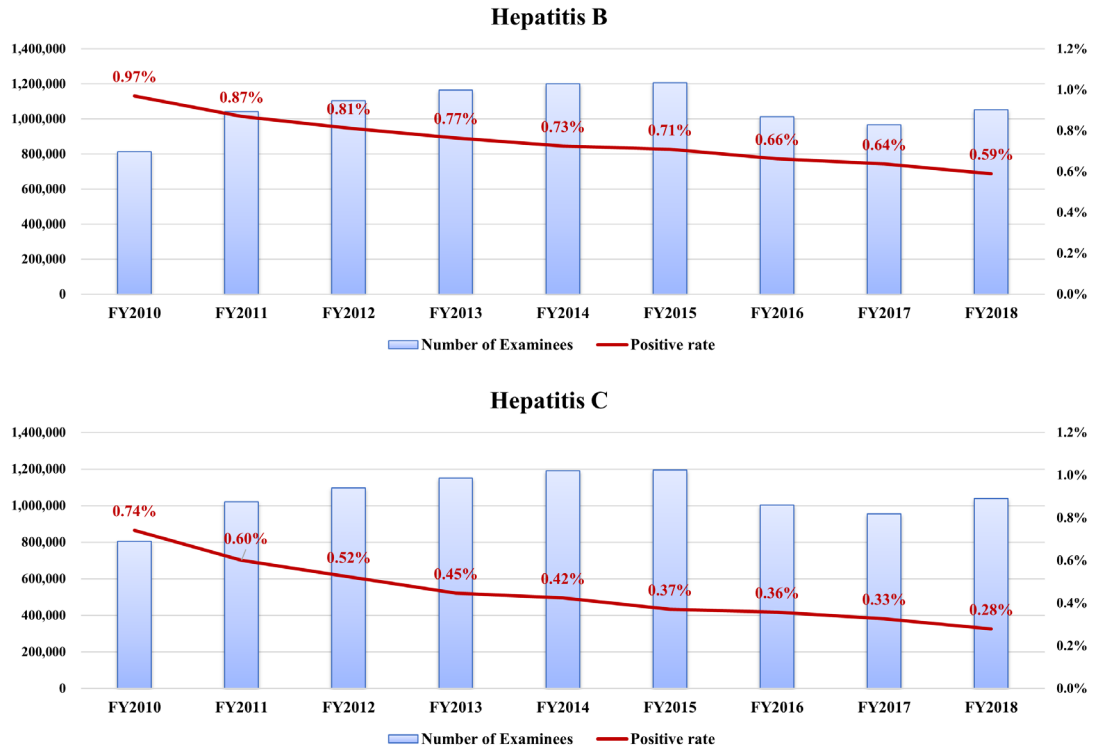

Figure 3. Hepatitis screening conducted by local governments in Japan. The bars show the number of people being tested for viral hepatitis, and the line shows the rate of positive results at the local government level. Since the 2010 financial year, when the awareness-raising program was started, the number of people undergoing testing has increased, and the rates of positive tests for HBV and HCV have decreased year to year. *Abbreviations*: FY, financial year.

20,049 HMCCs had been certified in Japan. The expected role of HMCCs includes: *i*) to share up to date knowledge about viral hepatitis; *ii*) to support patients and their families by providing information and advice on hepatitis, directing them to consultation services, encouraging them to undergo examinations and consultations, and explaining the system; and *iii*) to play a coordinating role in promoting appropriate hepatitis medical care. HMCCs are located in communities, workplaces, hospitals, and other places that are familiar to patients. By providing materials and encouraging celebrities to attend events, the project aims to support the spread of awareness and further promotion about viral hepatitis. As of May 2021, 175 HMCCs have been registered as "*Shitte kan-en*" promoters.

As an example of an activity organized by promotors, a special educational class was held by a hepatologist, following a talk with a special supporter in a school. The special class was reported in both local and regional newspapers and on many websites.

Future tasks

A strong correlation is found between awareness of hepatitis testing and awareness-raising activities, and the hepatitis virus testing rate (*7*). Disseminating information about hepatitis is therefore desirable. The number of people tested for hepatitis by the local government has increased since the project started, although it seems to have decreased slightly again more recently. The proportion of people testing positive for HBV and HCV has also been decreasing from year to year (Figure 3) (*12*). However, the national sampling surveys found that the proportion of people who tested positive and then sought medical help was 32.8% in 2011 and 31.9% in 2017. In other words, the link between obtaining a positive test result and seeking treatment did not improve over this period (*1,9*). We therefore know that even with awareness-raising, not all those who received a positive test for hepatitis will visit medical institutions specializing in liver disease. Those who do not may not receive further examinations and appropriate treatment. One of the motives for launching the "*Shitte kan-en*" project was to reduce undiagnosed and untreated cases.

To pick up latent hepatitis virus carriers who remain unaware of their status, it is essential to target awareness-raising. In general, positive feedback is important in knowledge retention for learners. For example, a concise Q&A may be a helpful way to determine how much knowledge has been retained. A survey on how many participants at events eventually responded to Q&A also provides feedback. Tailoring approaches to particular target groups could improve

awareness-raising, and hopefully also enhance the link from testing to treatment in patients with viral hepatitis. We recommend that central and local governments take action to create an environment where everyone can easily get access to testing and treatment.

Conclusion

Choosing appropriate methods of awareness-raising to match target groups is likely to be the key to success. Evaluation of the effectiveness of this type of multifaceted approach is warranted, to reduce the undiagnosed population and improve the link from testing to care for viral hepatitis in Japan. Programs to raise awareness using a variety of methods are necessary to eliminate viral hepatitis.

Acknowledgements

We thank those involved in community-based hepatitis measures at the 71 regional core centers across Japan, medical personnel at specialized institutions and those involved in providing medical care for hepatitis, those responsible for related matters in the prefectural and municipal governments, hepatitis medical care coordinators, and hepatitis patients and their families.

Funding: This review was supported by research group on "New Approaches to Expanding Comprehensive Hepatitis Policy", Ministry of Health, Labour and Welfare Sciences Research Grants in Japan (Grant number 20HC2002).

Conflict of Interest: Tatsuya Kanto received a lecture fee from AbbVie and Gilead Sciences. The other authors have no conflicts of interest to disclose.

References

1. MHLW GRANTS SYSTEM. Report on epidemiological studies to assess the status of hepatitis virus infection and to contribute to designing measurements against the elimination of viral hepatitis (Tanaka J). Japan: MHLW scientific research subsidy, Research Project for Emergency Measures to Conquer Hepatitis FY2019. *https://mhlw-grants.niph.go.jp/node/61182* (accessed May 10, 2021). (in Japanese)
2. Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Japan (Vital Statistics of Japan). *https://ganjoho.jp/reg_stat/statistics/dl/index.html#mortality* (accessed May 10, 2021). (in Japanese)
3. Enomoto H, Ueno Y, Hiasa Y, *et al.* Transition in the etiology of liver cirrhosis in Japan: a nationwide survey. J Gastroenterol. 2020; 55:353-362.
4. Tateishi R, Uchino K, Fujiwara N, *et al.* A nationwide survey on non-B, non-C hepatocellular carcinoma in Japan: 2011-2015 update. J Gastroenterol. 2019; 54:367-376.
5. Ministry of Health, Labour and Welfare. Basic Act on Hepatitis Measures. *http://www.japaneselawtranslation.go.jp/law/detail_main?re=&vm=01&id=1995* (accessed March 31, 2021). (in Japanese)
6. Ministry of Health, Labour and Welfare. Basic guidelines for promotion of control measures for hepatitis. *https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/pdf/hourei-27.pdf* (accessed March 31, 2021). (in Japanese)
7. Official homepage of "*Shitte kan-en*". *https://www.kanen.org/about/taisaku/* (accessed May 25, 2021). (in Japanese)
8. World Health Organization. World Hepatitis Day. *https://www.who.int/campaigns/world-hepatitis-day* (accessed March 31, 2021).
9. Ministry of Health, Labour and Welfare. FY2011 Report on the Current Extent of Hepatitis Testing. *https://www.mhlw.go.jp/stf/houdou/2r9852000002gd4j-att/2r9852000002gd60.pdf* (accessed May 10, 2021). (in Japanese)
10. Oza N, Isoda H, Ono T, Kanto T. Current activities and future directions of comprehensive hepatitis control measures in Japan: The supportive role of the Hepatitis Information Center in building a solid foundation. Hepatol Res. 2017; 47:487-496.
11. Setoyama H, Korenaga M, Kitayama Y, Oza N, Masaki N, Kanto T. Nationwide survey on activities of regional core centers for the management of liver disease in Japan: Cumulative analyses by the Hepatitis Information Center 2009-2017. Hepatol Res. 2020; 50:165-173.
12. Ministry of Health, Labour and Welfare. Material 1 at the 25th Meeting of the Council for Promotion of Hepatitis Measures. *https://www.mhlw.go.jp/content/10901000/000719442.pdf* (accessed May 10, 2021). (in Japanese)

Received May 31, 2021; Revised July 1, 2021; Accepted August 6, 2021.

Released online in J-STAGE as advance publication September 5, 2021.

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Global Health & Medicine. 2021; 3(5):308-313.
REVIEW
DOI: 10.35772/ghm.2021.01072

Testing, diagnosis of viral hepatitis, and the follow-up policy in Japan

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Abstract: Viral hepatitis is one of the major infectious diseases in Japan and causes liver cirrhosis and liver cancer. Therefore, screening for hepatitis viruses was started in 2002, based on the geriatric health care program. The screening plan has now been transferred to the Health Promotion Project and it is estimated that more than half of the population has been tested for hepatitis viruses. The Basic Act on Hepatitis Measures was enacted in 2009 and the Basic Guidelines for Promotion of Control Measures for hepatitis was issued in 2011. It reported that there were about 770,000 positive people who were unaware that they were infected, and about 0.5 to 1.2 million positive people who knew they were infected but did not continue to receive medical examinations. Ten years have passed since that report and it is estimated that the number of hepatitis virus-positive individuals who need medical examination/treatment is decreasing. Therefore, in order to eradicate viral hepatitis, it is essential to identify areas and age groups in which hepatitis virus testing is inadequate, to encourage people to undergo testing and to promptly send positive patients to hepatologists for continued medical care. This review describes the current status and challenges of hepatitis virus testing measures in Japan, led by the Ministry of Health, Labour and Welfare, and the promotion of visits to medical institutions by positive patients.

***Keywords*:** hepatitis screening test in Japan, follow-up of individuals positive for viral hepatitis, Basic Act on Hepatitis Measures, hepatitis B surface antigen, hepatitis C virus antibody

Introduction

Tests for hepatitis viruses as part of the milestone checkups of the Health Care for Elderly Service began in Japan in 2002. The liver cancer mortality rate in Japan has fallen steadily because of measures such as the establishment of the Basic Act on Hepatitis Measures (*1*) and Basic Guidelines for Promotion of Control Measures for Hepatitis (*2*), the Hepatitis Information Center, the establishment of regional core centers (*3,4*), and subsidization of interferon treatment for hepatitis C virus (HCV). On the other hand, it is estimated that there are about 770,000 individuals who do not know they are persistently infected with hepatitis B virus (HBV) or HCV because they have not yet undergone screening, and about 0.5 to 1.2 million positive individuals who know they are infected but do not continue to visit a hospital care (*5,6*).

According to a report in 2011(*7*), the preferred option for hepatitis virus testing was free screening at public health centers, but this had a very low uptake rate of about 6%, because the testing days were limited to one or two per month. Only a further 17.1% were tested for hepatitis viruses in checkups at their workplaces. Many workers have taken mandatory health examinations which did not include screening for viral hepatitis. As a result, they are unwilling to visit a public health center solely for viral hepatitis screening.

On the other hand, 25% of the respondents were tested for hepatitis viruses in hospitals and clinics, the majority (49%) of whom were tested as part of pre-surgery examinations. However, hepatitis virus-positive individuals may not be directed to consultation/treatment because of a lack of awareness by non-specialist doctors and a lack of intra-hospital cooperation.

Considering that the treatments for HBV and HCV infections are now oral antiviral drugs with almost no adverse reactions, new measures are urgently needed for positive patients who do not currently receive medical examinations or treatment.

Current status and issues of viral hepatitis testing through local governments

Hepatitis virus screening was available for individuals between the ages of 40 and 70 for five years from 2002 under the Health Care for Elderly Service, at 5-year intervals (milestone checkup), with additional screening available for those with abnormal liver function, extensive surgical procedures, or a history of heavy bleeding

Table 1. Number of viral hepatitis screening tests and positive rates from 2002-2006, under the geriatric health care program

(a) Hepatitis B surface antigen (HBsAg)

	Milestone checkup		Out of milestone checkup		Total		
	Number of tests	Number of positive	Number of tests	Number of positive	Number of tests	Number of positive	Positive rate
FY2002	1,291,195	15,239	631,918	9,191	1,923,113	24,430	1.27%
FY2003	1,382,663	15,842	466,462	6,678	1,849,125	22,520	1.22%
FT2004	1,279,704	13,950	356,230	4,804	1,635,934	18,754	1.15%
FY2005	1,205,423	12,735	341,400	4,395	1,546,823	17,130	1.11%
FY2006	1,145,291	11,742	604,301	6,407	1,749,592	18,149	1.04%
total	6,304,276	69,508	2,400,311	45,207	8,704,587	100,983	1.16%

(b) HCV antibody (anti-HCV)

	Milestone checkup		Out of milestone checkup		Total		
	Number of tests	Number of positive	Number of tests	Number of positive	Number of tests	Number of positive	Positive rate
FY2002	1,298,746	14,672	624,734	16,721	1,923,480	31,393	1.63%
FY2003	1,375,583	13,324	454,687	10,167	1,830,270	23,491	1.28%
FT2004	1,271,320	10,385	347,431	6,446	1,618,751	16,831	1.04%
FY2005	1,196,457	8,909	331,356	5,067	1,527,813	13,976	0.91%
FY2006	1,138,005	7,453	596,190	6,806	1,734,195	14,259	0.82%
total	6,280,111	54,743	2,354,398	45,207	8,634,509	99,950	1.16%

Milestone checkup: between the ages of 40 and 70 at 5-year intervals. Out of milestone checkup: abnormal liver function and history of extensive surgical procedures or heavy bleeding.

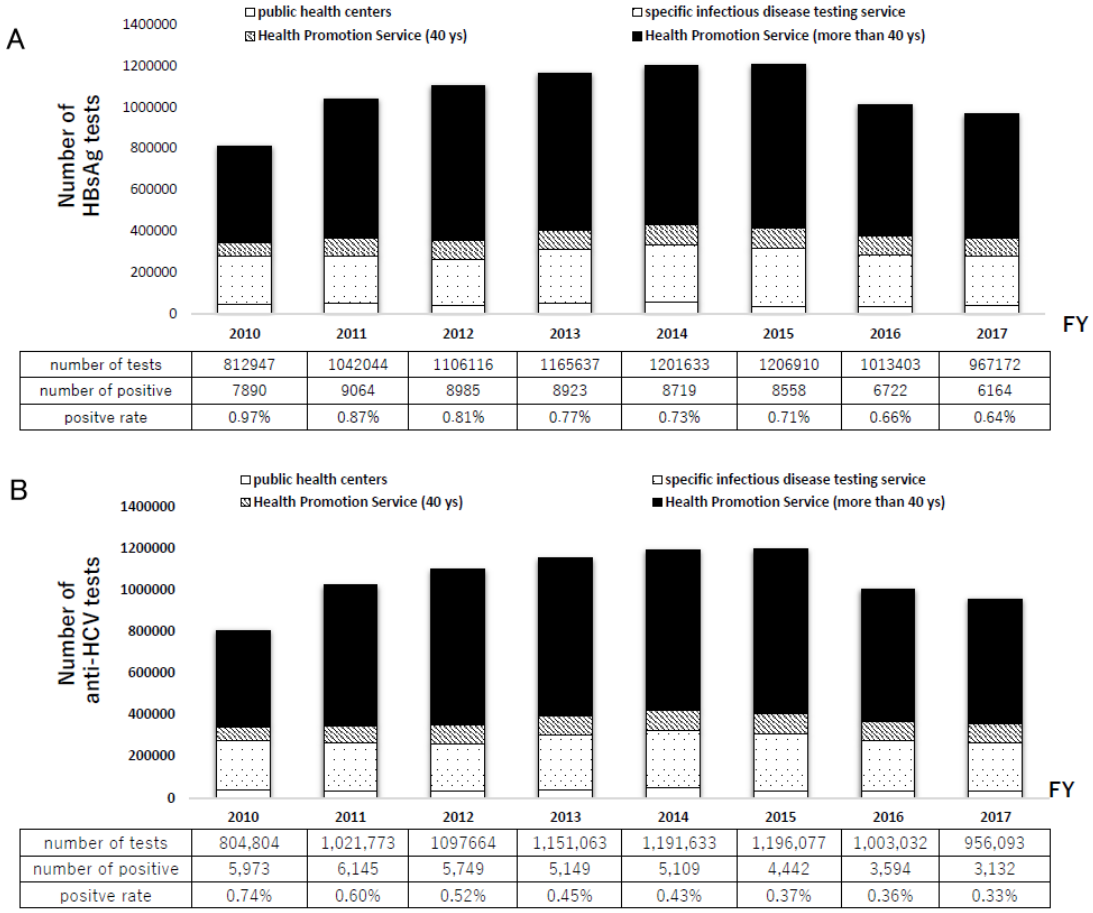
(out with the milestone checkups). As a result, about 87 million people were tested for hepatitis B surface antigen (HBsAg) and HCV antibody (anti-HCV) and about 200,000 positive cases were discovered (Table 1). However, uptake of testing by eligible subjects was only 27% among the recipients of milestone checkups. One of the reasons for the lack of increase in the screening rate was the variable efforts made by local governments. In addition, it is assumed that only National Health Insurance subscribers were eligible to take the test.

In 2008, the testing program was taken over by the Health Promotion Service. Many local governments provide opportunities for hepatitis virus testing at the same time as specific medical examinations and cancer screening, for greater convenience. However, most workers did not receive a checkup, even when they received a "Notice of Hepatitis Virus Screening with the annual checkup" from the municipal authorities, because they had health examinations provided by their employers. Individuals of working age rarely took advantage of this program by taking tests for hepatitis viruses.

In order to cope with this situation, in 2008, as an urgent hepatitis virus testing service (specific infectious disease testing service), prefectures, government-ordinance-designated cities, core cities, *etc.*, in cooperation with medical associations, selected medical institutions for commissioned testing, so that testing was more widely available for those who were not able to receive medical checkups conducted under the Health Care for Elderly Service (or Health Promotion Service) from 2008. As a result, about 300,000 people are currently being tested every year as part of the specific infectious disease testing program. From 2010 to 2017, about 10 million people were tested by the projects, and the positive rates in 2017 were 0.64% for HBV and 0.33% for HCV (*8*) (Figure 1).

It is not clear how many of those found to be positive for HBV or HCV have been followed up with examinations and hospital treatment. Originally, the purpose of hepatitis virus screening by the Health Promotion Service was stated to be "to spread correct knowledge about the hepatitis viruses and promote medical examinations for hepatitis viruses, so that individuals can recognize their own hepatitis virus infection status, receive health guidance as necessary, and visit medical institutions to avoid health problems caused by hepatitis, reduce symptoms, or delay the progression of the disease". At a time when the number of positive cases is declining, it is of utmost importance that the hepatitis virus screening program not only promotes testing but also directs those found to be positive to medical institutions and monitors their numbers.

Furthermore, if the prefectural government takes the lead in conducting hepatitis virus testing, it will retain the personal information of those who test positive. Because the prefectures are also the main implementers of the subsidies for hepatitis virus testing and treatment, which are unique to Japan, it is easy to monitor the status of positive patients receiving medical examinations and treatment. On the other hand, the burden of examination costs in prefectures is higher than that of hepatitis virus examinations by the Health Promotion Service, and the number of tests conducted by prefectural governments



	2010	2011	2012	2013	2014	2015	2016	2017
number of tests	812947	1042044	1106116	1165637	1201633	1206910	1013403	967172
number of positive	7890	9064	8985	8923	8719	8558	6722	6164
positve rate	0.97%	0.87%	0.81%	0.77%	0.73%	0.71%	0.66%	0.64%

	2010	2011	2012	2013	2014	2015	2016	2017
number of tests	804,804	1,021,773	1097664	1,151,063	1,191,633	1,196,077	1,003,032	956,093
number of positive	5,973	6,145	5,749	5,149	5,109	4,442	3,594	3,132
positve rate	0.74%	0.60%	0.52%	0.45%	0.43%	0.37%	0.36%	0.33%

Figure 1. Number of viral hepatitis screening and positive rate from 2010-2017 under urgent hepatitis virus testing project and Health Promotion Project. (A) HBsAg, **(B)** anti-HCV.

is only 50,000, with Saga, Yamaguchi, and Osaka prefectures accounting for more than 50% of the total (Figure 2). Osaka prefecture is actively confirming the diagnosis of positive patients, and the consultation rate shows that more than 60% are followed up (*9*).

The Severe Disease Prevention (Follow up) Project for people who test positive for viral hepatitis, through local governments

In the Severe Disease Prevention Project, which started in April 2014, the prefectural government or other authority, after obtaining the consent of the individual, confirms the status of visits to medical institutions and medical treatment by sending a survey sheet once a year and, if the individual has not yet visited a hospital, recommends that the individual visits a specialist and receives medical consultation by telephone or other means (=Follow-up). If an individual is found to be positive for a hepatitis virus and consents to undergo follow-up, with a detailed examination by a specialist designated by the prefectural government within one year of the positive result, the cost of the examination, about 8,000 yen, will be reimbursed (subsidy for the initial detailed examination). In addition, if patients with viral hepatitis were diagnosed with chronic hepatitis or cirrhosis, or post-elimination of HCV following anti-HCV treatment, their medical expenses will be partially reduced twice a year after obtaining the consent of the individual (subsidy for periodic examinations). Recently, the subsidy for the initial detailed examination is being extended, not only to those who are positive for hepatitis virus tests in local governments, but also to those who are found positive at workplace check-ups, preoperative examinations, and prenatal checkups (*3,10*). Through these subsidy programs, efforts are being made to encourage people to visit specialized medical institutions and to encourage those who are positive to continue to receive examinations; however, the number of first-time specialist examinations and subsidized periodic examinations has been static nationwide.

The situations of local governments with a high consent rate are as follows: *i*) Advice is given to the patient at the time of hepatitis screening that all applicants should see a specialist in the case of a positive result (consent is obtained before screening, as in Osaka); *ii*) A physician from the medical institutions for commissioned testing, who is familiar with the provisions of the subsidy system, explains that system to the patient at the time of confirmation of a positive test; and *iii*) Public health nurses responsible for hepatitis in local areas contact the positive person, as soon as

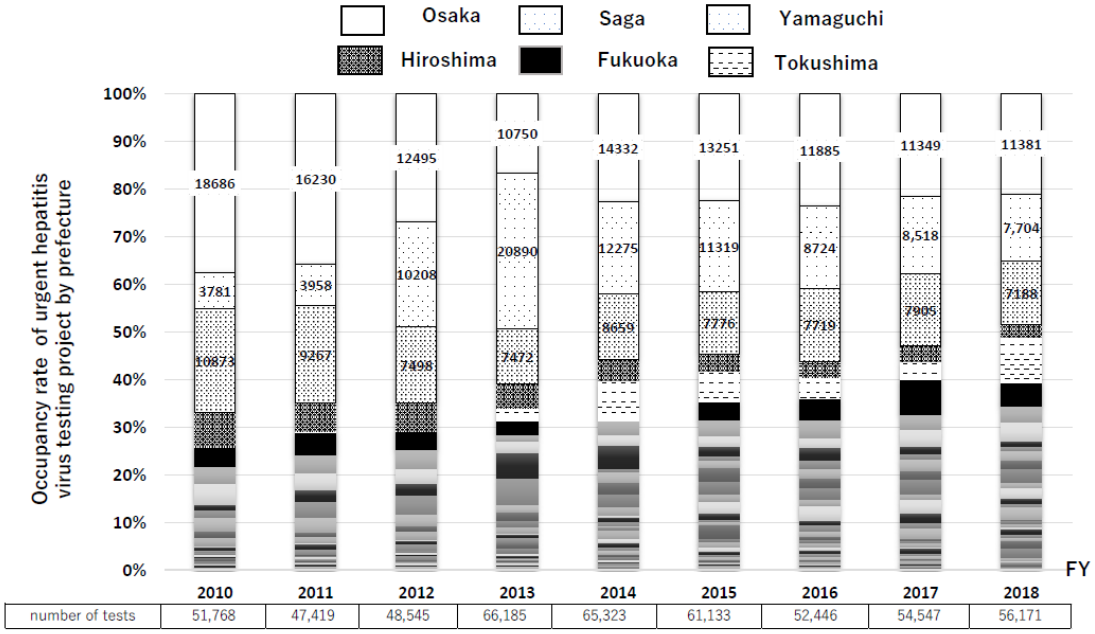


Figure 2. Occupancy rate of urgent hepatitis virus testing project by prefecture from 2010-2018. White column is Osaka prefecture, wide dots in column is Saga prefecture, and narrow dots in column is Yamaguchi prefecture. These three prefectures account for more than 50% of the total.

possible after confirmation of the positive result, and visit that person's home or interview him/her at the hepatitis countermeasure department to provide advice.

If the number of positive patients is about ten per year, it is possible to use measure *iii*. However, if the number of positives is much higher or there is no public health nurse, the burden on the person in charge is heavy and it is better to obtain consent at the time of examination (*i* and *ii*). Starting in 2018, the Ministry of Health, Labour and Welfare has also been promoting the follow-up consent for hepatitis virus testing.

Current status and issues of viral hepatitis in the workplace

Although about 20 million community residents have been provided with an opportunity to undergo HBsAg and anti-HCV testing, actions against hepatitis in the workplace in Japan have not yet been fully implemented, and the prevalence of hepatitis virus infections in the workplace remains unknown. Individuals in "the workplace" are non-national insurance subscribers, broadly speaking, who are members of the Japan Health Insurance Association (JHIA) and Union Health Insurance (UHI). The government does not subsidize screening of general workers for viral hepatitis, and the coverage of screening is at the discretion of each health insurance union and company. It would be beneficial if hepatitis virus screening could be conducted by local governments at the time of workplace checkups, but this is not possible in conjunction with the Health Promotion Service. Consequently, it was thought that the hepatitis virus testing system is not sufficiently widespread in the workplace.

We investigated institutions that conducted health screenings in the FY 2016 and reported examination rates of 7.8% and 4.9% for HBsAg and anti-HCV, respectively, in the health insurance association for hepatitis virus testing during workplace checkups in the UHI (*11*). In this survey, there were many people who are examined every year in same Health Administration Center, and it was revealed that about 70% of the respondents underwent hepatitis screening every year over three years, regardless of whether the test was negative or positive. These results suggest that there remain many UHI members who have not yet been tested.

On the other hand, since 2008 the JHIA has been offering hepatitis virus tests at a partial cost to those who are insured but have never been tested for the viruses. As of 2018, about 19 million people over the age of 40 were insured (*12*). To date, about two million people have taken the test (Table 2) but, in addition to the fact that less than 10% of subscribers have taken the test, the annual rate in recent years has been as low as 1 to 2%. The JIHA is Japan's largest health insurer and covers the healthcare costs of workers for many small to medium-sized companies in Japan, therefore, there is an urgent need to promote hepatitis virus screening at the JHIA.

We simplified the hepatitis virus testing form used by the JHIA using nudge theory, created a leaflet emphasizing the fact that the test can be taken at a reduced cost, and verified the increase of hepatitis virus

Table 2. Number of viral hepatitis screening tests in the Japan Health insurance from 2008-2018

Year	The number of hepatitis virus screening recipients	The cumulative number of hepatitis virus screening recipients
2008	253,840	253,840
2009	203,213	457,053
2010	194,268	651,321
2011	167,451	818,772
2012	156,364	975,136
2013	147,734	1,122,870
2014	143,916	1,266,786
2015	146,077	1,412,863
2016	137,382	1,550,245
2017	205,285	1,755,530

tests in workplace checkups of JHIA members. In this survey, fully subsidized screening led to the highest hepatitis screening rates, and the leaflet modified using nudge theory significantly increased hepatitis screening uptake at lower costs per person (*13*). Furthermore, a validation study was conducted at the F branch, which includes about 400,000 people who underwent a workplace checkup in 2017, and the examination rate increased about seven-fold, compared to the previous year (*14*). The positive rate in F branch was almost the same as the rate from local governments and about 30% of patients positive for anti-HCV were treated with IFN-free direct-acting antivirals. As a result, the Ministry of Health, Labor and Welfare notified insurers and health administration centers to promote hepatitis virus testing during occupational examinations in 2017, (*15*) and from 2019, the subsidy for the first detailed examination could be used for patients found to be positive from hepatitis virus testing in the workplace (*16*).

The hepatitis virus tests are non-statutory tests and not included among the mandatory test items for workplace examinations described in Article 66 of the Industrial Safety and Health Act. There is no obligation for business establishments or insurers to add these items. Therefore, when promoting hepatitis virus testing at workplaces, it is desirable to specify which department will manage the results and what recommendations for medical treatment will be made in the event of a positive result. It is critical that results of non-statutory tests are not obtained without the consent of the examinee. Therefore, if the follow-up procedures of a positive test result are not announced before the test, the employer cannot recommend for that person to visit a specialist, even if the result is positive.

It is known that viral hepatitis carriers feel uneasy because they "do not want their workplaces to know about this", so a certain level of consideration must be given to promoting hepatitis virus testing in the workplace.

Viral hepatitis testing before surgery and the consultation status of positive patients

Hepatitis virus testing before surgery is part of routine medical care, as a precautionary measure against infection in hospitals. Nevertheless, not all people who test positive for hepatitis viruses are examined by specialist physicians or receive appropriate treatment. In 2016, the Ministry of Health, Labour and Welfare stated that the results of hepatitis virus tests should be explained to examinees, regardless of the purpose of the test. In addition, they instructed the medical institution (doctor in charge) that conducted the test to refer the patient to a specialist, in the case of a positive result. For this situation, an alert system was developed through an electronic medical record (EMR) order to introduce viral hepatitis-positive individuals to hepatologists, mainly in large hospitals. This system has been reported as useful for promoting appropriate examinations and treatment of individuals with positive results of preoperative and other in-hospital hepatitis virus tests (*17,18*). However, not all patients with positive hepatitis test results are referred to specialists, solely based on EMR alerts.

We assessed the level of awareness among healthcare professionals about hepatitis virus infection and the electronic medical records alert system and the most common reasons for not referring patients previously were "I had no knowledge and/or interest" and "All I did was explain the results orally" (*19*).

The doctors who did not respond to the EMR alerts were: *i*) physicians who were less aware of hepatitis viruses; *ii*) physicians in departments with more operations and shorter hospital stays (ophthalmology, orthopedics); and *iii*) physicians with less experience or who were older.

It is thought that more widespread education of healthcare personnel, such as non-specialists and other medical staff, is important to increase the number of individuals receiving appropriate treatment from specialist physicians.

Conclusion

The number of hepatitis virus-positive individuals who need medical examination and treatment is decreasing because viral hepatitis screening by local governments was initiated from 2002. However, when patients received viral hepatitis screening by non-specialist physicians, not all of those with positive hepatitis test results were referred to a specialist.

There are still many patients who are infected with HBV and HCV in workplaces in Japan and promoting hepatitis virus screening for workers at checkups can help detect carriers who are unaware of their infection and require treatment.

Funding: This study was supported financially by the Ministry of Health, Labour and Welfare, Japan (grant number: H26-kansei-ippan-001, H29-kansei-ippan-004).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Ministry of Health, Labour and Welfare. Basic Act on Hepatitis Measures. *http://www.japaneselawtranslation.go.jp/law/detail/?id=1995&vm=04&re=01* (accessed May 31, 2021). (in Japanese)
2. Ministry of Health, Labour and Welfare. Basic guidelines for promotion of control measures for hepatitis. *http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/pdf/hourei-17e.pdf* (accessed May 31, 2021).
3. Oza N, Isoda H, Ono T, Kanto T. Current activities and future directions of comprehensive hepatitis control measures in Japan: The supportive role of the Hepatitis Information Center in building a solid foundation. Hepatol Res. 2017; 47:487-496.
4. Setoyama H, Korenaga M, Kitayama Y, Oza N, Masaki N, Kanto T. Nationwide survey on activities of regional core centers for the management of liver disease in Japan: Cumulative analyses by the Hepatitis Information Center 2009-2017. Hepatol Res. 2020; 50:165-173.
5. Tanaka J, Akita T, Ohisa M, Sakamune K, Ko K, Uchida S, Satake M. Trends in the total numbers of HBV and HCV carriers in Japan from 2000 to 2011. J Viral Hepat. 2018; 25:363-372.
6. Tanaka J, Akita T, Ko K, Miura Y, Satake M. Countermeasures against viral hepatitis B and C in Japan: An epidemiological point of view. Hepatol Res. 2019; 49:990-1002.
7. Ministry of Health, Labor and Welfare. FY2011 hepatitis test examination status. *https://www.mhlw.go.jp/stf/houdou/2r9852000002gd4j-att/2r9852000002gd60.pdf* (accessed May 31, 2021). (in Japanese)
8. Ministry of Health, Labor and Welfare. About viral hepatitis tests. Available at: *https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/hepatitis_kensa.html* (accessed May 30, 2021). (in Japanese)
9. Ministry of Health, Labor and Welfare. About 26th Council for Promotion of Hepatitis Measures. *https://www.mhlw.go.jp/content/10901000/000781260.pdf* (accessed May 20, 2021). (in Japanese)
10. Ministry of Health, Labor and Welfare. About related decree. Released on March 27, 2020. *https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/pdf/hourei-200327-1.pdf* (accessed May 20, 2021). (in Japanese)
11. Tatemichi M, Furuya H, Nagahama S, Takaya N, Shida Y, Fukai K, Owada S, Endo H, Kinoue T, Korenaga M. A nationwide cross-sectional survey on hepatitis B and C screening among workers in Japan. Sci Rep. 2020; 10:11435.
12. Basic information on subscribers and medical fees 2018 in Japan Health Insurance Association. *https://www.kyoukaikenpo.or.jp/g7/cat740/sb7200/sbb7204/h30.* (accessed May 30, 2021). (in Japanese)
13. Fukuyoshi J, Korenaga M, Yoshii Y, Hong L, Kashihara S, Sigel B, Takebayashi T. Increasing hepatitis virus screening uptake at worksites in Japan using nudge theory and full subsidies. Environ Health Prev Med. 2021; 26:18.
14. Korenaga M, Ooe C, Kamimura K, Fukuyoshi J, Ide T, Okada H, Kato F, Mochida S, Inoue T, Akahane T, Kanto T. Tailored message interventions using social marketing approach increase the number of participants in viral hepatitis screening for Japanese workers -multicenter trial of 880,000 general checkup applicants. Hepatology. 2019; 70(Suppl 1):460A. *https://aasldpubs.onlinelibrary.wiley.com/doi/epdf/10.1002/hep.30941* (accessed July 17, 2021).
15. Ministry of Health, Labor and Welfare. About related decree. Released on May 30, 2017. *https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/pdf/hourei-170530-1.pdf* (accessed May 30, 2021). (in Japanese)
16. Ministry of Health, Labor and Welfare. About related decree. Released on March 27, 2019. *https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/pdf/hourei-190329-2.pdf* (accessed March 27, 2021). (in Japanese)
17. Uchida-Kobayashi S, Enomoto M, Fujii H, *et al.* Promotion of intra-hospital referral of hepatitis B and C virus carriers to hepatology specialists by electronic medical record-based alert system: a case study at a university hospital. Kanzo. 2016; 57:7-16. (in Japanese with English abstract)
18. Fujii H, Yamaguchi S, Kurai O, Miyano M, Ueda W, Oba H, Aoki T, Enomoto M, Kawada N, Okawa K. Putting "sticky notes" on the electronic medical record to promote intra-hospital referral of hepatitis B and C virus-positive patients to hepatology specialists: an exploratory study. BMC Infect Dis. 2016; 16:410.
19. Hidaka I, Enomoto M, Sato S, Suetsugu A, Matono T, Ito K, Ogawa K, Inoue J, Horino M, Kondo Y, Sakaida I, Korenaga M. Establishing efficient systems through electronic medical records to promote intra-hospital referrals of hepatitis virus carriers to hepatology specialists: A multicenter questionnaire-based survey of 1,281 healthcare professionals. Intern Med. 2021; 60:337-343.

Received June 10, 2021; Revised July 19, 2021; Accepted July 26, 2021.

Released online in J-STAGE as advance publication July 29, 2021.

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Global Health & Medicine. 2021; 3(5):314-320.
REVIEW
DOI: 10.35772/ghm.2021.01061

Use of information and communication technology in the support of viral hepatitis patients in Japan

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Abstract: In Ishikawa Prefecture, Japan, the regional core center for hepatitis care coordination (Kanazawa University Hospital, the only regional core center in the prefecture) conducts follow-ups with people who tested positive for viral hepatitis at screenings organized primarily by municipal governments. This program, called the Ishikawa Hepatitis Follow-up Program, has been operating since 2010. The regional core center has conventionally verified the status of program participants using a paper-based system of "examination letters" which specialized institutes mail to the regional core center when a program participant visits a physician there. However, only a low 40% to 50% of examination letters were returned to the regional core center. The program is now using the information and communication technology tool ID-Link to help the regional core center participate in care and provide support through mutual sharing of clinical information with specialized institutes. Currently, 1,632 of the 3,202 people who had tested positive for hepatitis testing since 2002 have consented to participate in the Ishikawa Hepatitis Follow-up Program, and as of the end of March 2021, information about 132 among those 1,632 people is being shared between specialized institutes and the regional core center using ID-link. Sharing of clinical information between the regional core center and specialized institutes enabled by ID-Link provided a more accurate picture of how many people who tested positive for viral hepatitis had visited a specialized institute compared with the previous paper-based system of examination letters, making follow-up more efficient.

***Keywords*:** viral hepatitis, information and communication technology

Introduction

It is estimated that 1.12-1.27 million and 0.98-1.58 million people were persistently infected with hepatitis B virus and hepatitis C virus, respectively, in 2011 in Japan (*1,2*). People with hepatitis B or C are at high risk for developing cirrhosis and liver cancer, which makes it important to test for hepatitis (screening), refer those who test positive to a specialized institute (consultation), and have them start antiviral therapy (treatment). Besides these steps of screening, consultation, and treatment, it is extremely important to conduct follow-ups by tracking which patients have visited a specialized institute and recommending a visit to those who have not.

In Ishikawa Prefecture, Japan, municipal public health staffs have conducted hepatitis screenings as part of the national government's senior health promotion program and later the general health promotion program since 2002, and have been conducting follow-ups with people who tested positive. In 2010, the prefecture also launched the Ishikawa Hepatitis Follow-up Program, in which Kanazawa University Hospital, the only regional core center for hepatitis care in the prefecture, conducts follow-ups with people who tested positive for hepatitis at local screening programs. At the end of 2019, of the 3,202 people who had tested positive for hepatitis testing since 2002, 1,632 had consented to participate in the follow-up program, 525 had declined to participate, and 1,045 did not respond.

The mortality rate due to liver cancer of Ishikawa Prefecture has generally been lower than that of Japan as a whole. It has especially sharply dropped since 2017 (*3*) (Figure 1), suggesting that this follow-up program may be contributing to this decline. The regional core center has conventionally verified the status of program participants by having specialized institutes mail paper examination letters to show that the participant had made their annual visit to that institute. However, only a low 40% to 50% of these letters were returned from the specialized institutes to the regional core center.

The Ishikawa Hepatitis Follow-up Program is now using the information and communication technology (ICT) tool, ID-Link, to share clinical information about program participants between specialized institutes and the regional core center. As of the end of March 2021, information about 132 patients of 18 specialized institutes is being shared between these institutes and the regional core center using ID-link. ID-Link provides

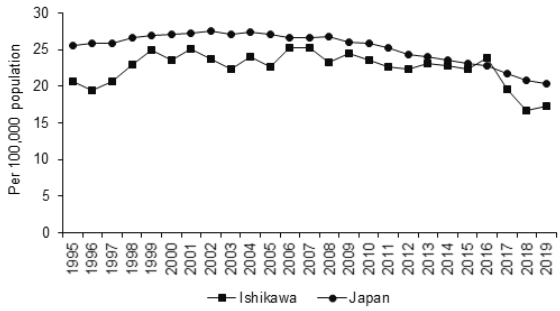

Figure 1. Trend mortality rate cause by liver cancer in Ishikawa Prefecture and Japan. The mortality rate caused by liver cancer in Ishikawa Prefecture and all of Japan is shown. It was calculated per 100,000 population.

a more accurate picture of the visit status of people who tested positive for hepatitis and the details of their care compared with the previous paper-based system using examination letters. This review article provides an overview of the Ishikawa Hepatitis Follow-up Program and how it utilizes ICT.

Follow-up of people who tested positive for hepatitis in Ishikawa Prefecture

The Basic Act on Hepatitis Measures was enacted in 2010, and the Basic Guidelines on Hepatitis Measures were published in 2011 to provide guidance on specific measures. These guidelines were revised in 2016. In the 2016 revisions, the Japanese government recommended that local governments coordinate with stakeholders, including local organizations and medical institutions, to conduct follow-ups after hepatitis testing and recommend further care to ensure that people with hepatitis receive appropriate individualized care. In response to these revised guidelines, each prefecture in Japan began efforts to conduct follow-ups with people who test positive for hepatitis (*1,4,5*). However, municipal governments across Ishikawa Prefecture had already been conducting follow-ups with people who tested positive for hepatitis at local screening programs since 2002, before these revised guidelines were issued.

Follow-up of people who tested positive for hepatitis in Ishikawa Prefecture from 2002 to 2009

In Japan, municipal governments have conducted screenings for hepatitis B and C, first as part of a national senior health promotion program from 2002 to 2008, then as part of a general health promotion program from 2008 onward. In Ishikawa Prefecture, 222,029 and 221,967 people had been tested under these programs for hepatitis B virus and hepatitis C virus, respectively. Between 2002 and 2019, 1,956 and 1,655 people were positive for hepatitis B virus and hepatitis C virus, respectively. The positive ratio was 0.88% and 0.75% for hepatitis B virus and hepatitis C

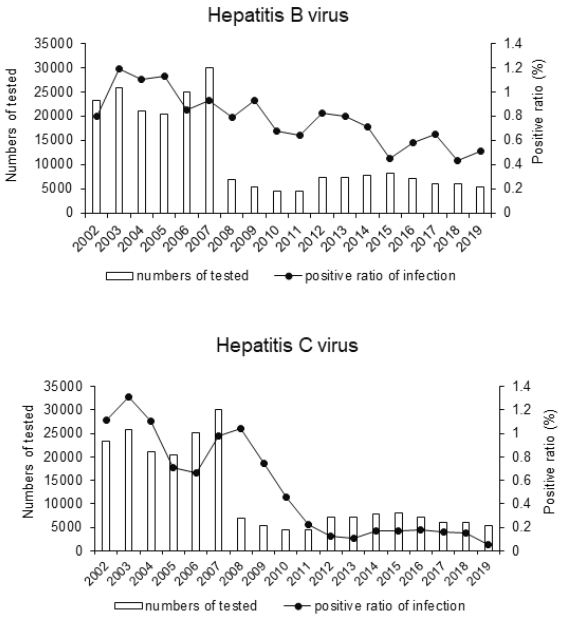

Figure 2. Numbers of people tested for hepatitis B virus and hepatitis C virus infection and positive ratio between 2002 and 2019 in Ishikawa Prefecture.

virus, respectively (Figure 2). In Ishikawa Prefecture, municipal public health staff have conducted follow-ups with people who tested positive for hepatitis at local screening programs since 2002. Municipal public health staff conduct follow-ups every year by making home visits or phone calls to verify which patients have visited a specialized institute and by recommending a visit to those who have not. Kanazawa City, the capital of Ishikawa Prefecture, has a large number of people who tested positive for hepatitis, which made it difficult for public health staff to conduct follow-ups in person. Therefore, the city contracted the Kanazawa Medical Association to conduct follow-ups by contacting medical institutions that conducted hepatitis screenings to confirm whether people who tested positive for viral hepatitis at that institution ever visited a specialized institute. Follow-up data from these municipal governments were anonymized and reported to the Ishikawa Prefecture office for assessing measures against viral hepatitis (Figure 3). However, several problems emerged with this process, including that the increase in people to follow up caused an increase in the workload of municipal public health staff, and that follow-up was not being conducted directly with people who tested positive for viral hepatitis in Kanazawa City due to the larger size of that group.

Follow-up of people who tested positive for hepatitis in Ishikawa Prefecture from 2010 onward

In 2010, the regional core center for hepatitis care coordination (Kanazawa University Hospital, the only regional core center in the prefecture) began conducting the follow-up process that was previously

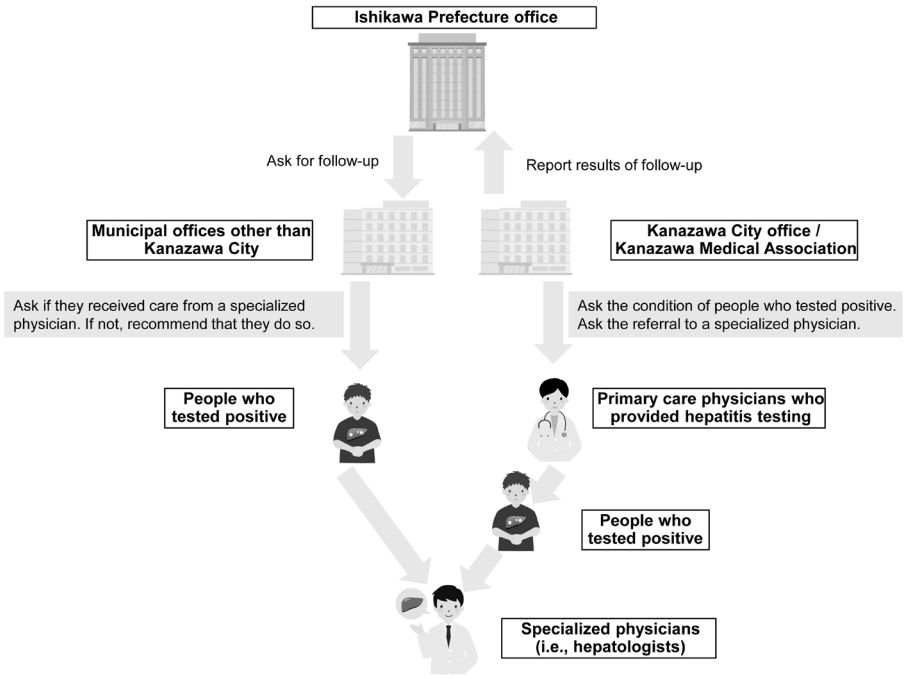

Figure 3. Schematic representation of follow-up for viral hepatitis patients since 2002.

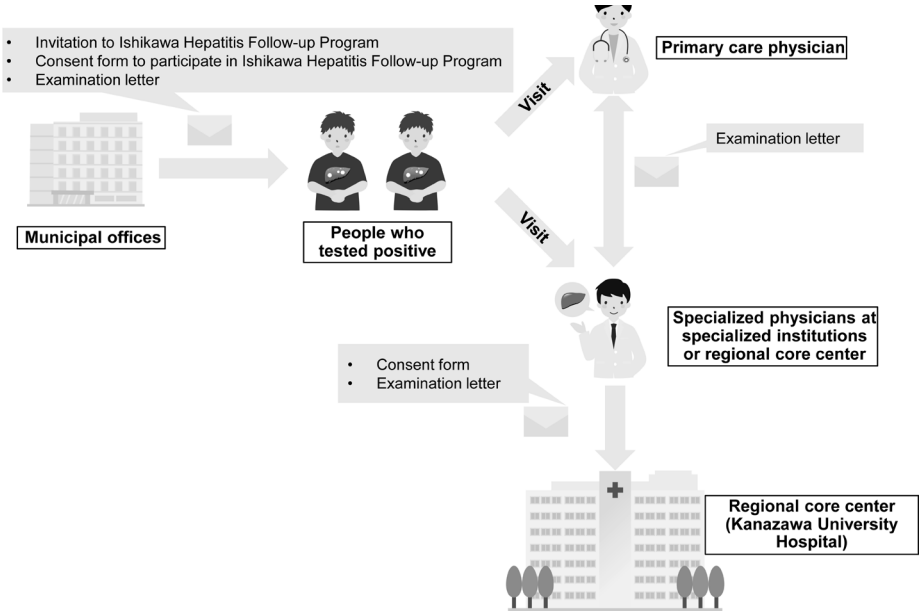

Figure 4. Schematic representation of the approval process for participation in the Ishikawa Hepatitis Follow-up Program.

the responsibility of municipal public health staff. The program, called the Ishikawa Hepatitis Follow-up Program, is run jointly by Ishikawa Prefecture, municipal governments, and the Ishikawa Medical Association. Program staff recommend that participants visit a specialized institute for hepatitis care selected by Ishikawa Prefecture (21 institutes as of April 2021) to be examined by a hepatologist and undergo liver imaging at least once a year. When this follow-up program was launched, municipal staff could not directly transfer personal information such as the names and addresses of people who tested positive for hepatitis to the regional core center due to policies about protecting personal information. However, municipal staff solved this problem by mailing people who tested positive for hepatitis a consent form to participate in the follow-up program and have their personal information shared between the regional core center and municipal government. This enabled the regional core center to send mail directly to people who tested positive for hepatitis and consented to participate in the program (Figure 4).

Every year in July, the regional core center directly mails the program participants a leaflet recommending

that they visit a specialized institute as well as an examination letter for their physician to complete with the details of their visit. The participant brings this letter with them to the specialized institute for the hepatologist they visited to record on the letter, the date of examination, diagnosis, the liver imaging tests performed, the recommendations for further testing and treatment, and the next appointment (Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=28*). If the participant initially visited a primary care physician (*i.e.*, not a hepatologist), they can use the examination letter as a referral form to visit a specialized institute. The letter is completed in triplicate, and copies are sent to the primary care physician and the regional core center. The examination letter is used to provide details of the examination at the specialized institute for the primary care physician's reference. In addition, the regional core center uses returned examination letters to confirm whether each participant visited a specialized institute, and enters data such as treatment and condition details into a database (Figure 5). After the first round of examination letters are mailed, participants whose examination letters have not been returned to the regional core center by November of that year are once again sent a leaflet recommending they visit a specialized institute along with an examination letter around December.

Initially, participation in the Ishikawa Hepatitis Follow-up Program was restricted to people who tested positive for hepatitis at local screening programs conducted as part of a national senior health promotion program or a general health promotion program. However, the program has now been extended to anyone who tests positive for hepatitis at any kind of screening, such as the specified infectious diseases screening program, a prenatal checkup, a workplace health checkup, or preoperative testing.

Current state of the Ishikawa Hepatitis Follow-up Program and issues to be resolved

At the end of 2019, 1,632 (51%) of the 3,202 people who had tested positive for hepatitis since 2002 had consented to participate in the follow-up program, 525 (16.3%) had declined to participate, and 1,045 (32.7%) did not respond. Program staffs continue to send these 1,045 people who did not respond, a leaflet encouraging their participation along with a consent form. Those who declined or did not respond are still followed annually by municipal public health staff, as they have done since 2002, and follow-up data from these municipal governments were anonymized and reported to the Ishikawa Prefecture office for assessing measures against viral hepatitis.

Only 40% to 50% of examination letters are returned to the regional core center in an average year, suggesting that only 40% to 50% of participants are making their recommended annual visit to a specialized institute. Consequently, efforts must be made to increase this percentage.

However, another method of confirming participant status besides examination letters may also be needed, given that some participants had made their visit but the specialized institute did not return their examination letter to the regional core center. In addition, the regional core center enters data from returned examination letters such as treatment and condition details into a database but can only collect limited data through these letters. As the age of this group of hepatitis patients increases, they may develop comorbidities such as dementia and

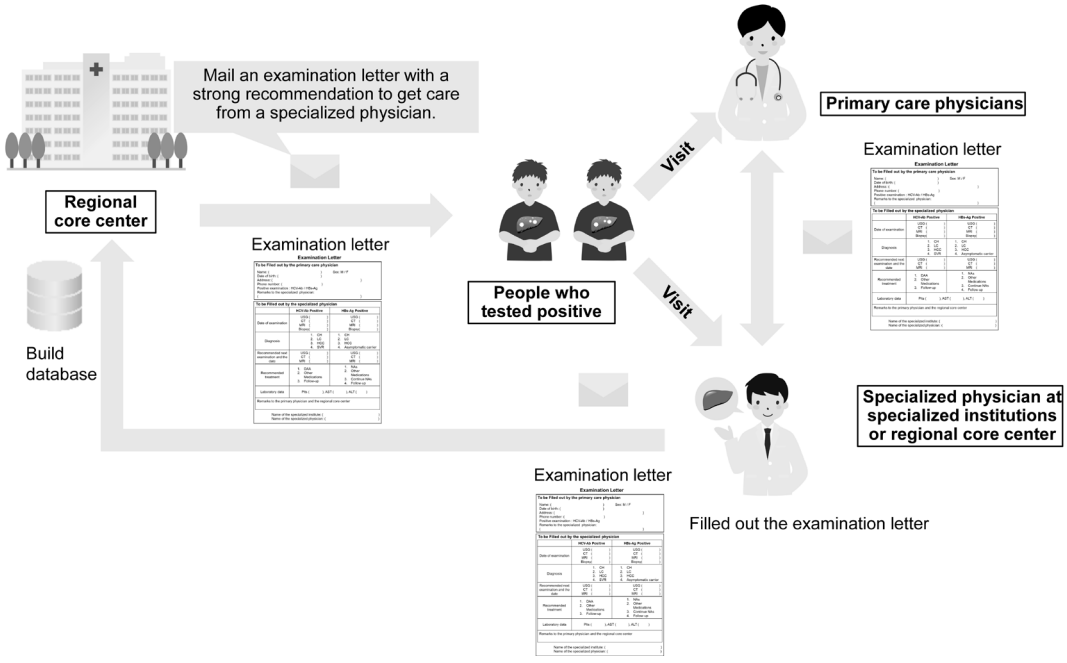

Figure 5. Schematic representation of the Ishikawa Hepatitis Follow-up Program.

cancers other than liver cancer, become more limited in their activities of daily living, or move into an elder care facility. It is important to conduct follow-up with these patients in a way that suits their individual circumstances, and this requires accurate knowledge of their health status. In addition, a review of examination letters revealed that some patients had made the effort to visit a specialized institute but had seen a physician other than a hepatologist or had not undergone annual liver imaging tests. This illustrated a problem with the system: regional core center staff had no means of notifying the physician at the specialized institute if they had suggestions regarding the participant's treatment at that institute based on the content of the examination letter.

Utilization of ICT in the Ishikawa Hepatitis Follow-up Program

Ishikawa Prefecture has been actively promoting the use of the Ishikawa Clinical Information Sharing Network, which uses ID-Link, in order to realize collaborative care by sharing clinical information among medical institutions in the prefecture. A plan was made to utilize this system in the Ishikawa Hepatitis Follow-up Program based on the idea that it might help to solve the various problems with hepatitis follow-up that had been uncovered.

ID-Link

ID-Link is a nationally standardized cloud service developed by NEC Corporation that aggregates clinical information dispersed throughout a region. It connects participating regional medical institutions over an internet connection, enabling institutions to reference each other's clinical information and to closely coordinate care. The Ishikawa Clinical Information Sharing Network is run primarily by the Ishikawa Medical Association. The institutions participating in the Ishikawa Clinical Information Sharing Network are broadly classified into "information-sharing hospitals" (with 32 institutions as of May 2021) and "information-viewing institutions" such as primary care physicians, pharmacies, home nursing stations, and dentists' offices (with 566 institutions as of May 2021). The "sharing" institutions have servers allowing them to share clinical information specified by each institution such as images, blood test results, and prescriptions. The "viewing" institutions are authorized to view information only for the purpose of providing care.

All 21 specialized institutes in Ishikawa Prefecture participate in the Ishikawa Clinical Information Sharing Network and are classified as information-sharing hospitals authorized to share clinical information with other hospitals. To participate in the Ishikawa Clinical Information Sharing Network, the patients must submit the names of the institutions with which they wish to share clinical information and the ID numbers of each institution and then sign the designated consent form. The service is free for patients and the system allows the sharing of clinical information only for patients who have ID numbers at both institutions between which clinical information will be shared (in this case, the regional core center and a specialized institute). In other words, they must have previously visited both the regional core center and a specialized institute (Figure 6). At the end of 2017, only 312 of the 1,358 participants in the Ishikawa Hepatitis Follow-up Program had an ID at both the regional core center

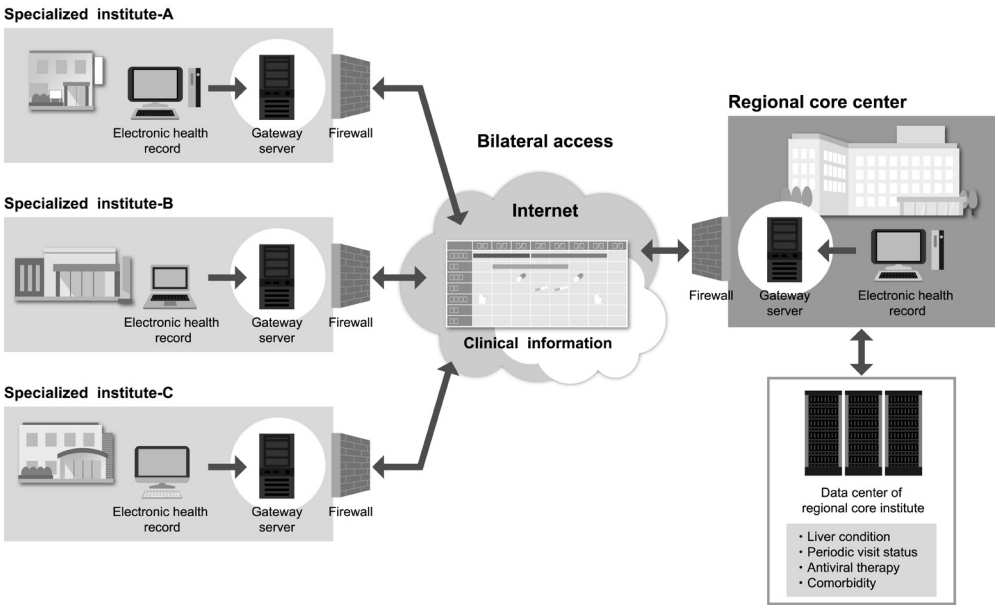

Figure 6. Schematic representation of the use of ID-Link in the Ishikawa Hepatitis Follow-up Program.

and any of the 21 specialized institutes. These 312 people were asked for their consent to participate in the Ishikawa Clinical Information Sharing Network. When the decision was made to use ID-Link for the Ishikawa Hepatitis Follow-up Program, agreements were reached and the implementation process was coordinated in advance between stakeholders, including the prefectural government, the Ishikawa Medical Association, and specialized institutes.

Current sharing of clinical information through ID-Link

In November 2018, the Ishikawa Hepatitis Follow-up Program began obtaining consent from program participants to participate in the Ishikawa Clinical Information Sharing Network to enable sharing of clinical information between specialized institutes and the regional core center. As of the end of March 2021, information about 132 patients of 18 specialized institutes is being shared between these institutes and the regional core center.

Benefits of sharing of clinical information through ID-Link

There were 57 examination letters returned to the regional core center by the end of November 2020 from the 131 patients who consented to participate in the Ishikawa Clinical Information Sharing Network using ID-Link up to June 2020 (a 43.5% response rate). When the statuses of the 74 individuals whose examination letters had not been returned were checked using ID-Link, it was found that 62 had indeed visited a specialized institute after April 2020. These results show that a total of 119 participants (90.8%), comprising the 57 whose status was verified by their examination letter and the 62 whose status was verified by ID-Link, had visited a specialized institute (Figure 7). In addition, 5 of these 62 patients had visited a specialized institute but did not see a hepatologist.

By referencing both ID-Link and examination letters, it was determined that 119 of 131, or about 90% of patients, had visited a specialized institute in 2020. Although there were still 12 patients who had not visited a specialized institute, this number is much smaller than the 62 counted from examination letters alone. Referencing both ID-Link and examination letters enabled a more accurate counting of patients who had not visited a specialized institute, which should facilitate more focused and efficient efforts to encourage visits.

Challenges and future outlook of sharing clinical information through ID-Link

At present, only patients who have ID numbers at both the regional core center and a specialized institute can use this system. However, about 75% of participants in the Ishikawa Hepatitis Follow-up Program do not have an ID at the regional core center, so their clinical information cannot be shared with the regional core center. Going forward, a strategy must be devised to ensure that the clinical information of patients who do not have an ID at the regional core center can be shared

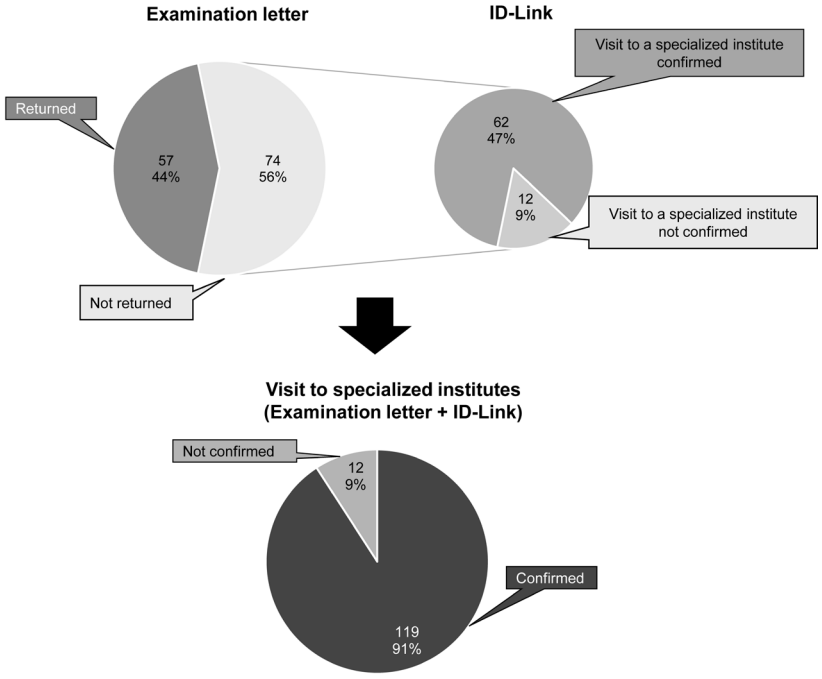

Figure 7. Comparison of data collection by examination letter and ID-Link.

with the regional core center.

When patient status was verified by ID-Link, it was discovered that some patients had not been seen by a hepatologist or gastroenterologist, even though they visited a specialized institute. Efforts must be made to allow regional core center staff to provide feedback on information sent by specialized institutes and request coordination between departments at the specialized institute.

The program is currently using ID-Link to share clinical information only between specialized institutes and the regional core center, but many primary care physicians also have information-viewing authorization on ID-Link. Going forward, the program will work to promote the use of ID-Link by not only the regional core center and specialized institutes but also by primary care physicians.

Recently, the Extension for Community Healthcare Outcomes (ECHO) Model was developed by the University of New Mexico Health Sciences Center as a platform to deliver complex specialty medical care to underserved populations through an innovative educational model of team-based interdisciplinary development. By using state-of-the-art multipoint telehealth technology and clinical management tools, ECHO trains and supports primary care providers to develop knowledge and self-efficacy on a variety of diseases. Now, the ECHO model is reported to enhance the competency of community-based based physicians to deliver optimal care to patients with HCV infection (*6*-*8*). While we have been using ID-Link mainly for collecting accurate clinical information of the participants and confirming the participants' periodic visit to specialized institutes, we would like to use ID-Link for encouraging introduction of anti-HCV therapy and continuous care after HCV elimination.

Conclusion

The use of ICT provided a more accurate picture of which participants had visited a specialized institute compared with the previous paper-based method involving examination letters. Sharing clinical information via ICT should improve the efficiency of follow-ups with hepatitis patients and allow for multiple physicians to collaborate in these patients' care. Going forward, individual regions will likely adopt various forms of ICT to promote coordination between hospitals. When doing so, they should actively consider using ICT to support viral hepatitis patients as well.

Funding: This work was supported by the Ministry of Health, Labour and Welfare Policy Research for Hepatitis Measures Program (grant numbers JPMH18HC1001 and JPMH21HC1001).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Tanaka J, Akita T, Ko K, Miura Y, Satake M; Epidemiological Research Group on Viral Hepatitis and its Long-term Course, Ministry of Health, Labour and Welfare of Japan. Countermeasures against viral hepatitis B and C in Japan: An epidemiological point of view. Hepatol Res. 2019; 49:990-1002.
2. Tanaka J, Akita T, Ohisa M, Sakamune K, Ko K, Uchida S, Satake M. Trends in the total numbers of HBV and HCV carriers in Japan from 2000 to 2011. J Viral Hepat. 2018; 25:363-372.
3. Cancer Statistics. Cancer Information Service, National Cancer Center, Japan (Vital Statistics of Japan, Ministry of Health, Labour and Welfare). *https://gdb.ganjoho.jp/graph_db/gdb1* (accessed June 24, 2021)
4. Oza N, Isoda H, Ono T, Kanto T. Current activities and future directions of comprehensive hepatitis control measures in Japan: The supportive role of the Hepatitis Information Center in building a solid foundation. Hepatol Res. 2017; 47:487-496.
5. Kanto T, Yoshio S. Hepatitis action plan and changing trend of liver disease in Japan: viral hepatitis and nonalcoholic fatty liver disease. Euroasian J Hepatogastroenterol. 2017; 7:60-64
6. Arora S, Kalishman S, Thornton K, *et al.* Expanding access to hepatitis C virus treatment – Extension for Community Healthcare Outcomes (ECHO) project: disruptive innovation in specialty care. Hepatology. 2010; 52:1124-1133.
7. Arora S, Thornton K, Murata G, Deming P, Kalishman S, Dion D, Parish B, Burke T, Pak W, Dunkelberg J, Kistin M, Brown J, Jenkusky S, Komaromy M, Qualls C. Outcomes of treatment for hepatitis C virus infection by primary care providers. N Engl J Med. 2011; 364:2199-2207.
8. Ni Cheallaigh C, O'Leary A, Keating S, Singleton A, Heffernan S, Keenan E, Robson L, Sears J, Moloney J, Arora S, Bergin C, Norris S; Irish Hepatitis C Outcomes Research Network. Telementoring with project ECHO: a pilot study in Europe. BMJ Innov. 2017; 3:144-151.

Received May 28, 2021; Revised June 27, 2021; Accepted July 27, 2021.

Released online in J-STAGE as advance publication September 5, 2021.

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Global Health & Medicine. 2021; 3(5):321-334.
DOI: 10.35772/ghm.2021.01083

REVIEW

Treatment progress and expansion in Japan: From interferon to direct-acting antiviral

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Abstract: Hepatitis C virus (HCV) was first discovered in 1989, and patients infected with HCV were initially treated with interferon (IFN) monotherapy. In the 2000s, pegylated IFN combined with ribavirin was the mainstay of therapy for infected patients, but the sustained virologic response (SVR) rate was less than 50% for patients with HCV genotype 1. To further improve the therapeutic effect, direct-acting antiviral (DAA) was developed, and combination therapy with DAA and IFN has been available since 2011. In addition, IFN-free DAA therapy became available in 2014, and SVR was achieved in more than 95% of patients with chronic hepatitis and compensated cirrhosis. Thus, in just 30 years since the discovery of HCV, we aim to eliminate HCV in almost all patients. However, there are remaining issues to be addressed. Many of the patients who achieved SVR with DAA therapy had advanced liver fibrosis, and it is necessary to verify to what extent DAA therapy improves their prognosis in terms of liver function, hepatocellular carcinoma occurrence, and mortality. Resistance-associated substitutions can cause failure of DAA therapy, and the search for an effective therapy for high-level resistant viruses such as P32 deletion is particularly important. DAA therapy was approved for use in patients with decompensated cirrhosis in Japan in 2019, which is an unmet need so far. It is also important to verify the efficacy and safety in real-world settings. The World Health Organization aims to eliminate HCV by 2030, and Japan must tackle its remaining issues to achieve this goal.

***Keywords*:** hepatitis C virus, interferon, direct-acting antiviral, elimination

Introduction

Hepatitis C virus (HCV) was discovered in 1989 (*1*), with more than 90% of patients previously diagnosed with non-A and non-B hepatitis having HCV infection. Once HCV infection is established, approximately 30% of patients are cured during the acute infection stage, while approximately 70% remain infected with HCV, leading to chronic hepatitis C. In patients with chronic hepatitis C, spontaneous elimination of HCV is rare (annual rate of approximately 0.2%), and persistent inflammation caused by HCV infection induces liver fibrosis, which progresses to cirrhosis and hepatocellular carcinoma (HCC) (*2*). Antiviral therapy has been administered to reduce the progression of liver pathologies.

Initially, interferon (IFN) therapy was administered as antiviral therapy, but the therapeutic effect was unsatisfactory. Thereafter, the structure of viral protein which is essential for HCV replication was elucidated, and a culture system for HCV replication was created, leading to the development of direct-acting antivirals (DAAs). DAA was initially administered in combination with and greatly improved the therapeutic effect of IFN, but problems such as IFN intolerance persisted. IFN-free DAA therapy has been available since 2014, and has enabled us to eliminate HCV safely and at a high rate in elderly patients and patients with cirrhosis, who were difficult to treat in the IFN era. In addition, since February 2019, DAA therapy has been available for patients with decompensated cirrhosis, and it is now possible to consider the indication for DAA therapy in all HCV patients. However, new problems have emerged. Since many patients with cirrhosis are included in those who achieved sustained virologic response (SVR) with DAA therapy, it is necessary to verify the degree of improvement in liver fibrosis, suppression of HCC occurrence, and improvement in mortality. Furthermore, there are issues that need to be clarified, such as the problem of resistance-associated substitutions (RASs) in patients for whom previous DAA therapy failed. Real-world data on the efficacy and safety of DAA therapy in patients with decompensated cirrhosis also requires clarification. This review article describes the progress and the remaining issues of HCV therapy in Japan.

Changes in antiviral therapy for HCV

IFN-based therapy

The beginning of IFN therapy

IFN therapy for patients with HCV began in 1986, when Hoonfnagle *et al.* reported that elevated serum aminotransferase levels in patients with chronic non-A and non-B hepatitis decreased after administration of recombinant human interferon-alpha (*3*). Thereafter, with the development of a highly sensitive polymerase chain reaction technique, serum HCV-RNA was found to be undetectable in patients whose serum aminotransferase levels were improved by IFN therapy (*4*). Thus, the antiviral and anti-inflammatory effects of IFN therapy for patients with HCV were confirmed, and the clinical use of IFN therapy for patients with HCV was approved in Japan in 1992.

IFN monotherapy

Therapeutic effects of IFN were classified into four types: SVR (serum HCV-RNA undetectable at 24 weeks after the cessation of therapy), relapse (serum HCV-RNA undetectable during the therapy but detectable after the cessation of therapy), breakthrough (serum HCV-RNA detectable during therapy after once being undetectable), and nonresponse (serum HCV-RNA detectable throughout the course of antiviral therapy). The SVR rate of IFN monotherapy has been reported to vary depending on the viral genotype and load (*5,6*). Namely, patients with HCV genotype 1 have been shown to be more resistant to IFN monotherapy than those with HCV genotype 2, and patients with a high viral load are less responsive than those with a low viral load. Of the patients with HCV genotype 1 (which accounts for approximately 70% of Japanese HCV patients), those with a high viral load are particularly difficult to treat, and the SVR rate of IFN monotherapy for these patients was approximately 5% (*7*).

Various efforts have been made to improve the limited therapeutic effect of IFN monotherapy, especially in patients with HCV genotype 1 (Figure 1). Kasahara *et al.* reported that the SVR rate in patients with HCV genotype 1 who received IFN therapy for 12 months was higher than that of those who received IFN therapy for 6 months (*8*). The meta-analysis also showed the superiority of IFN therapy for 12 months over that for 6 months (*9*). Based on these results, long-term IFN administration became available in Japan in 2002. In addition, self-injection of IFN was approved in 2005, and long-term IFN administration has become widely used in clinical practice.

Development of Peg-IFN

Pegylated interferon (Peg-IFN) is an IFN to which polyethylene glycol has been added, and the advent of Peg-IFN has brought dramatic advances in IFN therapy. Pegylation is performed to delay drug elimination, reduce immunogenicity and regulate the effects of the drug. Conventional IFN has a short half-life and needs to be administered three times a week. Since Peg-IFN has a slower drug clearance rate and a longer half-life than conventional IFN, it makes it possible to maintain an effective blood concentration with once-weekly administration. Another advantage is that it has milder adverse effects than conventional IFN, including flu-like symptoms such as fever, joint pain, and fatigue.

Combination therapy with ribavirin

Development of ribavirin

Ribavirin (RBV), which was developed in 1972, is an oral nucleic acid analog with broad antiviral activity against RNA and DNA viruses. RBV monotherapy did

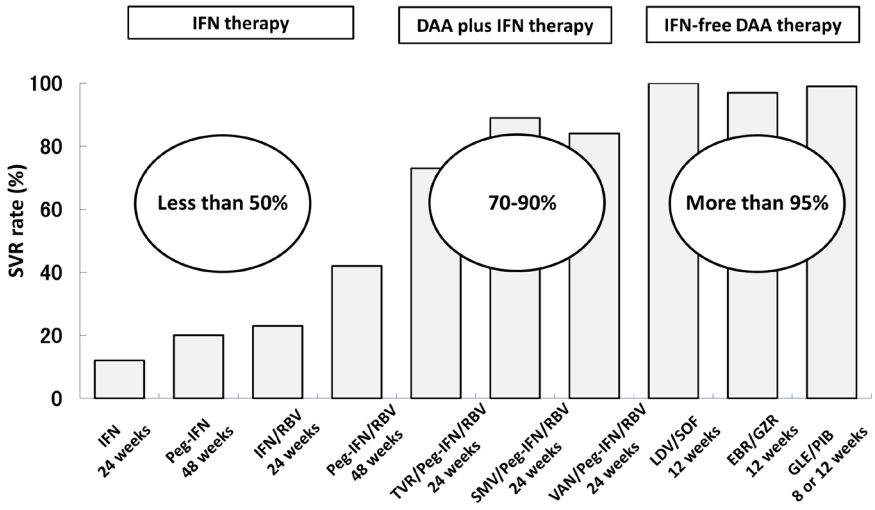

Figure 1. Changes in HCV therapy for patients with genotype 1. Abbreviations: DAA, direct-acting antiviral; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; IFN, interferon; LDV, ledipasvir; Peg-IFN, pegylated interferon; PIB, pibrentasvir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; TVR, telaprevir; VAN, vaniprevir.

not show antiviral effects against HCV (*10*); however, several studies reported that IFN and RBV combination therapy was more effective than IFN monotherapy for patients with HCV (*11-13*). In 2001, IFN and RBV combination therapy was approved in Japan. Although the exact antiviral mechanism of RBV is unknown, the possible mechanisms include immune induction from Th2 to Th1, reduction of glutamyl transpeptidase pool in hepatocytes, inhibition of HCV-RNA polymerase activity, and induction of HCV mutation (*14*). The adverse effects of RBV include hemolytic anemia and therefore, caution is needed when administering it to patients with coexisting anemia or cardiac disease. Since RBV is excreted by the kidney and is not removed by dialysis, it is contraindicated in patients with renal impairment and dialysis. Ochi *et al.* reported that single nucleotide polymorphisms (SNPs) near the gene inosinetriphosphatase (ITPA) on chromosome 20 were strongly associated with hemolytic anemia during Peg-IFN and RBV combination therapy (*15*).

Peg-IFN and RBV combination therapy

Large-scale clinical studies of Peg-IFN and RBV combination therapy from Europe and the United States reported that SVR rates in patients with HCV genotype 1 ranged from 42% to 52% (48 weeks administration) and that in patients with HCV genotype 2 or 3 ranged from 81% to 84% (24 weeks administration); moreover, they showed favorable therapeutic effects (*16,17*). In Japan, Peg-IFN and RBV combination therapy was approved in 2004. Peg-IFN and RBV combination therapy for 48 weeks in patients with HCV genotype 1 and for 24 weeks in patients with HCV genotype 2 had SVR rates of 40-50% and 80%, respectively (*7*).

Factors associated with therapeutic effect of Peg-IFN and RBV combination therapy

Peg-IFN and RBV combination therapy for 48 weeks for patients with HCV genotype 1 and for 24 weeks for patients with HCV genotype 2 or 3 became standard care and was widely used in clinical practice. Thereafter, with the accumulation of real-world data, various studies investigating the factors associated with the therapeutic effects of IFN-based therapy have been published. The following are reports addressing patients with HCV genotype 1, which is difficult to treat.

Host factors

Host factors such as age, sex and race have traditionally been reported to be associated with the therapeutic effects of Peg-IFN and RBV combination therapy. Younger, males and Asian patients show higher therapeutic effects, and older, females and African-American patients show lower therapeutic effects. On the other hand, associations between therapeutic effects and genetic polymorphisms have also been reported. Tanaka *et al.* reported that SNPs near the gene interleukin (IL) 28B on chromosome 19 were strongly associated with the effect of Peg-IFN and RBV combination therapy in 2009 (*18*). Patients with a minor allele of rs8099917, the G allele, showed resistance to Peg-IFN and RBV combination therapy.

Viral factors

As for viral factors that contribute to the therapeutic effect, amino acid sequence mutations in the nonstructural protein (NS) 5A and HCV core regions have been reported. Enomoto *et al.* reported that the number of amino acid mutations in NS5A is significantly associated with the response to IFN therapy (*19*). Since an increase in the number of mutations in the region that spans amino acid residues 2209 to 2248 of NS5A affected the effect of IFN monotherapy, they named this region the interferon sensitivity determining region.

El-Shamy *et al.* reported that the number of mutations in the variable region 3 (V3, amino acids 2356 to 2379) and pre V3 (amino acids 2334 to 2355) of NS5A were associated with IFN and RBV combination therapy, and they named this region IFN/RBV resistance-determining region (IRRDR) (*20*). Patients with six or more mutations in IRRDR showed a better response to Peg-IFN and RBV combination therapy compared to those with five or fewer mutations in IRRDR.

Akuta *et al.* reported that the SVR rate of Peg-IFN and RBV combination therapy in patients with substitutions of amino acids 70 and/or 91 in the HCV core region was lower than that in patients with double wild type in the core region (*21*).

These host and viral factors could be used to predict therapeutic effects before starting antiviral therapy and are useful for identifying patients who are likely and unlikely to respond to antiviral therapy.

Drug dose and treatment response

McHutchison *et al.* reported that patients who were able to maintain at least 80% of the scheduled dose of IFN or Peg-IFN and RBV combination therapy were more likely to achieve SVR (*22*). Thereafter, various studies investigating the relationship between drug adherence and the therapeutic effects of Peg-IFN and RBV have been reported.

In Peg-IFN and RBV combination therapy, the timing of HCV-RNA negativity was associated with SVR. Oze *et al.* reported that the dose of Peg-IFN was associated with complete early virologic response (c-EVR) defined as HCV-RNA negativity at week 12 of therapy (*23*). Hiramatsu *et al.* reported that the dose of RBV was associated with relapse after 48 weeks of Peg-IFN and RBV combination therapy (*24*). Maintaining a high dose of Peg-IFN and RBV as long as possible may lead to higher SVR rates.

In patients who did not achieve c-EVR, the SVR rate was very low even after 48 weeks of Peg-IFN and RBV combination therapy. Berg *et al.* and Pearlman *et al.* reported that 72 weeks of Peg-IFN and RBV combination therapy improved the SVR rate in patients with late virologic response, defined as HCV-RNA detectable at week 12 and undetectable at week 24, compared to 48 weeks of Peg-IFN and RBV combination therapy (*25,26*). Based on these results, response-guided therapy was administered.

Advent of DAA

Peg-IFN and RBV combination therapy was revolutionary; however, the SVR rate is approximately 50%, especially in difficult to treat patients with HCV genotype 1 and high viral load; the therapeutic effect of this regimen was not sufficient. Therefore, the development of DAAs, which directly inhibit the replication and proliferation of HCV, was promoted to improve the therapeutic effect. Among the NS protein regions of HCV, the NS3/4A, NS5A, and NS5B regions were the main targets for drug development (*27*), and DAAs were divided into three types: NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors (Figure 2). The establishment of an in vitro cell culture system for viral replication and viral lifecycle contributed largely to the development of DAA (*28*).

DAA and IFN combination therapy

DAA monotherapy is prone to viral mutations, and combination therapy with IFN is initially administered. Among the DAA, the NS3/4A protease inhibitor was the first to be developed. In Japan, the first-wave, first-generation NS3/4A protease inhibitor, telaprevir (TVR), for 12 weeks plus Peg-IFN and RBV combination therapy for 24 weeks was first developed. Although serious skin disorders including Stevens-Johnson syndrome, drug rashes, and serious anemia were more frequently observed in patients who were treated with TVR plus Peg-IFN and RBV combination therapy than in those who were treated with Peg-IFN and RBV combination therapy, SVR rates in treatment-naïve patients, relapsers and non-responders to previous therapy were 73%, 88% and 34%, respectively, and good therapeutic effects were observed (*29,30*). Based on these results, TVR plus Peg-IFN and RBV combination therapy was approved in Japan in 2011.

The next step in development was the second-wave, first-generation NS3/4A protease inhibitor, simeprevir (SMV) for 12 weeks plus Peg-IFN and RBV combination therapy for 24 weeks. SVR rates in treatment-naïve patients, relapsers and non-responders to previous therapy were 89%, 96% and 53%, respectively, and good therapeutic effects were observed (*31,32*). Based on these results, SMV plus Peg-IFN and RBV combination therapy was approved in Japan in 2013. Regarding the profile of adverse events, the frequency of hemoglobin decrease and drug eruption did not differ between patients who were treated with SMV plus Peg-IFN and RBV combination therapy and those who were treated with Peg-IFN and RBV combination therapy, but transient bilirubin increase after 1-2 weeks of therapy was more frequently observed in patients who were treated with SMV plus Peg-IFN and RBV combination therapy (*33*). Tahata *et al.* reported that the ITPA genotype was associated with hyperbilirubinemia during SMV plus Peg-IFN and RBV combination therapy (*34*).

Next came the second-wave, first-generation NS3/4A

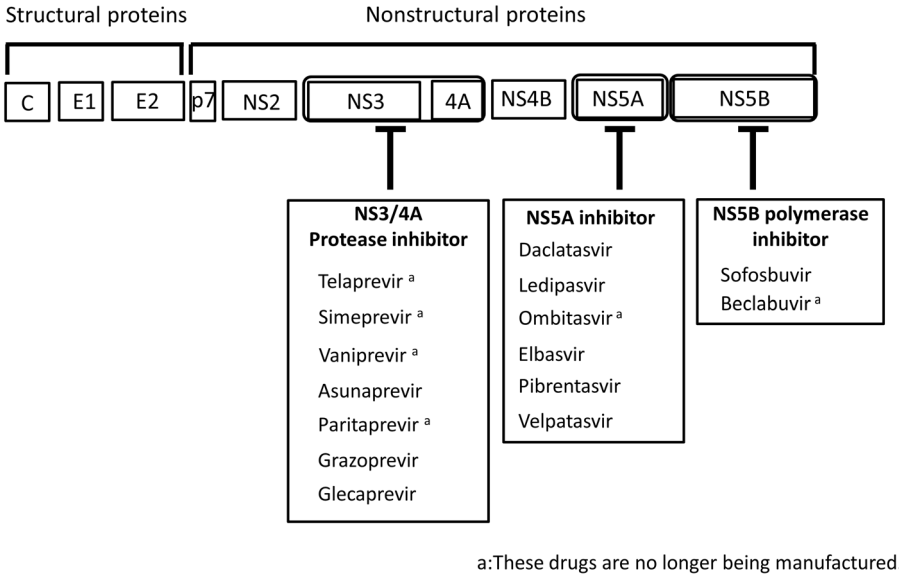

Figure 2. The structure of HCV and the action point of DAA. Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus; NS, nonstructural.

protease inhibitor, vaniprevir (VAN), for 12 weeks plus Peg-IFN and RBV combination therapy for 24 weeks was developed. SVR rates for treatment-naïve patients and relapsers to previous therapy were 84% and 92%, respectively, and the profile of adverse events in patients who were treated with this combination was comparable to those who were treated with Peg-IFN and RBV combination (*35,36*). In this triple therapy, patients with partial (detectable but decreased by more than 2 $\log_{10}$ in HCV-RNA after 12 weeks of therapy) or null response (detectable and decreased by less than 2 $\log_{10}$ in HCV-RNA after 12 weeks of therapy) to previous therapy were treated with VAN plus Peg-IFN and RBV combination therapy for 24 weeks. SVR rates were 62% in patients with partial or null responses to previous therapy and 55% in patients only with a null response to previous therapy (*36*).

IFN-free DAA therapy

The aforementioned NS3/4A protease inhibitor plus Peg-IFN and RBV combination therapy showed a high therapeutic effect, but had some problems; these triple therapies were not sufficiently effective for patients such as the elderly or those with poor response to IFN therapy, who had difficulty receiving IFN therapy due to adverse effects. In addition, patients with cirrhosis were not eligible for this therapy because of concerns about hepatotoxicity due to the combination of NS3/4A protease inhibitor plus IFN. Following the development of NS 3/4A protease inhibitors, drugs that inhibit the function of NS5A or NS5B proteins have been developed, and combination therapy with multiple DAAs targeting different proteins is now being used.

In Japan, combination therapy with daclatasvir (DCV, NS5A inhibitor) and asunaprevir (ASV, the second-wave, first-generation NS3/4A inhibitor), was the first to be available for clinical use in patients with HCV genotype 1. In a phase 3 study of DCV plus ASV therapy for 24 weeks, SVR rates were 87% in patients with IFN-ineligibility and intolerance, 81% in patients with non-responder to previous IFN-based therapy, and 91% in patients with cirrhosis (*37*). Favorable therapeutic effects were observed, and DCV plus ASV therapy for 24 weeks was approved in Japan in 2014. However, the SVR rate was approximately 40% in patients with NS5A L31 and/or Y93 RASs. Therefore, it was strongly recommended that NS5A RAS be investigated before starting DCV plus ASV therapy and not to use this regimen in patients with NS5A RAS.

In Europe and the United States, several phase 3 studies have shown the efficacy and safety of sofosbuvir (SOF, nucleotide polymerase inhibitor of NS5B), plus RBV therapy for patients with HCV genotype 2, 3 (*38-40*), and SOF plus ledipasvir (LDV, NS5A inhibitor), therapy for those with HCV genotype 1 (*41,42*). SOF plus RBV therapy for patients with HCV genotype 2 and 3 was approved in 2013, and SOF plus LDV therapy for patients with HCV genotype 1 was approved in 2014. In Japan, a phase 3 study of SOF plus RBV therapy for patients with HCV genotype 2 showed that the overall SVR rate was 97% and that 98% of treatment-naïve patients and 95% of previously treated patients achieved SVR (*43*). A phase 3 study of SOF plus LDV therapy for patients with HCV genotype 1 showed 100% SVR regardless of the presence or absence of cirrhosis, previous history of antiviral therapy, or IL28B genotype (*44*). Based on these results, SOF plus RBV therapy for patients with HCV genotype 2 and SOF plus LDV therapy for patients with HCV genotype 1 were approved in 2015. In real-world data of SOF plus RBV therapy for patients with HCV genotype 2, SVR rates ranged from 94% to 97%, which was equivalent to a phase 3 study (*45-47*). Because this regimen included RBV, a decrease in hemoglobin was observed during therapy, and the ITPA genotype was reported to be associated with this decrease in hemoglobin levels (*45,46*). Since the SVR rate was 100% in a phase 3 study of SOF plus LDV therapy, drug development for patients with HCV genotype 1 seemed to be solved. However, in real-world data of SOF plus LDV therapy for patients with HCV genotype 1, SVR rates ranged from 96% to 99% (*48-50*), which is slightly lower than the SVR rates in the phase 3 study. Some studies have reported that baseline NS5A RASs are involved in attenuating therapeutic effects (*48,49*). In another study, Akuta *et al.* reported that the SVR rate of SOF plus LDV therapy for patients in whom therapy with DCV plus ASV failed, was 71% (*51*). Developing effective DAAs for patients (particularly, those with HCV genotype 1) with RASs due to failed DAA therapy was desired. On the other hand, for patients with HCV genotype 2, a phase 3 study of SOF plus LDV therapy was conducted, with SOF plus RBV therapy as the control group (*52*). SVR rates were 96% in SOF plus LDV therapy and 95% in SOF plus RBV therapy, and SOF plus LDV therapy proved to be non-inferior to SOF plus RBV therapy. Regarding safety, few patients experienced grade 3 or 4 adverse effects in both groups, although anemia was more frequently observed in patients treated with SOF plus RBV than in those treated with SOF plus LDV. Based on these results, SOF plus LDV therapy for patients with HCV genotype 2 was approved in Japan in 2018. SOF plus LDV therapy for 12 weeks has become one of the first-line therapies for patients with HCV genotype 1 and 2; SOF plus RBV therapy for 12 weeks has become one of the first-line therapies for patients with HCV genotype 2 (*53*). Doi *et al.* reported that hepatitis B virus (HBV) reactivation was observed in 3.4% of HCV patients who are seropositive for the HBV core antibody during SOF-based therapy (*54*). Takayama *et al.* reported a case of HBV/HCV coinfection in a patient who experienced HBV reactivation during therapy with DCV plus ASV (*55*). The Japanese guidelines state that

careful monitoring of HBV reactivation during DAA therapy is necessary for patients with HBV coinfection or with a history of HBV infection (*53*).

The next DAA to be developed in Japan was ombitasvir (OBV, NS5A inhibitor) plus paritaprevir (PTV, second-wave, first-generation NS3/4A protease inhibitor that is administered with low-dose ritonavir (r) to improve the activity of PTV) for 12 weeks for patients with HCV genotype 1. A Japanese phase 3 study showed that SVR rates ranged from 94.9% (for patients without cirrhosis) to 90.5% (for patients with cirrhosis) (*56*). The aforementioned SOF is mainly excreted by the kidney and is not removed by dialysis, and it is contraindicated in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] less than 30 mL/min/1.73m^2) and those on dialysis. On the other hand, OBV plus PTV/r is mainly metabolized in the liver and excreted in the feces, and it can be used for patients with severe renal impairment and those on dialysis. Japanese real-world data showed that the SVR rate of OBV plus PTV/r therapy for patients on dialysis was 97%. A good therapeutic effect was observed in them (57). This regimen was approved in 2015, but was discontinued in 2018.

Next, elbasvir, (EBR, NS5A inhibitor) plus grazoprevir, (GZR, second-generation NS3/4A protease inhibitor) therapy for 12 weeks for patients with HCV genotype 1 was developed in Japan. A Japanese phase 2/3 study showed that SVR rates were 96.5% in patients without liver cirrhosis and 97.1% in patients with cirrhosis (*58*). As for the influence of baseline NS3 or NS5A RASs on SVR, SVR rates were 100% and 96.8% in patients with and without NS3 RASs and 93.1% and 98.9% in patients with and without NS5A RASs, respectively; and preferable therapeutic effects were observed in patients with NS3 or NS5A RASs. Although patients with a creatinine clearance rate of < 50 mL/min were excluded from the Japanese phase 2/3 study, real-world data on patients undergoing dialysis reported that all patients completed EBR plus GZR therapy and that the SVR rate was 96.7% (*59*). EBR plus GZR therapy for 12 weeks was approved in Japan in 2016 and has become one of the first-line therapies for patients with HCV genotype 1 (*53*).

The next DAAs to be developed in Japan were the first triple combination therapy with DCV plus ASV plus beclabuvir, (BCV, non-nucleoside polymerase inhibitor of NS5B) for 12 weeks. A Japanese phase 3 study showed that the SVR rate was 96%, which was comparable in subgroup analyses of age, sex, IL28B genotype, and the presence or absence of cirrhosis (*60*). BCV is a non-nucleoside polymerase inhibitor of NS5B, and SOF is a nucleotide polymerase inhibitor of NS5B. While SOF is incorporated into viral genes and inhibits RNA replication, BCV binds NS5B polymerase protein and inhibits its enzymatic activity. This triple therapy was approved in 2016 but was discontinued in 2018. As another triple DAA combination therapy, adafosbuvir (nucleotide polymerase inhibitor of NS5B) plus odalasvir (NS5A inhibitor) plus SMV (NS3/4A protease inhibitor), was being tested in clinical trials (*61*). SVR rates of this regimen for 8 weeks in patients with chronic hepatitis and for 12 weeks in those with cirrhosis were both 100%; however, this regimen was never used clinically.

Next, glecaprevir, (GLE, second-generation NS3/4A protease inhibitor) plus pibrentasvir (PIB, NS5A inhibitor) therapy was developed in Japan. For patients with HCV genotype 1 (without cirrhosis), a phase 3 study of GLE plus PIB therapy for 8 weeks was conducted, with OBV plus PTV/r therapy for 12 weeks as the control group (*62*). In this study, all patients with HCV genotype 1 and cirrhosis were treated with GLE plus PIB for 12 weeks. SVR rates were 99.1%, 100% and 100% in GLE plus PIB therapy for 8 weeks, OBV plus PTV/r therapy for 12 weeks, and GLE plus PIB therapy for 12 weeks, respectively. For patients with HCV genotype 2 and without cirrhosis, a phase 3 study of GLE plus PIB therapy for 8 weeks was conducted, with SOF plus RBV therapy for 12 weeks as the control group (*63*). In this study, all patients with HCV genotype 2 and cirrhosis were treated with GLE plus PIB for 12 weeks. SVR rates were 97.6%, 93.5% and 100% in GLE plus PIB therapy for 8 weeks, SOF plus RBV therapy for 12 weeks, and GLE plus PIB therapy for 12 weeks, respectively. As for difficult to treat patients, three groups were established in a phase 3 study: patients with HCV genotype 1 or 2 and failure to previous DAA therapy, patients with HCV genotype 1 or 2 and renal impairment (eGFR less than 30 mL/min/1.73m^2), and patients with HCV genotype 3 (*64*). DAA-naïve patients with HCV genotype 1 or 2, renal impairment, and without cirrhosis were treated with GLE plus PIB for 8 weeks; all other patients were treated for 12 weeks. SVR rates were 93.9%, 100% and 83.3% in patients with HCV genotype 1 or 2 in whom previous DAA therapy failed, in those with renal impairment, and in patients with HCV genotype 3, respectively. Based on these results, GLE plus PIB therapy was approved in Japan in 2017; and GLE plus PIB therapy for 8 weeks became one of the first-line therapies for DAA-naïve patients with HCV genotype 1 or 2 without cirrhosis, and GLE plus PIB therapy for 12 weeks became one of the first-line therapies for patients with cirrhosis, failure to respond to previous DAA therapy, and HCV genotype 3 (*53*). GLE plus PIB therapy shortened the therapeutic period from 12 weeks to 8 weeks for patients with HCV genotype 1 or 2, those who were DAA-naïve, and without cirrhosis. Although GLE plus PIB therapy had a high SVR rate and good tolerability regardless of HCV genotype, renal impairment, or the presence of cirrhosis, it was not a panacea. Of 33 patients who failed to respond to previous DAA therapy and who were treated with GLE plus PIB, two experienced virologic failures.

Both patients were previously treated with DCV plus ASV and had NS5A P32 deletion at baseline. Research on effective therapies for NS5A 32 deletion has become a new challenge.

Next, SOF plus velpatasvir, (VEL, NS5A inhibitor) therapy was developed in Japan. Two phase 3 studies were conducted; one targeting patients with failure to respond to previous DAA therapy and the other targeting patients with decompensated cirrhosis. For the former study group, SOF plus VEL plus RBV therapy was administered for 12 weeks or 24 weeks (*65*). SVR rates were 85% for 12 weeks administration and 98% for 24 weeks administration in patients with HCV genotype 1; they were 70% for 12 weeks and 92% for 24 weeks in patients with HCV genotype 2. For patients with NS5A RASs at baseline, SVR rates were 85% and 96% after 12 and 24 weeks, respectively. On the other hand, for patients with NS5A P32 deletion at baseline, SVR rates were 100% (2/2) after 12 weeks of administration and 67% (2/3) for 24 weeks. In response to this result, SOF plus VEL plus RBV therapy for 24 weeks was approved for patients who failed to respond to previous DAA therapy in 2019 and became one of the therapeutic options for such patients.

DAAs described above have been targeted for patients with chronic hepatitis or compensated cirrhosis, and patients with decompensated cirrhosis have long been an unmet need. SOF plus VEL therapy was finally available in Japan in 2019 for patients with decompensated cirrhosis. In a Japanese phase 3 study, patients with decompensated cirrhosis were randomly treated with SOF plus VEL with or without RBV for 12 weeks (*66*). SVR rates were 92% in both regimens, and four patients in the group without RBV and seven in the group with RBV experienced severe adverse effects. In addition, three patients died during the study, and all three patients were part of the RBV group. In response to this result, SOF plus VEL therapy for 12 weeks was approved for patients with decompensated cirrhosis in 2019.

Future tasks

Long term prognosis after SVR in patients with cirrhosis

HCC occurrence

In the early days after IFN-free DAA therapy was introduced, some European study groups reported that early HCC occurrence and recurrence were observed after starting DAA therapy (*67,68*), and it was discussed whether or not DAA therapy could inhibit the occurrence of HCC. However, there were some problems with these reports. Namely, the number of patients was small, the control group was not established, and the observation period was short. Thereafter, various study groups reported that DAA therapy suppresses the development of HCC in a larger number of patients (*69-72*). Ioannou *et al.* compared the HCC occurrence rates between patients with and without SVR among 21,948 U. S. veterans treated with DAA. During the 1.5 years observation period, 280 out of 19,909 patients experienced HCC occurrence in patients with SVR and 165 out of 2,039 patients experienced HCC occurrence in patients without SVR, and a 71% reduction in the risk of HCC occurrence was observed in patients with SVR compared to those without SVR. Similar results were observed in a subgroup analysis limited to patients with cirrhosis (*69*). Nahon *et al.* reported that there was no difference in HCC occurrence rates between patients who were treated with DAA and those who achieved SVR by IFN therapy in 1,270 patients with histologically diagnosed cirrhosis, adjusting for patients' background (*70*). Kanwal *et al.* reported that in 18,076 U. S. veterans who achieved SVR with DAA therapy, HCC occurrence was observed in 544 patients over an observation period of approximately 2.9 years, and the cumulative HCC occurrence rates at 1 year, 2 years, and 3 years were 1.1%, 1.9%, and 2.8%, respectively (*73*). The cumulative HCC occurrence rates at 1, 2, and 3 years were 2.2%, 3.8%, and 5.6%, respectively, in patients with cirrhosis, and cirrhosis was a significant risk factor associated with HCC occurrence (hazard ratio: 4.13). Thus, even in patients with advanced liver fibrosis, DAA therapy is expected to reduce the risk of HCC. However, the HCC occurrence rate after SVR in patients with cirrhosis is higher than that in patients without cirrhosis, and careful surveillance for HCC is recommended after SVR.

The elimination of HCV by DAA therapy is generally thought to suppress HCC occurrence but does not completely eliminate the risk of HCC occurrence. The risk of HCC occurrence is particularly high in patients with cirrhosis, and it is important to identify the risk factors for its occurrence. Age, male sex, diabetes mellitus, liver stiffness measurement (LSM) at baseline, model for end stage liver disease (MELD) score (≥ 10), albumin levels at baseline (< 3.5 g/dL), platelet counts at baseline (< 12.0 $\times 10^4/\mu L$) and alpha-fetoprotein levels at the end of therapy (EOT) have been reported as risk factors for HCC after DAA therapy in patients with cirrhosis (*73-76*) (Table 1). In the future, it will be important to validate effective HCC surveillance using these risk factors.

Mortality

The ultimate goal of HCV therapy is to suppress the progression of liver fibrosis and the development of HCC by eliminating HCV, thereby improving prognosis. In the era of IFN-based therapy, overall and liver-related mortality was significantly reduced in patients with SVR compared to those without SVR (*77,78*). In recent years, there have been some reports of improved prognosis in patients treated with DAA (*71,79*). Backus *et al.* compared the overall survival rates among 15,059 patients (with advanced liver fibrosis) with and without

SVR. During the 1.6 years observation period, 598 out of 13,992 patients with SVR and 195 out of 1,067 patients without SVR died; a 78.9% reduction in the risk of death was observed in patients with SVR compared to those without SVR (*79*). Carrat *et al.* compared mortality between 6,320 patients with cirrhosis who were treated with DAA and 1,578 patients with cirrhosis who were not treated within the 33.4 months observation period and reported that DAA therapy reduced all-cause mortality by 66%, liver-related mortality by 72%, and non-liver-related mortality by 60% (*71*). In a Japanese study comparing IFN-based therapy with IFN-free DAA therapy, Tahata *et al.* reported that overall survival rates among patients with a previous history of HCC treatment did not differ between patients with SVR by IFN-based therapy and those with SVR by IFN-free DAA therapy after adjusting for patients' characteristics by propensity score matching (*80*). Thus, in patients with cirrhosis, the achievement of SVR with DAA therapy as well as IFN therapy can be expected to improve mortality, but the observation periods in these previous studies were short; thus, studies with a longer observation period are necessary.

Improvement in liver fibrosis

The gold standard for the diagnosis of liver fibrosis is pathological evaluation of liver biopsy specimens, but liver biopsy has some limitations such as invasiveness, sampling error and inconsistency of diagnosis among pathologists. Furthermore, it is difficult to perform repeated evaluations of liver fibrosis, especially in patients with SVR. As such, there have been some reports in recent years on the use of non-invasive diagnostic methods such as elastography to evaluate liver fibrosis over time, instead of liver biopsy (*81,82*). Bachofner *et al.* examined the changes in liver stiffness at baseline and at 12 weeks after end of therapy (EOT) by using transient elastography in 392 patients who were treated with DAA; they reported that there was a significant decrease in liver stiffness measurement (LSM) in patients with SVR, whereas there was no significant decrease in patients without SVR (*82*). Knop *et al.* reported that in 54 patients with cirrhosis who achieved SVR after DAA therapy, liver stiffness was measured over time, and LSM at 24 weeks after the EOT was significantly lower compared to baseline LSM (*81*). In addition, in 46% of patients, there was a reduction in LSM of 30% or more at 24 weeks after EOT compared to baseline. Thus, although the observation periods in these studies were relatively short, improvement in liver fibrosis was expected in patients with SVR by DAA therapy. The advantage of liver fibrosis assessment by elastography is that it is non-invasive and repeatable. A disadvantage is that it is affected by liver inflammation. Since the degree of liver fibrosis improvement may be overestimated due to the elimination of HCV by DAA therapy and suppression of liver inflammation, caution should be exercised when assessing liver fibrosis by elastography.

Portal hypertension

In patients with cirrhosis, esophagogastric varices, splenomegaly, and pancytopenia are observed in association with increased portal pressure. The gold standard for the measurement of portal pressure is the measurement of hepatic venous pressure gradient (HVPG), but it is an invasive method and not widely used in Japan. Several studies in Europe and the United States have evaluated portal pressure by measuring the HVPG before and after DAA therapy (*83-85*). Lens *et al.* compared HVPG before and after DAA therapy in 226 cirrhotic patients with HVPG ≥ 10 mmHg before DAA therapy (*83*). At the time of SVR24, 140 (62%) of patients had a 10% or more reduction in HVPG compared with baseline, and 176 (78%) of patients had a HVPG ≥ 10 mmHg. A baseline albumin level of 3.5 g/dL or less was a significant factor associated with HVPG not decreasing by more than 10% compared to baseline. Lens *et al.* reported a study of HVPG over a longer period (SVR96) (*84*). Of the 176 patients with a HVPG of 10 mmHg or more at the time of SVR24, HVPG at SVR96 was measurable in 117 patients, and 55 (47%) of patients had a HVPG of less than 10 mmHg at SVR96. Mandorfer *et al.* measured HVPG before and after DAA

Table 1. Risk factors for HCC occurrence after SVR in patients with cirrhosis

Author (*Ref.*)	Patients	Observation period (months)	Risk factor	Hazard ratio
Calvaruso *et al.* 2018 (*75*)	2,249	14	Platelet count at baseline, < 12.0 ×10^4/μL	3.97
			Albumin at baseline, < 3.5 g/dL	1.77
Ogawa *et al.* 2018 (*76*)	271	17	AFP at EOT (every 1 ng/mL)	1.1
Degaspei *et al.* 2019 (*74*)	505	25	Male	6.17
			DM	2.52
			LSM at baseline (every 1 kPa)	1.03
Kanwal *et al.* 2020 (*73*)	6,938	35	Age (every 1 year)	1.02
			MELD score (< 10)	1
			10 - 15	1.74
			> 15	1.78

Abbreviations: AFP, alpha-fetoprotein; DM, diabetes mellitus; EOT, end of therapy; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; MELD, model for end-stage liver disease; SVR, sustained virologic response.

therapy in 60 patients with baseline HVPG of 6 mmHg or more who achieved SVR and reported that patients with Child-Pugh class B might have less improvement in HVPG than those with Child-Pugh class A (*85*). These results suggest that SVR may not be expected to improve portal pressure in patients with decompensated cirrhosis, suggesting the existence of a point of no return. Further studies are needed to determine which patient conditions lead to portal pressure improvements and which conditions do not.

Retreatment of patients with failure to respond to previous DAA

DAA therapy has revolutionized HCV therapy, with SVR being achieved in more than 95% of patients; however, in some patients HCV was not eliminated. In patients with failure to DAA therapy, RASs at NS3, NS5A and NS5B regions are generated (*86,87*) and may attenuate the therapeutic effect of retreatment. These RASs have become a problem in HCV therapy. Itakura *et al.* reported that dual RASs at NS5A L31 plus Y93 were observed in 63% of patients with failure to respond to DCV plus ASV therapy, co-existence of RASs at NS3 D168 plus NS5A L31 or Y93 was observed in 62% of patients, and NS5A P32 deletion was observed in approximately 5% of patients (*86*). Even in DAA therapy that appeared after DCV plus ASV therapy, various RASs were observed in patients who failed to respond to DAA therapy, and as the number of failures with DAA regimens increased, the prevalence of multiple RASs at NS3 or NS5A increased (*87*). Therefore, it is important to reliably eliminate HCV using a small number of DAA regimens.

NS5A inhibitors are key drugs in DAA therapy, and RASs at NS5A region are clinically important. In particular, NS5A P32 deletion, which is not detected in DAA-naïve patients, can be detected in patients with failed previous antiviral therapy involving NS5A inhibitors and has high-level resistance to all NS5A inhibitors (*88,89*). In a Japanese phase 3 study of patients with failed DAA therapy, the SVR rate of GLE plus PIB therapy for 12 weeks was 93.9% (31/33) and a good therapeutic effect was observed, but two patients with failure to respond to GLE plus PIB therapy both had NS5A P32 deletion. In contrast, the SVR rate of SOF plus VEL plus RBV therapy for 24 weeks was 96.7% (58/60), and the SVR rate of patients with NS5A P32 deletion at baseline was 66.6% (2/3). Of the two patients who had failed SOF plus VEL plus RBV therapy, one had HCV genotype 1 and NS5A P32 deletion at baseline and the other patient had HCV genotype 2 and NS5A L31 RAS at baseline. Several Japanese studies have reported the real-world efficacy of GLE plus PIB therapy for patients with failed DAA therapy, and SVR rates ranged from 92.9% to 97.7% (*90-92*). In these studies, seven patients did not achieve SVR, all patients had a previous history of DCV plus ASV therapy, four had NS5A P32 deletion and the other three had multiple RASs at NS5A other than P32 deletion at baseline. All four patients with NS5A P32 deletion at baseline did not achieve SVR with GLE plus PIB therapy. There are still few reports on the real-world efficacy of SOF plus VEL plus RBV therapy in patients with failed DAA therapy. One case report stated that SOF plus VEL plus RBV for 24 weeks was administered to three patients with HCV genotype 1b and NS5A P32 deletion; all patients had a history of DCV plus ASV therapy, and two out of three patients achieved SVR (*93*). Another case report stated that SOF plus VEL plus RBV for 24 weeks was administered to three patients with failed GLE plus PIB therapy, no patients had NS5A P32 deletion, and all three patients achieved SVR (*94*). Thus, although GLE plus PIB therapy for patients with failed DAA therapy shows good therapeutic efficacy, it is unlikely to be effective, especially in patients with NS5A P32 deletion at baseline. The Japanese guidelines also recommend the measurement of RASs prior to retreatment for patients with failure to respond to DAA therapy (*53*). There are few reports on the efficacy of SOF plus VEL plus RBV therapy in patients with NS5A P32 deletion at baseline, and further accumulation of these patients in clinical practice is desirable. It should be noted that GLE plus PIB therapy cannot be used for patients with decompensated cirrhosis, and SOF plus VEL plus RBV therapy cannot be used for patients with decompensated cirrhosis or severe renal impairment.

Patients with decompensated cirrhosis

Patients with decompensated cirrhosis have the worst prognosis among patients with liver disease, and Maesaka *et al.* reported that the overall survival rates of patients with HCV-related decompensated cirrhosis who were not treated with antiviral therapy at 1 and 2 years were 82.9% and 64.8%, respectively (*95*). However, antiviral therapy for patients with decompensated cirrhosis has long been an unmet need. In Japan, SOF plus VEL therapy for patients with decompensated cirrhosis was approved in 2019, and several studies on its short-term therapeutic effects have been reported (*96-98*). In these studies, SVR rates ranged from 90.2% to 95.8%, and treatment completion rates ranged from 96.3% to 97.2%. Although good therapeutic effects and tolerability were observed, most reasons for treatment discontinuation were due to worsening of hepatic encephalopathy, or ascites, or variceal bleeding, and clinicians should pay attention to the occurrence of decompensated cirrhotic events during treatment. With regard to changes in liver function, Tahata *et al.* reported that among patients with SVR, 50% of patients with CP class B at baseline improved to CP class A at SVR and 9% and 27% of patients with CP class C at baseline improved to CP class A and B, respectively, at SVR; and improvement of albumin levels had a

significant effect on the improvement of CP class (*96*). Thus, in the short-term, patients with SVR show improvement in liver function, mainly in albumin levels. However, the long-term effect of antiviral therapy on the prognosis of patients with decompensated cirrhosis is controversial. Verna *et al.* reported that MELD score decreased by 0.30 points, total bilirubin levels increased by 0.23 mg/dL and albumin levels increased by 0.36 g/dL in long-term follow-up of approximately four years; but improvement in liver function was limited (*99*). Krassenburg *et al.* reported that SVR was significantly associated with improvement in event-free survival in patients with CP class A, but not in those with CP class B or C (*100*). In patients with CP class B and C, a decrease in the MELD score by 2 points or more (considered clinically significant) was not associated with event-free survival. As shown above, some studies in Europe and the United States reported negative results regarding the impact of DAA therapy on the prognosis of patients with decompensated cirrhosis, and further studies are needed.

Conclusion: Expectations for HCV elimination

Approximately 30 years have passed since the discovery of HCV in 1989, and it is now possible to achieve an SVR of more than 95% in patients with chronic hepatitis and compensated cirrhosis by oral medications only. In recent years, patients with decompensated cirrhosis have become a new target for antiviral therapy, and their therapeutic outcomes are comparable to those of compensated cirrhosis. However, no matter how good a drug is, it is useless if it cannot be administered to patients, and it is important to detect and guide untreated HCV patients to adequate therapy. In Japan new infections from blood transfusions have almost disappeared, except among people who inject drugs, which may lead to the spread of new infections and the emergence of multidrug-resistant viruses. SVR is a surrogate indicator for HCV therapy, and its true goal is to reduce liver-related deaths. Since many patients with cirrhosis are included in those who achieve SVR with DAA therapy, proper surveillance for liver disease is also important even after SVR. The World Health Organization's goal for HCV elimination is a 65% reduction in mortality and an 80% reduction in incidence by 2030, using 2015 as a baseline. Japan also needs to address the remaining issues so that HCV can be eliminated by 2030.

Funding: None.

Conflict of Interest: Professor Tetsuo Takehara received grants from Gilead Sciences, Inc., MSD K. K. and Abbie Inc. and is on the speakers' bureau for Gilead Sciences, Inc., MSD K. K. and Abbie Inc. All other authors declare that they have no conflicts of interest.

References

1. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science. 1989; 244:359-362.
2. Kiyosawa K, Sodeyama T, Tanaka E, Gibo Y, Yoshizawa K, Nakano Y, Furuta S, Akahane Y, Nishioka K, Purcell RH, Alter HJ. Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma: analysis by detection of antibody to hepatitis C virus. Hepatology. 1990; 12:671-675.
3. Hoofnagle JH, Mullen KD, Jones DB, Rustgi V, Di Bisceglie A, Peters M, Waggoner JG, Park Y, Jones EA. Treatment of chronic non-A,non-B hepatitis with recombinant human alpha interferon. A preliminary report. N Engl J Med. 1986; 315:1575-1578.
4. Shindo M, Di Bisceglie AM, Cheung L, Shih JW, Cristiano K, Feinstone SM, Hoofnagle JH. Decrease in serum hepatitis C viral RNA during alpha-interferon therapy for chronic hepatitis C. Ann Intern Med. 1991; 115:700-704.
5. Hagiwara H, Hayashi N, Mita E, Takehara T, Kasahara A, Fusamoto H, Kamada T. Quantitative analysis of hepatitis C virus RNA in serum during interferon alfa therapy. Gastroenterology. 1993; 104:877-883.
6. Mita E, Hayashi N, Hagiwara H, Ueda K, Kanazawa Y, Kasahara A, Fusamoto H, Kamada T. Predicting interferon therapy efficacy from hepatitis C virus genotype and RNA titer. Dig Dis Sci. 1994; 39:977-982.
7. Hayashi N, Takehara T. Antiviral therapy for chronic hepatitis C: past, present, and future. J Gastroenterol. 2006; 41:17-27.
8. Kasahara A, Hayashi N, Hiramatsu N, Oshita M, Hagiwara H, Katayama K, Kato M, Masuzawa M, Yoshihara H, Kishida Y, Shimizu Y, Inoue A, Fusamoto H, Kamada T. Ability of prolonged interferon treatment to suppress relapse after cessation of therapy in patients with chronic hepatitis C: a multicenter randomized controlled trial. Hepatology. 1995; 21:291-297.
9. Poynard T, Leroy V, Cohard M, Thevenot T, Mathurin P, Opolon P, Zarski JP. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. Hepatology. 1996; 24:778-789.
10. Bodenheimer HC, Jr., Lindsay KL, Davis GL, Lewis JH, Thung SN, Seeff LB. Tolerance and efficacy of oral ribavirin treatment of chronic hepatitis C: a multicenter trial. Hepatology. 1997; 26:473-477.
11. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, Goodman ZD, Ling MH, Cort S, Albrecht JK. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med. 1998; 339:1485-1492.
12. Davis GL, Esteban-Mur R, Rustgi V, Hoefs J, Gordon SC, Trepo C, Shiffman ML, Zeuzem S, Craxi A, Ling MH, Albrecht J. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. International Hepatitis Interventional Therapy Group. N Engl J Med. 1998; 339:1493-1499.
13. Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, Bain V, Heathcote J, Zeuzem S, Trepo C, Albrecht J. Randomised trial of interferon alpha2b plus ribavirin

for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet. 1998; 352:1426-1432.
14. Lau JY, Tam RC, Liang TJ, Hong Z. Mechanism of action of ribavirin in the combination treatment of chronic HCV infection. Hepatology. 2002; 35:1002-1009.
15. Ochi H, Maekawa T, Abe H, Hayashida Y, Nakano R, Kubo M, Tsunoda T, Hayes CN, Kumada H, Nakamura Y, Chayama K. ITPA polymorphism affects ribavirin-induced anemia and outcomes of therapy – a genome-wide study of Japanese HCV virus patients. Gastroenterology. 2010; 139:1190-1197.
16. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, Jr., Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002; 347:975-982.
17. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001; 358:958-965.
18. Tanaka Y, Nishida N, Sugiyama M, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet. 2009; 41:1105-1109.
19. Enomoto N, Sakuma I, Asahina Y, Kurosaki M, Murakami T, Yamamoto C, Ogura Y, Izumi N, Marumo F, Sato C. Mutations in the nonstructural protein 5A gene and response to interferon in patients with chronic hepatitis C virus 1b infection. N Engl J Med. 1996; 334:77-81.
20. El-Shamy A, Nagano-Fujii M, Sasase N, Imoto S, Kim SR, Hotta H. Sequence variation in hepatitis C virus nonstructural protein 5A predicts clinical outcome of pegylated interferon/ribavirin combination therapy. Hepatology. 2008; 48:38-47.
21. Akuta N, Suzuki F, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, Hosaka T, Kobayashi M, Kobayashi M, Arase Y, Ikeda K, Kumada H. Predictive factors of early and sustained responses to peginterferon plus ribavirin combination therapy in Japanese patients infected with hepatitis C virus genotype 1b: amino acid substitutions in the core region and low-density lipoprotein cholesterol levels. J Hepatol. 2007; 46:403-410.
22. McHutchison JG, Manns M, Patel K, Poynard T, Lindsay KL, Trepo C, Dienstag J, Lee WM, Mak C, Garaud JJ, Albrecht JK; International Hepatitis Interventional Therapy Group. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. Gastroenterology. 2002; 123:1061-1069.
23. Oze T, Hiramatsu N, Yakushijin T, *et al.* Pegylated interferon alpha-2b (Peg-IFN alpha-2b) affects early virologic response dose-dependently in patients with chronic hepatitis C genotype 1 during treatment with Peg-IFN alpha-2b plus ribavirin. J Viral Hepat. 2009; 16:578-585.
24. Hiramatsu N, Oze T, Yakushijin T, *et al.* Ribavirin dose reduction raises relapse rate dose-dependently in genotype 1 patients with hepatitis C responding to pegylated interferon alpha-2b plus ribavirin. J Viral Hepat. 2009; 16:586-594.
25. Berg T, von Wagner M, Nasser S, *et al.* Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. Gastroenterology. 2006; 130:1086-1097.
26. Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis c genotype 1-infected slow responders. Hepatology. 2007; 46:1688-1694.
27. Schaefer EA, Chung RT. Anti-hepatitis C virus drugs in development. Gastroenterology. 2012; 142:1340-1350 e1341.
28. Wakita T, Pietschmann T, Kato T, Date T, Miyamoto M, Zhao Z, Murthy K, Habermann A, Kräusslich HG, Mizokami M, Bartenschlager R, Liang TJ. Production of infectious hepatitis C virus in tissue culture from a cloned viral genome. Nat Med. 2005; 11:791-796.
29. Kumada H, Toyota J, Okanoue T, Chayama K, Tsubouchi H, Hayashi N. Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan. J Hepatol. 2012; 56:78-84.
30. Hayashi N, Okanoue T, Tsubouchi H, Toyota J, Chayama K, Kumada H. Efficacy and safety of telaprevir, a new protease inhibitor, for difficult-to-treat patients with genotype 1 chronic hepatitis C. J Viral Hepat. 2012; 19:e134-142.
31. Hayashi N, Izumi N, Kumada H, Okanoue T, Tsubouchi H, Yatsuhashi H, Kato M, Ki R, Komada Y, Seto C, Goto S. Simeprevir with peginterferon/ribavirin for treatment-naive hepatitis C genotype 1 patients in Japan: CONCERTO-1, a phase III trial. J Hepatol. 2014; 61:219-227.
32. Izumi N, Hayashi N, Kumada H, Okanoue T, Tsubouchi H, Yatsuhashi H, Kato M, Ki R, Komada Y, Seto C, Goto S. Once-daily simeprevir with peginterferon and ribavirin for treatment-experienced HCV genotype 1-infected patients in Japan: the CONCERTO-2 and CONCERTO-3 studies. J Gastroenterol. 2014; 49:941-953.
33. Takehara T. Simeprevir for the treatment of chronic hepatitis C genotype 1 infection. Expert Rev Anti Infect Ther. 2014; 12:909-917.
34. Tahata Y, Hiramatsu N, Oze T, *et al.* The impact of an inosine triphosphate pyrophosphatase genotype on bilirubin increase in chronic hepatitis C patients treated with simeprevir, pegylated interferon plus ribavirin. J Gastroenterol. 2016; 51:252-259.
35. Hayashi N, Nakamuta M, Takehara T, Kumada H, Takase A, Howe AY, Ludmerer SW, Mobashery N. Vaniprevir plus peginterferon alfa-2b and ribavirin in treatment-naive Japanese patients with hepatitis C virus genotype 1 infection: a randomized phase III study. J Gastroenterol. 2016; 51:390-403.
36. Kumada H, Mochida S, Suzuki F, Chayama K, Karino Y, Nakamura K, Fujimoto G, Howe AY, Ludmerer SW, Mobashery N. Vaniprevir plus peginterferon alfa-2b and ribavirin in treatment-experienced Japanese patients with hepatitis C virus genotype 1 (GT1b) infection: Phase 3 studies. J Gastroenterol Hepatol. 2016; 31:1674-1683.
37. Kumada H, Suzuki Y, Ikeda K, *et al.* Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. Hepatology. 2014; 59:2083-2091.
38. Jacobson IM, Gordon SC, Kowdley KV, *et al.* Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013; 368:1867-1877.
39. Lawitz E, Mangia A, Wyles D, *et al.* Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl

J Med. 2013; 368:1878-1887.
40. Zeuzem S, Dusheiko GM, Salupere R, *et al.* Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. 2014; 370:1993-2001.
41. Afdhal N, Reddy KR, Nelson DR, *et al.* Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014; 370:1483-1493.
42. Afdhal N, Zeuzem S, Kwo P, *et al.* Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014; 370:1889-1898.
43. Omata M, Nishiguchi S, Ueno Y, *et al.* Sofosbuvir plus ribavirin in Japanese patients with chronic genotype 2 HCV infection: an open-label, phase 3 trial. J Viral Hepat. 2014; 21:762-768.
44. Mizokami M, Yokosuka O, Takehara T, *et al.* Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. Lancet Infect Dis. 2015; 15:645-653.
45. Morio K, Imamura M, Kawakami Y, *et al.* ITPA polymorphism effects on decrease of hemoglobin during sofosbuvir and ribavirin combination treatment for chronic hepatitis C. J Gastroenterol. 2017; 52:746-753.
46. Urabe A, Sakamori R, Tahata Y, *et al.* Predictive factors of anemia during sofosbuvir and ribavirin therapy for genotype 2 chronic hepatitis C patients. Hepatol Res. 2019; 49:853-859.
47. Akahane T, Kurosaki M, Itakura J, *et al.* Real-world efficacy and safety of sofosbuvir + ribavirin for hepatitis C genotype 2: A nationwide multicenter study by the Japanese Red Cross Liver Study Group. Hepatol Res. 2019; 49:264-270.
48. Ogawa E, Furusyo N, Nomura H, *et al.* NS5A resistance-associated variants undermine the effectiveness of ledipasvir and sofosbuvir for cirrhotic patients infected with HCV genotype 1b. J Gastroenterol. 2017; 52:845-854.
49. Tsuji K, Kurosaki M, Itakura J, *et al.* Real-world efficacy and safety of ledipasvir and sofosbuvir in patients with hepatitis C virus genotype 1 infection: a nationwide multicenter study by the Japanese Red Cross Liver Study Group. J Gastroenterol. 2018; 53:1142-1150.
50. Tahata Y, Sakamori R, Urabe A, *et al.* Liver Fibrosis Is Associated With Corrected QT Prolongation During Ledipasvir/Sofosbuvir Treatment for Patients With Chronic Hepatitis C. Hepatol Commun. 2018; 2:884-892.
51. Akuta N, Sezaki H, Suzuki F, Fujiyama S, Kawamura Y, Hosaka T, Kobayashi M, Kobayashi M, Saitoh S, Suzuki Y, Arase Y, Ikeda K, Kumada H. Retreatment efficacy and predictors of ledipasvir plus sofosbuvir to HCV genotype 1 in Japan. J Med Virol. 2017; 89:284-290.
52. Asahina Y, Itoh Y, Ueno Y, *et al.* Ledipasvir-sofosbuvir for treating Japanese patients with chronic hepatitis C virus genotype 2 infection. Liver Int. 2018; 38:1552-1561.
53. Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology. Japan Society of Hepatology guidelines for the management of hepatitis C virus infection: 2019 update. Hepatol Res. 2020; 50:791-816.
54. Doi A, Sakamori R, Tahata Y, *et al.* Frequency of, and factors associated with, hepatitis B virus reactivation in hepatitis C patients treated with all-oral direct-acting antivirals: Analysis of a Japanese prospective cohort. Hepatol Res. 2017; 47:1438-1444.
55. Takayama H, Sato T, Ikeda F, Fujiki S. Reactivation of hepatitis B virus during interferon-free therapy with daclatasvir and asunaprevir in patient with hepatitis B virus/hepatitis C virus co-infection. Hepatol Res. 2016; 46:489-491.
56. Kumada H, Chayama K, Rodrigues L, *et al.* Randomized phase 3 trial of ombitasvir/paritaprevir/ritonavir for hepatitis C virus genotype 1b-infected Japanese patients with or without cirrhosis. Hepatology. 2015; 62:1037-1046.
57. Atsukawa M, Tsubota A, Koushima Y, *et al.* Efficacy and safety of ombitasvir/paritaprevir/ritonavir in dialysis patients with genotype 1b chronic hepatitis C. Hepatol Res. 2017; 47:1429-1437.
58. Kumada H, Suzuki Y, Karino Y, *et al.* The combination of elbasvir and grazoprevir for the treatment of chronic HCV infection in Japanese patients: a randomized phase II/III study. J Gastroenterol. 2017; 52:520-533.
59. Suda G, Kurosaki M, Itakura J, *et al.* Safety and efficacy of elbasvir and grazoprevir in Japanese hemodialysis patients with genotype 1b hepatitis C virus infection. J Gastroenterol. 2019; 54:78-86.
60. Toyota J, Karino Y, Suzuki F, *et al.* Daclatasvir/asunaprevir/beclabuvir fixed-dose combination in Japanese patients with HCV genotype 1 infection. J Gastroenterol. 2017; 52:385-395.
61. Takehara T, Chayama K, Kurosaki M, *et al.* JNJ-4178 (adafosbuvir, odalasvir, and simeprevir) in Japanese patients with chronic hepatitis C virus genotype 1 or 2 infection with or without compensated cirrhosis: the Phase IIa OMEGA-3 study. J Gastroenterol. 2020; 55:640-652.
62. Chayama K, Suzuki F, Karino Y, *et al.* Efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 1 hepatitis C virus infection with and without cirrhosis. J Gastroenterol. 2018; 53:557-565.
63. Toyoda H, Chayama K, Suzuki F, *et al.* Efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 2 hepatitis C virus infection. Hepatology. 2018; 67:505-513.
64. Kumada H, Watanabe T, Suzuki F, *et al.* Efficacy and safety of glecaprevir/pibrentasvir in HCV-infected Japanese patients with prior DAA experience, severe renal impairment, or genotype 3 infection. J Gastroenterol. 2018; 53:566-575.
65. Izumi N, Takehara T, Chayama K, *et al.* Sofosbuvir-velpatasvir plus ribavirin in Japanese patients with genotype 1 or 2 hepatitis C who failed direct-acting antivirals. Hepatol Int. 2018; 12:356-367.
66. Takehara T, Sakamoto N, Nishiguchi S, *et al.* Efficacy and safety of sofosbuvir-velpatasvir with or without ribavirin in HCV-infected Japanese patients with decompensated cirrhosis: an open-label phase 3 trial. J Gastroenterol. 2019;54:87-95.
67. Reig M, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, Díaz A, Vilana R, Darnell A, Varela M, Sangro B, Calleja JL, Forns X, Bruix J. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol. 2016; 65:719-726.
68. Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, Foschi FG, Lenzi M, Mazzella G, Verucchi G, Andreone P, Brillanti S. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol. 2016; 65:727-733.

69. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol. 2017; S0168-8278(17)32273-0.
70. Nahon P, Layese R, Bourcier V, *et al.* Incidence of Hepatocellular Carcinoma After Direct Antiviral Therapy for HCV in Patients With Cirrhosis Included in Surveillance Programs. Gastroenterology. 2018; 155:1436-1450 e1436.
71. Carrat F, Fontaine H, Dorival C, *et al.* Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet. 2019; 393:1453-1464.
72. Tahata Y, Sakamori R, Urabe A, *et al.* Hepatocellular carcinoma occurrence does not differ between interferon-based and interferon-free treatment with liver histological assessment. Hepatol Res, 2019.
73. Kanwal F, Kramer JR, Asch SM, Cao Y, Li L, El-Serag HB. Long-Term Risk of Hepatocellular Carcinoma in HCV Patients Treated With Direct Acting Antiviral Agents. Hepatology. 2020; 71:44-55.
74. Degasperi E, D'Ambrosio R, Iavarone M, Sangiovanni A, Aghemo A, Soffredini R, Borghi M, Lunghi G, Colombo M, Lampertico P. Factors Associated With Increased Risk of De Novo or Recurrent Hepatocellular Carcinoma in Patients With Cirrhosis Treated With Direct-Acting Antivirals for HCV Infection. Clin Gastroenterol Hepatol. 2019; 17:1183-1191 e1187.
75. Calvaruso V, Cabibbo G, Cacciola I, *et al.* Incidence of Hepatocellular Carcinoma in Patients With HCV-Associated Cirrhosis Treated With Direct-Acting Antiviral Agents. Gastroenterology. 2018; 155:411-421 e414.
76. Ogawa E, Furusyo N, Nomura H, *et al.* Short-term risk of hepatocellular carcinoma after hepatitis C virus eradication following direct-acting anti-viral treatment. Aliment Pharmacol Ther. 2018; 47:104-113.
77. Nahon P, Bourcier V, Layese R, *et al.* Eradication of Hepatitis C Virus Infection in Patients With Cirrhosis Reduces Risk of Liver and Non-Liver Complications. Gastroenterology. 2017; 152:142-156 e142.
78. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol. 2011; 9:509-516 e501.
79. Backus LI, Belperio PS, Shahoumian TA, Mole LA. Impact of Sustained Virologic Response with Direct-Acting Antiviral Treatment on Mortality in Patients with Advanced Liver Disease. Hepatology. 2019; 69:487-497.
80. Tahata Y, Sakamori R, Urabe A, Yamada R, Ohkawa K, Hiramatsu N, Hagiwara H, Oshita M, Imai Y, Kodama T, Hikita H, Tatsumi T, Takehara T. Clinical outcomes of direct-acting antiviral treatments for patients with hepatitis C after hepatocellular carcinoma are equivalent to interferon treatment. Hepatol Res. 2020; 50:1118-1127.
81. Knop V, Hoppe D, Welzel T, Vermehren J, Herrmann E, Vermehren A, Friedrich-Rust M, Sarrazin C, Zeuzem S, Welker MW. Regression of fibrosis and portal hypertension in HCV-associated cirrhosis and sustained virologic response after interferon-free antiviral therapy. J Viral Hepat. 2016; 23:994-1002.
82. Bachofner JA, Valli PV, Kröger A, *et al.* Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. Liver Int. 2017; 37:369-376.
83. Lens S, Alvarado-Tapias E, Marino Z, *et al.* Effects of All-Oral Anti-Viral Therapy on HVPG and Systemic Hemodynamics in Patients With Hepatitis C Virus-Associated Cirrhosis. Gastroenterology. 2017; 153:1273-1283 e1271.
84. Lens S, Baiges A, Alvarado-Tapias E, *et al.* Clinical outcome and hemodynamic changes following HCV eradication with oral antiviral therapy in patients with clinically significant portal hypertension. J Hepatol. 2020; 73:1415-1424.
85. Mandorfer M, Kozbial K, Schwabl P, *et al.* Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. J Hepatol. 2016; 65:692-699.
86. Itakura J, Kurosaki M, Hasebe C, *et al.* Complex Pattern of Resistance-Associated Substitutions of Hepatitis C Virus after Daclatasvir/Asunaprevir Treatment Failure. PLoS One. 2016; 11:e0165339.
87. Itakura J, Kurosaki M, Kakizaki S, *et al.* Features of resistance-associated substitutions after failure of multiple direct-acting antiviral regimens for hepatitis C. JHEP Rep. 2020; 2:100138.
88. Doi A, Hikita H, Sakamori R, Tahata Y, Kai Y, Yamada R, Yakushijin T, Mita E, Ohkawa K, Imai Y, Furuta K, Kodama T, Tatsumi T, Takehara T. Nonstructural protein 5A/P32 deletion after failure of ledipasvir/sofosbuvir in hepatitis C virus genotype 1b infection. Hepatology. 2018; 68:380-383.
89. Hikita H, Takehara T. NS5A-P32 Deletion in Hepatitis C Genotype 1b Infection is the Most Refractory Treatment-Mediated Amino Acid Change Exhibiting Resistance to all NS5A Inhibitors. Semin Liver Dis. 2020; 40:143-153.
90. Osawa M, Imamura M, Teraoka Y, *et al.* Real-world efficacy of glecaprevir plus pibrentasvir for chronic hepatitis C patient with previous direct-acting antiviral therapy failures. J Gastroenterol. 2019; 54:291-296.
91. Sezaki H, Suzuki F, Hosaka T, Fujiyama S, Kawamura Y, Akuta N, Kobayashi M, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Kobayashi M, Kumada H. Initial- and re-treatment effectiveness of glecaprevir and pibrentasvir for Japanese patients with chronic hepatitis C virus-genotype 1/2/3 infections. J Gastroenterol. 2019; 54:916-927.
92. Uemura H, Uchida Y, Kouyama JI, Naiki K, Tsuji S, Sugawara K, Nakao M, Motoya D, Nakayama N, Imai Y, Tomiya T, Mochida S. NS5A-P32 deletion as a factor involved in virologic failure in patients receiving glecaprevir and pibrentasvir. J Gastroenterol. 2019; 54:459-470.
93. Takaki S, Imamura M, Yamaguchi S, Fukuhara T, Mori N, Tsuji K, Ohya K, Hayes CN, Aikata H, Chayama K. Real-word efficacy of sofosbuvir, velpatasvir plus ribavirin therapy for chronic hepatitis patients who failed prior DAA therapy with NS5A-P32 deletion mutated HCV infection. Clin J Gastroenterol. 2020; 13:1233-1238.
94. Nonomura A, Tamori A, Hai H, Kozuka R, Fujii H, Uchida-Kobayashi S, Enomoto M, Kawada N. Sofosbuvir/Velpatasvir Plus Ribavirin Combination Therapy for Patients with Hepatitis C Virus Genotype 1a, 2a, or 3b after Glecaprevir/Pibrentasvir Therapy Failed. Intern Med. 2021.
95. Maesaka K, Sakamori R, Yamada R, *et al.* Clinical course of hepatitis C virus-positive patients with decompensated liver cirrhosis in the era of direct-acting antiviral treatment. Hepatol Res. 2021; 51:517-527.
96. Tahata Y, Hikita H, Mochida S, *et al.* Sofosbuvir plus

velpatasvir treatment for hepatitis C virus in patients with decompensated cirrhosis: a Japanese real-world multicenter study. J Gastroenterol. 2021; 56:67-77.
97. Takaoka Y, Miura K, Morimoto N, *et al.* Real-world efficacy and safety of 12-week sofosbuvir/velpatasvir treatment for patients with decompensated liver cirrhosis caused by hepatitis C virus infection. Hepatol Res. 2021; 51:51-61.
98. Atsukawa M, Tsubota A, Kondo C, *et al.* Real-World Clinical Application of 12-Week Sofosbuvir/Velpatasvir Treatment for Decompensated Cirrhotic Patients with Genotype 1 and 2: A Prospective, Multicenter Study. Infect Dis Ther. 2020; 9:851-866.
99. Verna EC, Morelli G, Terrault NA, *et al.* DAA therapy and long-term hepatic function in advanced/decompensated cirrhosis: Real-world experience from HCV-TARGET cohort. J Hepatol. 2020; 73:540-548.
100. Krassenburg LAP, Maan R, Ramji A, Manns MP, Cornberg M, Wedemeyer H, de Knegt RJ, Hansen BE, Janssen HLA, de Man RA, Feld JJ, van der Meer AJ. Clinical outcomes following DAA therapy in patients with HCV-related cirrhosis depend on disease severity. J Hepatol. 2021; 74:1053-1063.

Received July 6, 2021; Revised August 24, 2021; Accepted September 10, 2021.

Released online in J-STAGE as advance publication September 21, 2021.

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Global Health & Medicine. 2021; 3(5):335-342.
REVIEW
DOI: 10.35772/ghm.2021.01079

Seamless support from screening to anti-HCV treatment and HCC/decompensated cirrhosis: Subsidy programs for HCV elimination

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Abstract: Viral hepatitis poses a major public health problem in Japan. Chronic viral hepatitis is a progressive liver disease that eventually develops into liver cirrhosis and liver cancer. Since nucleic acid analog therapy for hepatitis B and interferon-free therapy for hepatitis C have made it possible to control the disease status or eliminate the viruses, it is very important that more people receive hepatitis virus tests to confirm the presence of infection at an early stage, and that patients with hepatitis detected by the tests receive appropriate medical care. Currently, the government of Japan is implementing comprehensive measures for hepatitis control based on five key strategies. Moreover, the goal listed in the Basic Guidelines on Hepatitis Measures is to reduce the frequency of progression of hepatitis to cirrhosis or liver cancer through a scheme consisting of testing people for hepatitis, getting those who test positive to visit a medical institution and receive treatment, and providing appropriate and high-quality hepatitis care through specialized medical institutions and regional core centers for the management of liver disease. To achieve the goal, various subsidy programs including an expense subsidy system for hepatitis treatment have been implemented in Japan. It is important for healthcare professionals to have sufficient knowledge of public support for efficient hepatitis C virus (HCV)-related liver disease detection and care.

***Keywords*:** Basic Guidelines on Hepatitis Measures, viral hepatitis policy, public support, subsidy program, hepatitis

Introduction

In Japan, more than 3 million people are infected with hepatitis B or C virus (*1*), making them among the most common infectious diseases in the country. Chronic hepatitis B and C, if left untreated, can progress from chronic hepatitis to more serious conditions such as liver cirrhosis and cancer. Moreover, hepatitis patients may not be aware of their infection until the advanced stage of disease, or they may not recognize the need for medical attention even after learning of their infection. Now that nucleic acid analog therapy for hepatitis B and interferon-free therapy for hepatitis C have made it possible to control the disease status or eliminate the viruses, it is very important that more people receive hepatitis virus tests to confirm the presence of infection at an early stage, and that patients with hepatitis detected by the tests receive appropriate medical care. Thus, viral hepatitis is an important public health issue for the Japanese people, and comprehensive measures for hepatitis control are currently implemented in Japan (*2*) based on the following five key strategies (*3*) : *i*) promotion of liver disease treatment; *ii*) promotion of hepatitis virus testing and prevention of progression to severe disease; *iii*) reinforcement of regional cooperative systems for liver disease treatment; *iv*) dissemination of accurate information about hepatitis to the public; and *v*) promotion of hepatitis research. The Basic Guidelines on Hepatitis Measures, revised in 2016, aim to reduce the number of people who progress to liver cirrhosis/cancer through early detection and treatment of hepatitis. To accomplish the mission, various public supports have been implemented in Japan (Figure 1).

This article reviews the subsidy programs for efficient hepatitis C virus (HCV)-related liver disease detection and care in Japan and public support for these programs.

Promotion of hepatitis virus testing (subsidies for testing costs)

A national survey conducted in 2011 showed that about 57% of the Japanese population had been tested for hepatitis B virus (HBV) and 48% for HCV, revealing that about half had not been tested for these viruses (*4*). With the goal of having all citizens undergo hepatitis virus testing at least once in their lifetime, measures have been implemented to establish testing systems, subsidize testing costs, and encourage the public to

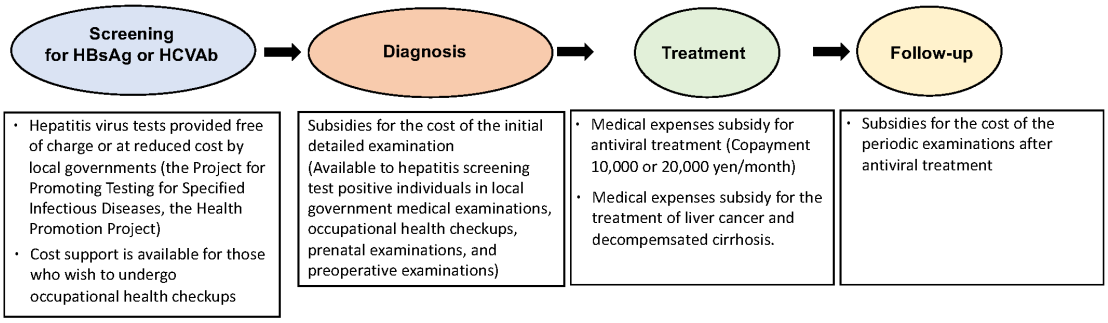

Figure 1. Seamless public support from screening to anti-HCV treatment and HCC/decompensated cirrhosis. HBsAg: hepatitis B surface antigen, HCC: hepatocellular carcinoma, HCV: hepatitis C virus, HCVAb: hepatitis C antibody.

undergo testing. As for subsidies for testing costs, prefectural governments provide hepatitis viral tests, whereas municipal governments provide hepatitis virus screening. Furthermore, to encourage the incorporation of hepatitis virus testing in occupational health checkups, the following three measures have been implemented since FY2017 in order to raise awareness at workplaces in collaboration with health insurance associations and the Japan Health Insurance Association.

Hepatitis virus tests provided by local governments (the Project for Promoting Testing for Specified Infectious Diseases, the Health Promotion Project)

Prefectural governments conduct hepatitis virus tests (as part of the Project for Promoting Testing for Specified Infectious Diseases), whereas municipal governments provide hepatitis screening (as part of the Health Promotion Project); these are provided free of charge or at reduced cost. In all prefectures (including cities with public health centers and special wards), the Project for Promoting Testing for Specified Infectious Diseases is implemented at public health centers and at contract medical institutions for residents of all ages, and 95% of municipalities provide follow-up services for individuals who test positive for hepatitis virus. The Health Promotion Project is implemented in 1,656 municipalities, of which 1,543 (93%) provide the hepatitis screening service free of charge to eligible individuals aged 40 years or older. Hepatitis screening is conducted at contract medical institutions, group health checkups, public health centers, and health centers. In FY2018, about one million four thousand people received HCV tests under the Project for Promoting Testing for Specified Infectious Diseases and the Health Promotion Project, respectively (Figure 2).

Various efforts are being made by local governments to encourage the public to undergo hepatitis virus testing. The most common way of raising public awareness of the tests is posting information on websites and distributing informational pamphlets and newsletters

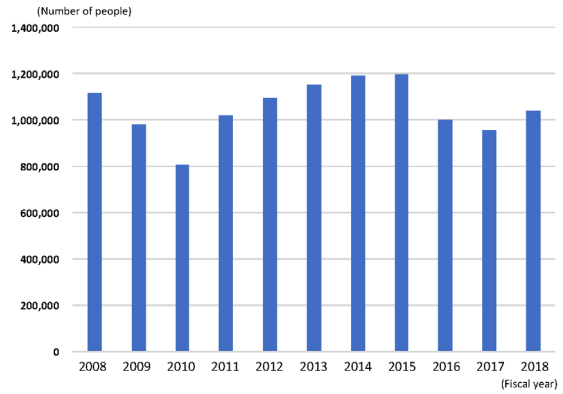

Figure 2. Development of the number of people who received HCV screening tests at local governments. The total number of the Project for Promoting Testing for Specified Infectious Diseases and the Health Promotion Project. HCV: hepatitis C virus.

within the prefecture, as well as providing guidance and encouragement to individual residents to undergo testing in municipalities (1,470 municipalities) (Figure 3). As for efforts to increase the convenience of hepatitis virus testing, simultaneous testing along with other tests is the most common approach among municipalities (1,590 municipalities) and is also increasingly being adopted in prefectural programs. In addition, 1,026 municipalities offer after-hours hepatitis virus testing at night, on weekends, and on holidays (*5*).

Hospitals that offer hepatitis virus testing can be searched from the Hepatitis Care Navigation System (*https://kan-navi.ncgm.go.jp*), which is provided by the Hepatitis Information Center of the National Center for Global Health and Medicine (Ichikawa, Chiba, Japan). The schedule, location, and sign-up procedures for hepatitis virus testing vary by municipality. Those who wish to be tested must either contact the municipality (city, town, or village) where they live or the appropriate health center, or check their websites.

Hepatitis virus testing at workplaces (Project to Promote Hepatitis Screening at Workplaces)

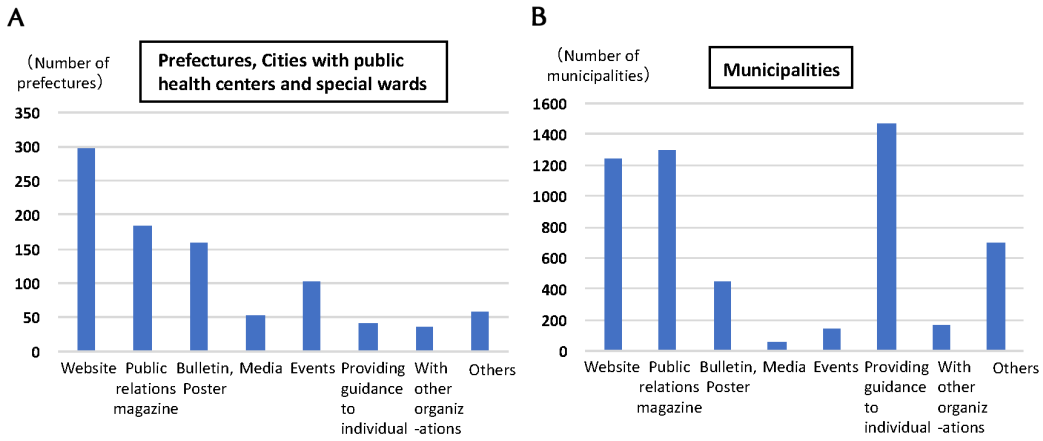

Figure 3. Efforts for raising public awareness of the hepatitis screening tests of the local governments. (A) The means used to make screening tests widely-known in Prefectures, Cities with public health centers and special wards. **(B)** The means used to make screening tests widely-known in municipalities.

Hepatitis virus testing at workplaces may be useful for detecting latent hepatitis virus carriers and guiding them to seek medical attention. In a pilot study conducted in Hiroshima Prefecture, Sugiyama *et al.* found that a certain percentage of hepatitis-positive individuals were detected by occupational health screenings, and that nearly half of them were found to be hepatitis positive for the first time (*6*).

To encourage the implementation of consultation services addressing hepatitis B and C virus infections as well as the incorporation of hepatitis virus testing in occupational health screenings, the Project to Promote Hepatitis Screening at Workplaces has been implemented since FY2017. The project's aim is to raise awareness at workplaces in collaboration with health insurance associations and the Japan Health Insurance Association. Posters and leaflets are the most common means for raising awareness among municipalities. In FY2018, the project was implemented in 15 prefectures and 5 cities with public health centers in order to encourage the public to undergo hepatitis virus testing in conjunction with occupational health screenings.

Existence of people unrecognized receiving hepatitis screening test

Among the people who had been tested, the percentage of those who were aware that they had been tested for hepatitis B and C ("recognized persons") was about 17.8% and 17.7%, respectively (*4*). Other test recipients may have been tested prior to major surgery, childbirth, or blood donation, but they were not aware of the test or its results ("unrecognized persons"). Problems concerning unrecognized persons include that they do no seek medical attention even if their test results are positive, and that they may receive hepatitis virus testing repeatedly. To ensure that all hepatitis test recipients are notified of test results, regardless of the purpose or results of the test, the Ministry of Health, Labour and Welfare (MHLW) issued a notice titled "Notification of the results of hepatitis virus tests conducted before surgery, *etc.*" (Notice No. 0423-1 issued by the director of the Specific Diseases Control Division, Health Service Bureau, MHLW) in April 2014. In addition, as part of the MHLW Scientific Research, an attempt to encourage patients to receive medical attention using the alert function of electronic medical records is being conducted mainly at core hospitals for collaborative liver disease care.

Promoting prevention of hepatitis progression (subsidies for the cost of the initial detailed examination and periodic examinations)

Despite the availability of effective treatments and medical expense subsidies, some people who test positive for hepatitis do not receive treatment. A national survey conducted in 2011 showed that only about 60% of hepatitis-positive individuals sought medical attention. In an awareness/trend survey of people who tested positive for hepatitis conducted by Kaishima *et al.* (2016), the most common reasons for not seeking medical attention were "I thought there was no need to visit a hospital" (35.2%), "The doctor said there was no need to visit a hospital" (20.7%), "There is nothing wrong with my liver function or my condition" (15.9%), and "I did not receive any information about what hospital I should visit" (13.1%) (*4*).

Based on these results, local governments are encouraging hepatitis-positive individuals to visit specialized medical institutions and are subsidizing the cost for the first detailed examination and periodic examinations at specialized medical institutions. The aim is to facilitate the early detection and treatment of

hepatitis.

It is recommended to undergo an initial detailed examination as soon as possible to prevent progression to severe conditions, including chronic hepatitis, cirrhosis, and liver cancer. Early treatment and prevention of progression are facilitated through periodic interventions for these patients. The subsidy for the initial detailed examination was previously available to only hepatitis-positive individuals detected by hepatitis virus testing provided by local governments. However, the scope has been expanded to include cases detected at workplaces since FY2019, as well as cases detected during prenatal checkups or preoperative hepatitis screening since FY2020. Patients with chronic hepatitis, cirrhosis, or liver cancer resulting from hepatitis virus infection (including those under post-treatment follow-up) can apply for the subsidy for periodic examinations up to twice a year, and this subsidy is being increased every year. In FY2017, the copayment to be paid by individuals whose annual municipal inhabitant tax is less than 235,000 JPY was reduced to 2,000 JPY per examination for those with chronic hepatitis and to 3,000 JPY for those with liver cirrhosis/cancer (free of charge for low-income households that do not pay municipal inhabitant tax).

Hyogo Prefecture has the largest number of users of the subsidy program for the initial detailed examination, followed by Tokyo, Fukuoka Prefecture, and Chiba Prefecture. The number of users of the subsidy for periodic examinations is highest in Saitama Prefecture, followed by Hiroshima, Fukuoka, and Ehime Prefectures (FY2018 results) (*5*).

Local governments regularly contact hepatitis-positive individuals, with their consent, to check whether they have received medical attention and treatment. Those who have not sought medical attention are encouraged to do so by phone or other means, as necessary. Individuals who apply for the subsidies to cover the cost of the initial detailed examination and periodic examinations must consent to the follow-up project.

Medical expense subsidy system for hepatitis treatment

Rapid progress has been made in hepatitis therapeutics. For hepatitis C, interferon-free therapy not only eliminates viruses at a high rate, but also allows for relatively safe treatment in elderly patients and patients with compensated cirrhosis, who tend not to tolerate interferon therapy. For hepatitis B, the advent of nucleic acid analogue therapy has enabled better disease control. However, because of increased monthly medical expenses or increased cumulative medical expenses from longer-term treatment, the Medical Expense Subsidy System for Hepatitis Treatment was launched in 2008 to facilitate early treatment, and the system has been expanded along with rapid progress in hepatitis treatments. The MHLW and prefectural governments provide medical subsidies for interferon therapy for hepatitis B and C, interferon-free therapy for hepatitis C, and nucleic acid analogue therapy for hepatitis B (*7,8*). Specifically, the subsidies are provided so that the copayment for medical treatment, including the cost of medicines and tests, does not exceed 10,000 JPY or 20,000 JPY per month, depending on the annual household income subject to municipal inhabitant tax. Applicants to this system need to submit their application to the appropriate office (*e.g.*, a public health center) of the prefecture where their residency is registered. As of the end of FY2017, 269 patients receiving interferon therapy (for hepatitis B or C), 31,507 patients receiving interferon-free therapy, and 79,817 patients receiving nucleic acid analogue therapy have been issued hepatitis treatment beneficiary certificates (Figure 4). Moreover, 57.6% of patients treated for liver disease caused by HBV infection received subsidies for nucleic acid analogue therapy, and 9.3% of patients treated for liver disease caused by HCV infection received subsidies for interferon-free therapy.

Project to promote research on treatment of liver cancer and severe cirrhosis

This project was launched in December 2018 and aims to reduce the burden of medical costs for patients with liver cancer or severe (decompensated) cirrhosis caused by hepatitis B or C virus infection. It also aims to collect clinical data and thereby promote research on treatment for liver cancer and severe cirrhosis with the aim of improving prognosis, enhancing quality of life, and reducing the recurrence of liver cancer.

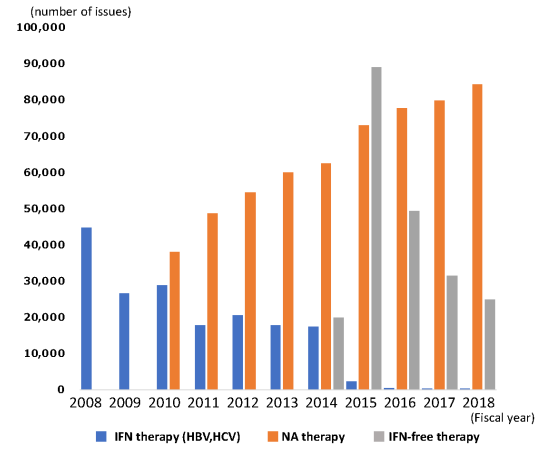

Figure 4. Development of the number of issued hepatitis treatment beneficiary certificates. In the roughly 5 years since interferon-free therapy was approved in Japan for chronic hepatitis C, the number of certificates regarding IFN-free therapy have decreased. IFN: interferon, NA: nucleic acid analogue.

The beneficiaries of this project are patients with liver cancer or severe cirrhosis caused by hepatitis B or C virus infection with an annual income of less than about 3,700,000 JPY. Applicants are required to complete and submit a clinical research form and an informed consent form. Medical expenses for treatment of liver cancer and severe cirrhosis are paid from public funds for patients who meet specified criteria, such as exceeding the maximum amount of high-cost medical care expenses a certain number of times in the past year.

Because this project is implemented primarily by prefectural governments, medical institutions through which patients can receive support for treatment costs (designated medical institutions) are determined by the prefectural governments. The designated medical institutions for this project can be searched for in the Hepatitis Medical Navigation System (*https://kan-navi.ncgm.go.jp*). As of June 2020, 1,393 institutions have been registered in this system. For more information about the project, visit the Ministry of Health, Labor and Welfare (MHLW) website (*https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kekkaku-kansenshou/kanen/kangan/index.html*).

As of December 2019, 391 people have been certified as eligible for the project and the cumulative total number of people who have received medical cost subsidies was 743 (*9*). There are continued efforts to make the operation more flexible and to publicize the project so that patients eligible for these subsidies can be smoothly guided to the system. Specifically, at the beginning of the project, all inpatient care from the 1st to 4th month of hospitalization had to be provided by designated medical institutions. However, from January 2020, 3 months of hospitalization, which is a requirement for certification of eligible patients, can be provided by non-designated medical institutions. Furthermore, since FY2021, the requirements have been relaxed as follows: *i*) molecular targeted therapy in outpatient as well as inpatient settings is covered; and *ii*) if the maximum amount of high-cost medical care expenses was exceeded in 2 or more months in the past year, medical expenses in the third and subsequent months exceeding the maximum amount of high-cost medical care expenses are paid from public funds (Figure 5). In other efforts, non-designated medical institutions are encouraged to apply for the designation when patients who have been hospitalized at the institutions apply for certification of eligibility in the project. In addition to posters and leaflets for patients, leaflets encouraging application for the designated medical institution status are also used to publicize the project.

Other social security systems (Certification of hepatic impairment under the Act on Welfare of Physically Disabled Persons and the disability pension)

Since April 2010, people with hepatic impairment who meet certain criteria have been issued a Physical Disability Certificate, which makes them eligible for partial reduction of medical expenses, depending on the severity of disability. In April 2016, the scope of certification was expanded and the requirements in the disability classification table were relaxed. The Physical Disability Certificate is issued by local governments including prefectures, designated cities, and core cities. Consultation and application for the certificate can be made at the office in charge of disability welfare (welfare office or section) in the municipality of residence.

Patients with hepatitis/cirrhosis who meet the eligibility criteria for the disability pension certified and provided by the Japan Pension Service can also apply for the pension. Inquiries and requests can be made to the municipality of residence or the Japan pension

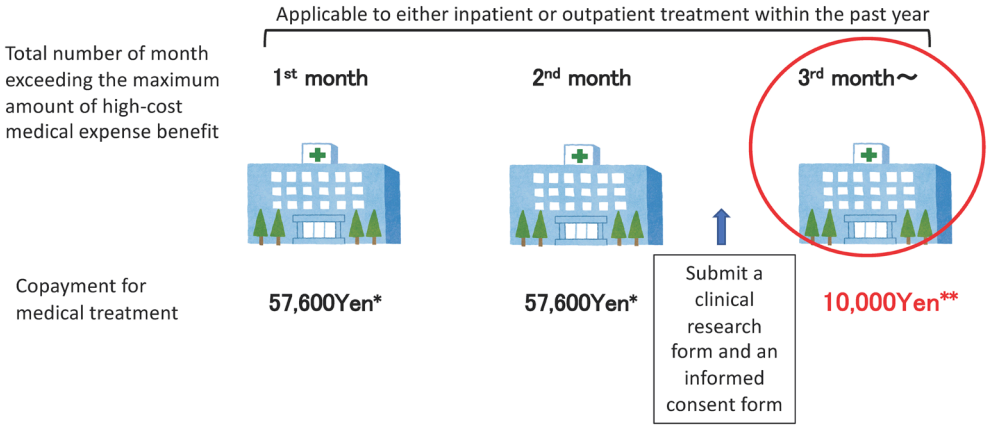

Figure 5. The image of project to promote research on treatment of liver cancer and severe cirrhosis. *Maximum amount of high-cost medical expense benefit. **Treatment should be done at designated medical institutions to receive support for treatment costs.

service (JPS) branch office for the disability basic pension, or to the JPS branch office for the disability employees' pension.

Establishment of medical care and support systems for liver diseases

Hepatitis care network in Japanese prefectures

In 2007, the Guidelines for the Establishment of Post-Hepatitis Test Care System for Liver Diseases in Prefectures was released in a report of the National Medical Conference on Hepatitis C Countermeasures on January 26, 2007, in which it listed three roles required of medical institutions for liver disease care: primary care physicians, specialized institutions for liver diseases, and medical institutions that provide highly advanced medical care for liver diseases (regional core centers for the management of liver disease, hereinafter referred to as "regional core centers"). Based on these guidelines, the MHLW issued the "Notice on the Establishment of Liver Disease Care Systems" (Notice No. 0419001 issued by the Director of the Health Service Bureau, MHLW) in April 2007. In response to this, the construction of liver disease care systems began nationwide, starting with regional core centers and specialized institutions.

Regional core centers are designated by the Council for Hepatitis Measures in each prefecture from among medical institutions that currently play a central role in the liver disease care network in each prefecture. Regional core centers are required to *i*) provide general medical information on liver diseases; *ii*) collect information on medical institutions in the prefecture and refer patients to these institutions; *iii*) provide training for healthcare professionals and education for community residents; *iv*) set up opportunities for consultation with specialized medical institutions for liver diseases; and *v*) provide multidisciplinary treatment for liver cancer. Currently, at least one regional core center is designated in each prefecture, with a total of 71 institutions nationwide, all of which have established liver disease consultation and support centers to provide support to patients and their families. Specialized institutions are selected by the Council for Promotion of Hepatitis Measures in each prefecture and are required to i) make a diagnosis and determine a treatment strategy, as recommended by specialists; ii) appropriately implement antiviral therapy; and iii) identify groups at high risk of liver cancer and perform early diagnosis. Over 3,000 specialized medical institutions have been designated nationwide.

In the process of developing regional liver disease care systems, the environment surrounding liver disease care has also changed, including the improvement of hepatitis control measures and development of new treatments. Against this background, in March 2017, the MHLW issued the "Notice on the Establishment of Liver Disease Care Systems and Support Systems for Liver Disease Patients" (*10*) (Notice No. 0331-8 issued by the Director of the Health Service Bureau, MHLW; hereafter referred to as the "new notice"). The new notice, while maintaining the previous basic policies, sets out the following new basic approaches: *i*) setting of goals and milestones; *ii*) establishment of a system to ensure the smooth linkage of hepatitis screening, examination, treatment, and follow-up; *iii*) realization of patient-centered liver disease care; *iv*) improvement of and elimination of disparities in liver disease care; and *v*) provision of consultation and appropriate support for hepatitis patients. The aim is to establish hepatitis care networks based on these approaches and thereby promote hepatitis control measures that are tailored to local needs.

Hepatitis medical care coordinator

Some local governments also began training hepatitis medical care coordinators in 2003 to facilitate the awareness-raising and education for residents as well as dissemination of information to patients and their families. However, there were large regional differences in these efforts, and after some debate, the basic roles and activities of hepatitis medical coordinators were defined in April 2017 (*11*) ("Notice on the Training and Utilization of Hepatitis Medical Care Coordinators" [Notice No. 0425-4 issued by the Director of the Health Service Bureau, MHLW]). Hepatitis medical care coordinators are located in local communities, workplaces, hospitals, and the like, and their activities include providing the basic knowledge and information on hepatitis that are required for each area, promoting understanding of hepatitis, providing assistance for consultation, guiding residents to the consultation centers, encouraging residents to receive hepatitis screening and examination, and providing explanations of the system. These coordinators are from various fields and include nurses, public health nurses, pharmacists, local government officials, and workplace representatives. Rather than one coordinator taking on all the roles, coordinators from various fields use their strengths to support patients from the general public and coordinate to ensure the appropriate promotion of hepatitis care. Cooperation and collaboration among hepatitis medical care coordinators from various fields is expected to facilitate hepatitis prevention, screening, diagnosis, treatment, and follow-up. It is also hoped that the activities of hepatitis medical care coordinators in local communities and workplaces will foster a foundation for spreading understanding of hepatitis in society, leading to the elimination of discrimination and prejudice against hepatitis patients. Hepatitis medical care coordinators are located at core hospitals, specialized medical institutions, public health centers, municipalities, pharmacies, and other facilities, although their main places of activity

currently appear to be core hospitals and public health centers (*12*). An increasing number of prefectures are providing training to improve the skills of hepatitis medical care coordinators and conducting supportive activities to revitalize their efforts, such as publishing the list of institutions with coordinators, creating coordinator's badges, and establishing a consultation system for coordinators.

Consultation support system for patients with liver diseases

Consultations provided at the liver disease consultation and support centers of core hospitals cover a wide range of topics. The most common topics are medical expense subsidy systems, treatment, and the disease itself, and there has been recent growth in the number of consultations on things to keep in mind in daily life as well as medical institutions, livelihood support, and hepatitis-related lawsuits (*13*). In response to the need to improve the consultation system for hepatitis patients in various situations, the Consultation Support System for Patients with Liver Diseases was introduced at core hospitals across Japan in July 2018 to provide consultation support for hepatitis patients. This system is managed and operated by the Hepatitis Information Center, which is described below. This system is designed to create a database of consultations received by hepatitis patients; entries can be searched and edited by consultation staff at core hospitals and other related facilities. The database is shared among core hospitals and is utilized to ascertain the number and trends of consultations, search for model answers to consultations, and exchange opinions among consultation staff. This enables the hospitals to share the trends of diversifying consultation content and difficult-to-answer questions nationwide and to use the database as an auxiliary tool for responding appropriately to individual consultations. Thus, it is expected that these capabilities will help to alleviate hepatitis patients' concerns and improve their quality of life.

Conclusion

Now that advances in treatment have made it possible to control hepatitis or eliminate the viruses, it is critical that hepatitis patients detected by testing receive appropriate medical care as soon as possible. At the same time, many patients require long-term treatment due to the nature of the disease, and measures are needed to ensure that these patients can continue to receive treatment with peace of mind.

Hepatitis control measures in Japan have been developed mainly based on the Basic Act on Hepatitis Measures, and extensive efforts have been made accordingly. In addition to providing subsidies for testing and medical expenses, it is necessary to further strengthen cooperation among the national and local governments, Hepatitis Information Center, core hospitals, specialized medical institutions, primary care physicians, and others. Thereby, hepatitis control measures may be promoted in line with local needs, thus encouraging the public to receive hepatitis virus testing in various settings, including the workplace, and promoting follow-up of individuals who test positive for hepatitis virus infection.

Funding: The data included in this review article were partly granted by the Ministry of Health, Labour and Welfare, Japan (20HC2002).

Conflict of Interest: Tatsuya Kanto receives lecture fees from Gilead Sciences and Abbvie. Yasuhito Tanaka is currently conducting research sponsored by Fujifilim Corp., Janssen Pharmaceutical K.K, Gilead Sciences, GlaxoSmithKline Pharmaceuticals Ltd, and Stanford University. Lecture fees are as follows: Fujirebio Inc., Abbvie. and Gilead Sciences. Scholarship Donations from Abbvie. The other authors have no conflicts of interest to disclose.

References

1. Ministry of Health, Labour and Welfare. Promotion of comprehensive measures for hepatitis control - What is hepatitis -. *http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/hepatitis_about.html* (accessed June 10, 2021). (in Japanese)
2. Oza N, Isoda H, Ono T, Kanto T. Current activities and future directions of comprehensive hepatitis control measures in Japan: The supportive role of the Hepatitis Information Center in building a solid foundation. Hepatol Res. 2017; 47:487-496.
3. Health, Labour and Welfare Statistics Association. Viral Hepatitis. In:Trends in national health, 2016/2017. Health, Labour and Welfare Statistics Association. Tokyo, Japan, 2016; pp.146-148. (in Japanese)
4. Kaishima T, Fujii T, Matsuoka T, *et al.* Study of the issues of receiving hepatitis screening and the rate of consulting hospitals - The rate of recognized receiving hepatitis screening and that of the unrecognized. Kanzo. 2016; 57:634-648. (in Japanese)
5. Ministry of Health, Labour and Welfare. The 25th Meeting of the Council for Promotion of Hepatitis Measures. Document 1. *https://www.mhlw.go.jp/content/10901000/000719442.pdf* (accessed June 10, 2021). (in Japanese)
6. Sugiyama A, Fujii T, Nagashima S, Ohisa M, Yamamoto C, Chuon C, Akita T, Matsuo J, Katayama K, Takahashi K, Tanaka J. Pilot study for hepatitis virus screening among employees as an effective approach to encourage employees who screened positive to receive medical care in Japan. Hepatol Res. 2018; 48:E291-E302.
7. Ministry of Health, Labour and Welfare. Promotion of comprehensive measures for hepatitis control - Medical expense subsidy system for hepatitis treatment -. *http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/080328_josei.html* (accessed December 1,

2017). (in Japanese)
8. Hepatitis Information Center, National Center for Global Health and Medicine. Medical expense subsidy system for hepatitis treatment. *http://www.kanen.ncgm.go.jp/cont/040/zyosei.html* (accessed June 10, 2021). (in Japanese)
9. Hepatitis Information Center, National Center for Global Health and Medicine. The 1st liaison meetings among the regional core centers (FY2019). Document *http://www.kanen.ncgm.go.jp/archive/conference/council/20200710_kourou.pdf* (accessed June 10, 2021). (in Japanese)
10. Ministry of Health, Labour and Welfare. Promotion of comprehensive measures for hepatitis control - Notice on the Establishment of Liver Disease Care Systems and Support Systems for Liver Disease Patients -. *http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/pdf/hourei-170404-2.pdf* (accessed June 10, 2021). (in Japanese)
11. Ministry of Health, Labour and Welfare. Promotion of comprehensive measures for hepatitis control - Notice on the Training and Utilization of Hepatitis Medical Care Coordinators -. *http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/pdf/hourei-170425-1.pdf* (accessed June 10, 2021). (in Japanese)
12. Ministry of Health, Labour and Welfare. The 24th Meeting of the Council for Promotion of Hepatitis Measures. Document 1. *https://www.mhlw.go.jp/content/10901000/000576275.pdf* (accessed June 10, 2021). (in Japanese)
13. Setoyama H, Korenaga M, Kitayama Y, Oza N, Masaki N, Kanto T. Nationwide survey on activities of regional core centers for the management of liver disease in Japan: Cumulative analyses by Hepatitis Information Center 2009-2017. Hepatol Res. 2020; 50:165-173.

Received June 26, 2021; Revised August 17, 2021; Accepted Revised August 20, 2021.

Released online in J-STAGE as advance publication September 5, 2021.

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Global Health & Medicine. 2021; 3(5):343-350.
REVIEW
DOI: 10.35772/ghm.2021.01073

Hepatitis medical care coordinators: Comprehensive and seamless support for patients with hepatitis

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Abstract: Chronic liver disease, especially viral hepatitis, is an urgent issue in Japan. Human resource management is important to promote appropriate care for patients with chronic liver disease in medical institutions and in the community. In 2011 the Ministry of Health, Labour and Welfare in Japan started training hepatitis medical care coordinators (HMCCs). Various medical professionals (such as public health nurses, general nurses, and clinical technicians), patients, and ordinary citizens are certified as HMCCs by the prefectural government after learning about liver diseases in a training program. The training program can be optimized in accordance with the regional circumstances and basic knowledge and skills of the applicants. HMCCs encourage residents and patients to undergo a hepatitis screening test, after which positive patients undergo detailed examination, treatment, and follow-up. HMCCs contribute to the expansion of knowledge about hepatitis in their workplace and community. By 2018, there were HMCCs in all 47 prefectures of Japan. There were 20,049 HMCCs in 2019. The most common professions of HMCCs were public health nurses, followed by general nurses, hospital pharmacists, laboratory technicians, and medical social workers. After certification, the activities of HMCCs vary; to ensure that HMCCs are adequately used in medical institutions, the supervisor and physicians must recognize the importance of HMCCs and generate opportunities for HMCC activity. The training and effective utilization of HMCCs is a promising way to decrease the prevalence and mortality of chronic liver diseases in Japan.

***Keywords*:** hepatitis, coordinators, chronic liver disease, screening, treatment, follow-up

Introduction

The national survey of Japanese citizens conducted by the Ministry of Health, Labour and Welfare (MHLW) in 2011 revealed that approximately 50% of Japanese citizens had been screened for viral hepatitis (*1*). According to research supported by the Health and Labour Sciences Research Grant, the number of Japanese people who underwent detailed examination at a medical institution from 2014-2016 following a positive result in a screening test for viral hepatitis was estimated to be 0.53 to 1.2 million (*2*).

In 2009, the MHLW published the Basic Act based on Hepatitis Measures as a national action plan for addressing viral hepatitis. The Basic Guidelines on Hepatitis Measures was then issued in 2011 and revised in 2016. All measures and policies against hepatitis reflect these guidelines, which aim to reduce the number of patients with progression to cirrhosis and liver cancer. The guidelines recommend the spread of basic knowledge about hepatitis among the general population and relevant professionals, and promotion of screening tests for viral hepatitis, detailed examination after screening and continuing appropriate treatment. The guidelines state that it is important for individuals with positive hepatitis screening test results at regional medical health check-ups and medical institutions to receive appropriate information and referral to a hepatologist for further detailed examination and treatment.

Along with these comprehensive measures and guidelines against hepatitis, there is a need for human resource personnel who support the decision-making and actions of the general population and hepatitis virus-positive population. Nationwide training of such human resource personnel started in 2009, and the training of hepatitis medical care coordinators (HMCCs) was promoted under a MHLW project from 2011. The revised Basic Guidelines issued in 2016 defined fundamental roles of HMCCs as: spreading awareness of hepatitis in their community or workplace, encouraging people to get screened for hepatitis, and following up with people who receive a positive hepatitis screening result (*3-6*). The name "hepatitis medical care coordinator" was proposed by the MHLW. The word "coordinator" was used in the name because the expected role of HMCCs includes collaboration with medical institutions, government

agencies, and other relevant parties in the community and workplace. The director of the Health Services Bureau (HSB) of the MHLW issued a notification stating that training of HMCCs should be promoted in a nationwide effort as part of a plan to implement measures to support patients with hepatitis (*7*). Various medical professionals, patients and citizens are eligible to be HMCCs. The training course consists of an education program about hepatitis, hepatitis management, and public medical services.

Yamanashi Prefecture used to have the highest mortality rate for liver cancer in Japan. In 2009, the Yamanashi prefectural government started training human resource personnel referred to as "liver disease coordinators" who contributed to a prefectural primary measure to decrease the regional mortality rate. A total of 23 liver disease coordinators were certificated in the first round of the training program. The liver disease coordinators of Yamanashi Prefecture were later recognized as performing unique and important activity that fits the national measures against hepatitis, and this inspired similar training programs of HMCCs in other prefectures across Japan.

Chapter 5 of the revised Basic Guidelines on Hepatitis Measures asked individual prefectures to follow the basic roles of HMCCs as defined in the Guidelines (*5*). Subsequently, a document compiling recommendations for the training and utilization of HMCCs was drafted at the 19th annual meeting of the Council for Promotion of Hepatitis Measures organized by the MHLW. This document was called the "Notification Regarding Training and Utilization of Hepatitis Medical Care Coordinators" and was issued to prefectural governments by the director of the HSB of the MHLW on April 25, 2017 (MHLW HSB Notification No. 0425-4) (*7*). This document also defined the roles and activities of HMCCs, which should be flexibly optimized to fit the regional circumstances regarding hepatitis care. This optimization should reflect feedback from stakeholders such as municipal government officials, healthcare professionals at regional core centers for liver disease care and other institutions, and patients with hepatitis; even the name "HMCCs" can be modified. Moreover, the training program and contents can be optimized depending on the placement and occupation of the HMCCs. Each individual prefecture should update the roles, activities, and training of HMCCs in accordance with the changes in the regional measures against hepatitis. By 2018, HMCCs were available in all 47 prefectures of Japan. This review summarizes the current state and issues of HMCCs and discusses further utilization of HMCCs based on related documents, measures, literature and survey results.

Role of HMCCs as coordinators

Role of HMCCs in the community

The constitutive network of professionals such as primary care physicians, public health nurses and medical workers in the community and workplace is important to promote screening for hepatitis, detailed examination after screening, and treatment with appropriate antiviral therapy. The primary role of HMCCs involves direct engagement with residents and patients with hepatitis in the community. HMCCs working at medical institutions are also expected to collaborate with those working at government agencies. The extensive engagement of HMCCs across communities and workplaces is effective in increasing public understanding of hepatitis and is expected to reduce the discrimination and prejudice against patients with hepatitis that impedes the smooth transition through screening, detailed examination after screening, treatment, and follow-up.

Role of HMCCs for individuals

The most important role of HMCCs is to support patients with hepatitis and their family members to promote a seamless transition through the four stages of measures against hepatitis (screening, detailed examination, treatment, and follow-up). Depending on the placement and profession of the HMCC, the roles of HMCCs are divided into: *i*) offering advice to patients with hepatitis and their family members through counseling, *ii*) referring people to government agencies and regional core centers for liver disease care, *iii*) encouraging people to undergo a screening test for viral hepatitis, *iv*) encouraging people with positive screening test results to undergo detailed examination at a specialized medical institution, and *v*) providing information about medical expenses and other relevant programs (Figure 1). HMCCs activities engage medical workers such as public health nurses, general nurses, pharmacists, clinical technicians and nutritionists, medical administrators, general citizens, and patients with hepatitis. Therefore, the activities of HMCCs vary depending on their site of placement in a medical institution or screening organization, public health center or municipal government agency, or health service section in a private company or health insurance company. Recruiting people with various professions and backgrounds as HMCCs contributes to covering the entire activity and concept of HMCCs. Table 1 shows the roles of HMCCs as suggested by the MHLW.

The activity of HMCCs is basically voluntary work in addition to or concurrent with their original job tasks in the medical profession. HMCCs expertly support people and patients affected by hepatitis. Legal compliance related to the background quantification and workplace should be maintained throughout any HMCC activity. Private information should be protected in accordance with the relevant laws.

Training and education of HMCCs

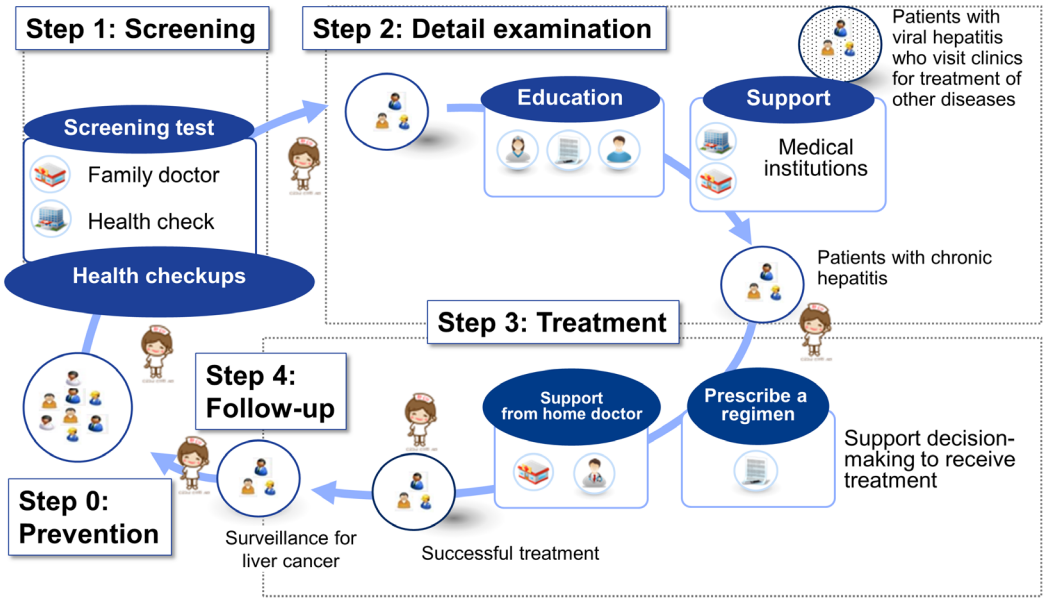

Figure 1. Hepatitis medical care coordinators (HMCCs) activity at each step of hepatitis care. HMCCs promote hepatitis screening tests (step 1), detailed examination (step 2), treatment (step 3), and follow-up after treatment. HMCCs also promote the prevention of liver disease and hepatitis virus infection (step 0).

Training of HMCCs

Prefectural governments are primarily responsible for the training of HMCCs. Training seminars and qualification examinations are organized in collaboration with the regional core center. Individuals are certified as HMCCs and registered on the official list. Although the eligibility requirements for HMCCs vary among prefectures, several prefectures do not require HMCCs to be qualified experienced medical workers. The common topics included in the HMCC training program are described in Table 2. The contents of the program are designed to be flexible and to be optimized in accordance with the regional circumstances and differences in the baseline knowledge and experiences of applicants. The program may also include upcoming topics that might be associated with the roles of HMCCs in the future.

Certification of HMCCs

Most prefectures issue HMCC certificates signed by the prefectural governor or the director of the government department responsible for measures against hepatitis. An increasing number of prefectures also issue a badge that is worn on the professional uniform to identify the wearer as a HMCC. Recently, several prefectures have begun to require periodical renewal of HMCC certification, and provide advanced programs for further learning (*8*). Several prefectures ask the institutions where HMCCs work to submit periodic reports about HMCC activities.

Continuous education of HMCCs

Following changes in hepatitis care such as drug development and amendment of measures, it is important for HMCCs to update their knowledge. Opportunities for HMCCs to learn the newest information should be provided. Sharing the experiences of HMCC activities, especially successful activities, encourages HMCCs and increases their motivation. Interdisciplinary collaboration among HMCCs and other professionals will extend the possibility of HMCC activities. Joining patient group meetings provides different viewpoints and thoughts of patients with hepatitis and their family members. Prefectures and regional core centers organize various lectures, meetings, and educational events for HMCCs. In many prefectures, these opportunities are available and open to all people involved in hepatitis care.

Activation of HMCC activity

Several prefectures do not track the activity of HMCCs after their certification. Our questionnaire-based self-evaluation survey found that approximately 60% to 70% of HMCCs were underutilized (*9*). Prefectures and regional core centers for liver disease care need to establish an implementation strategy for the better utilization of HMCCs. Possible approaches to increase the utilization of HMCCs include *i*) increasing the awareness of HMCCs and their activities among the general public and patients with hepatitis, *ii*) making the list of organizations with HMCCs available to the general public and patients with hepatitis, *iii*) creating badges or other items to identify HMCCs, *iv*) encouraging collaboration with other medical institutions and groups (including patient groups) to identify potential opportunities for HMCC activity,

Table 1. Roles of hepatitis medical care coordinators (HMCCs)

Segment	1) Regional core centers, medical institutions, and screening organizations	2) Public health centers and municipal government offices	3) Private companies or health insurers	4) Other organizations
Basic roles	Provide information, counseling, and support regarding health and lifestyle, and carry out follow-up to ensure that patients with hepatitis and people who test positive for hepatitis receive appropriate medical care; coordinate the collaboration between government agencies and workplaces to provide appropriate information and opportunities for patients with hepatitis.	Raise public awareness and disseminate information about all aspects of hepatitis prevention; coordinate with regional core centers and other related community organizations and occupational health-focused organizations to promote screening, detailed examination after screening, treatment, and follow-up through their agencies.	Promote hepatitis screening in the workplace and strive to create a work environment that allows patients with hepatitis to continue working comfortably as they undergo treatment.	Raise public awareness in their local community, serve as a source of advice for patients with hepatitis and their family members, and link patients to medical institutions and government agencies.
Specific examples of the job description	√ Explain information related to hepatitis care and direct people to hepatitis screening services √ Encourage people who screen positive for hepatitis to undergo detailed examination, and refer them to a specialized medical institution √ Explain the importance of continuing follow-up examinations (such as blood tests including tumor markers and ultrasonography) after antiviral therapy √ Offer lifestyle advice and guidance on medication use and nutrition to patients with hepatitis and their family members √ Explain public subsidy programs for regular testing expenses or medical expenses and the disability certificate program, or assistance from the appropriate government agency √ Direct people to resources for assistance with settlements from class-action lawsuits regarding hepatitis C and B √ Direct people to resources for assistance with working or parenting while receiving hepatitis treatment √ Organize workshops for medical institution staff √ Participate in educational sessions on liver disease and patient support groups held by regional core centers or medical institutions that specialize in liver disease √ Participate in public awareness events in the community or workplace and publicize those events	√ Explain basic information about hepatitis and encourage people to undergo screening for hepatitis √ Refer people to medical institutions or organizations where they can be screened for hepatitis √ Refer people to regional core centers for liver disease care, consultation and support centers for liver disease, and specialized medical institutions √ Encourage people who screen positive for hepatitis to undergo detailed examination √ Direct people to follow-up programs run by the national government, or carry out independent follow-up (in the case of some prefectural governments) √ Direct people to subsidy programs to cover regular testing expenses or medical expenses and the disability certificate program √ Explain and direct people to programs for periodic immunization against hepatitis B and conduct outreach and educational programs to inform people about infection prevention √ Direct people to resources for assistance with settlements from lawsuits regarding hepatitis C and B √ Direct people to resources for assistance with working or parenting while receiving hepatitis treatment √ Participate in public awareness events in the community or workplaces and direct people to those events	√ Provide information about hepatitis to business owners, management, and human resource departments √ Raise awareness among employees of the basic facts about hepatitis √ Direct people to hepatitis virus testing services and counseling resources √ Offer advice on how to continue working while receiving hepatitis treatment and accommodate patients in the workplace (*e.g.*, direct them to counseling resources) √ Refer people to support and counseling services such as consultation and support centers for liver disease at regional core centers for liver disease care √ Explain subsidy programs to cover regular testing expenses or medical expenses and the disability certificate program, or direct people to resources for assistance from the appropriate government agency √ Participate in public awareness events in the community or workplace and direct people to those events	√ Raise awareness among community members and facility residents of the basic facts about hepatitis √ Direct people to hepatitis testing √ Direct people to information sources about hepatitis and to the nearest consultation and support center for liver disease √ Participate in public awareness events in the community or workplace and direct people to those events

Possible occupation and background of a HMCC in each segment: 1) Medical professionals such as doctors, nurses, pharmacists, registered dieticians, clinical technicians, medical social workers, and other staff at medical institutions. 2) Public health nurses, public health professionals, and government agency staff. 3) Occupational health managers, human resource and labor relations managers, and labor and social security attorneys. 4) Patient advocacy group members, employees of pharmacies, welfare offices, or nursing care offices, and community association members.

Table 2. Topics commonly included in the hepatitis medical care coordinator (HMCC) training program

i) Expected roles and outlook of HMCCs	√ Learn to be cautious in giving information and advice to patients with hepatitis and people who test positive for hepatitis, and to be conscious of their role in linking these individuals to relevant institutions.
	√ Understand the general picture of prefectural goals for measures against hepatitis and the flow of screening, detailed examination after screening, treatment, and testing in their prefecture and understand their role and methods for coordination as determined by their site of placement or their profession. Ministry of Health, Labour and Welfare notifications state that it is important for local governments, medical institutions, and hepatologists in leadership roles to make concessions and ensure that HMCCs feel fulfilled in their work. These concessions were put into a guidebook and distributed to prefectures and regional core centers for liver disease care across Japan as part of a project funded by a Health and Labour Sciences Research Grant (*9*).
	√ Understand the feelings of patients, develop a compassionate mindset, and learn techniques for compassionate engagement. Understand how to protect patients' rights, prevent discrimination and bias, and handle personal information. Several prefectures organize opportunities for trainees to hear directly from patients and their family members during HMCC training.
ii) Basic knowledge of liver diseases	√ Have basic knowledge of topics such as infection prevention, pathology, testing (*e.g.*, perspectives on hepatitis testing and liver function testing), and treatment related to hepatitis B, hepatitis C, nonalcoholic steatohepatitis, cirrhosis, and liver cancer. Encourage people who screen positive for hepatitis to receive detailed examination and refer them to a specialized medical institution.
iii) Knowledge of local circumstances and public programs	√ Understand the epidemiology of liver disease in their prefecture, regional characteristics and challenges, and plans and targets for prefectural measures against hepatitis.
	√ Be familiar with periodic immunization schedules against hepatitis B, hepatitis screening programs in their prefecture or city, public subsidy programs for medical expenses associated with further testing after an initial diagnosis of hepatitis infection and periodic testing for hepatitis, and counseling services under the Act on Special Measures Concerning Hepatitis B and the Act on Special Measures Concerning Hepatitis C.
	√ Provide basic information about the High-Cost Medical Expense Benefit, policies to support people with disabilities, and social programs to support working while receiving treatment (*e.g.*, programs that allow patients to take time off, take a leave of absence from work, or to work reduced hours) and provide the contact information of places that offer counseling on these matters.
iv) Regional systems for the coordination of liver disease care	√ Know the roles and availability of regional core centers for liver disease care (liver disease counseling and support centers), specialized medical institutions, and hepatologists in their prefecture, and develop a system for coordination between primary care physicians and these institutions.
v) Specific tasks	√ Have knowledge of effective methods for encouraging hepatitis screening and detailed examination, methods for counseling and supporting patients with hepatitis and their family members, specific approaches for hosting educational sessions on liver diseases, patient support groups, and high-level case studies.
	√ New HMCCs are expected to acquire skills that enable them to respond flexibly to meet various needs in the field by learning from case studies of real-world challenges encountered by experienced HMCCs.

v) promoting understanding of HMCC activity by hepatologists and providing an environment where HMCCs can work effectively, and *vi*) asking the administrators of individual institutions to support the activities of HMCCs (*9*). The Hepatitis Information Center shares case studies about HMCC initiatives and methods to support HMCCs (*10*).

Maximization of the advantages based on the professional backgrounds of HMCCs

HMCCs can be placed at regional core centers for liver disease care, specialized medical institutions that employ hepatologists, other general medical institutions, public health centers and municipal government offices, screening organizations, pharmacies, disability welfare and nursing care offices, private companies and organizations, health insurers, patient groups, and others. To promote referral to hepatitis specialists when needed, it is important that HMCCs are placed at general clinics without a hepatologist (*e.g.*, ophthalmology clinics, orthopedic surgeries, and obstetric clinics) that commonly perform screening for viral hepatitis, as well as at specialized medical institutions with hepatologists that provide hepatitis treatment. Patients with hepatitis and their family members can become HMCCs and can offer support based on their own personal experience as a person affected by hepatitis. Engagement of HMCCs across local communities and workplaces is expected to reduce discrimination and bias against patients with hepatitis and to increase public understanding of hepatitis. It is important that an individual coordinator does not have to take on all roles, but rather utilizes the advantages of their field and collaborates with others to promote appropriate hepatitis care. In accordance with the regional implementation of measures against hepatitis (*8*), many prefectures have a defined policy for HMCC placement and have specific targets for the number of HMCCs and the number of medical institutions with HMCCs.

Current HMCCs in Japan

By 2018, there were HMCCs in all 47 prefectures of

Japan. There were 20,049 HMCCs in 2019 (Figure 2) (*11*). According to a survey by the Hepatitis Information Center, more than 3,800 HMCCs were trained at 50 of the 71 regional core centers (*12*). In Hiroshima Prefecture and Saga Prefecture, more than 1,000 HMCCs were trained by 2017 (*13*). In 2018, the most common professions of HMCCs were general nurses and were available in 46 prefectures (98%), followed by public health nurses (45 prefectures, 96%), laboratory technicians (38 prefectures, 81%), hospital pharmacists (37 prefectures, 79%), and medical social workers (36 prefectures, 77%) (Figure 3) (*14*). Enomoto *et al.* conducted a questionnaire survey about the placement and degree of activity of HMCCs at 17 regional core centers in 2019 (*15*). The total number of HMCCs was 480, and the number of HMCCs at each center

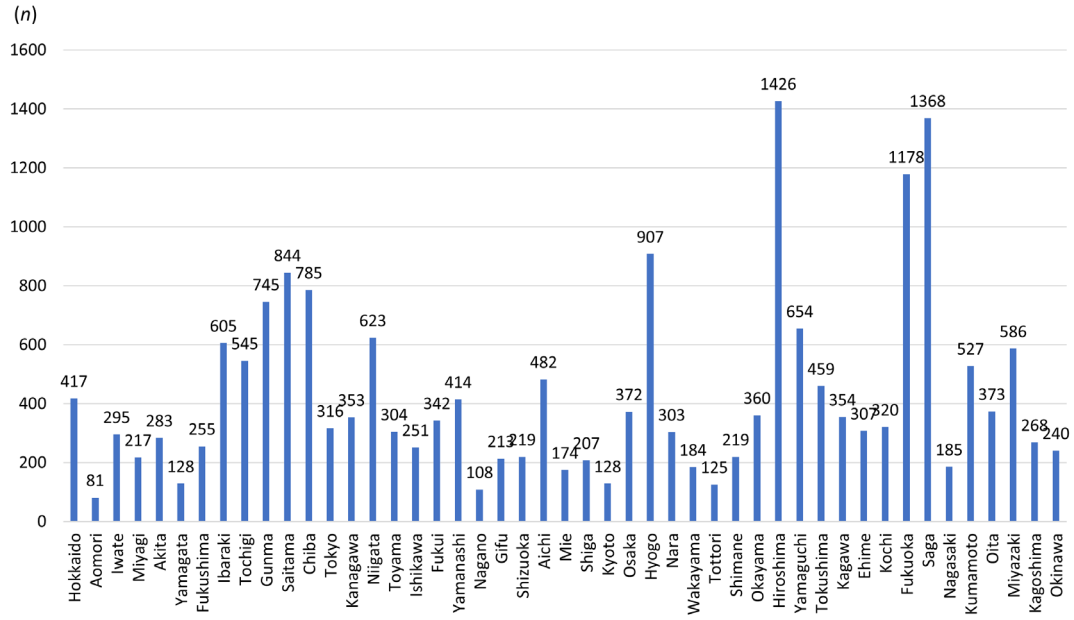

Figure 2. Number of hepatitis medical care coordinators (HMCCs) in Japan. In 2019, there were a total of 20,049 HMCCs in 47 prefectures. All prefectures had started training HMCCs by 2018.

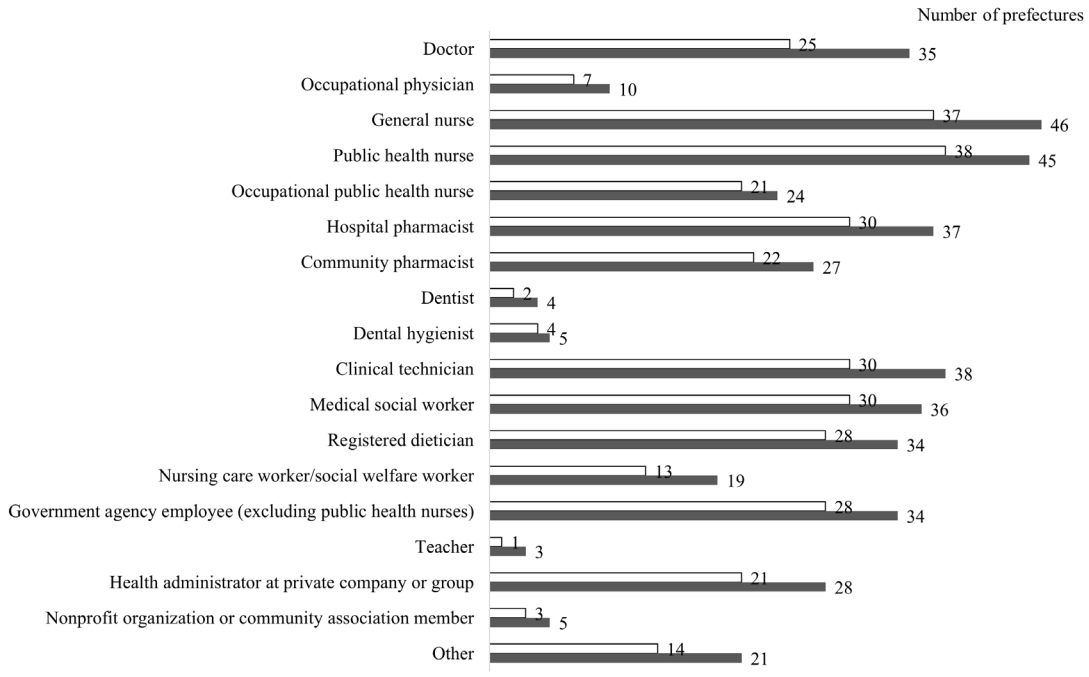

Figure 3. Professions of hepatitis medical care coordinators (HMCCs). The bar graph shows the number of prefectures that trained people from individual professions as HMCCs. The open bars and gray bars represent the number of prefectures in 2017 and 2018, respectively.

varied from eight to 77. The overall mean percentage of active HMCCs in all facilities was 78% (374/480), and this varied from 7.9 to 100% among the facilities. The most common occupations of the HMCCs were nurses (50%), followed by clinical laboratory technicians (11%), pharmacists (8.0%), nutritionists (8.0%), and doctors (3.5%); 29.3% of the nurses were assigned to the department in charge of liver disease.

Challenges in HMCC work

The current state of HMCC activity and issues were surveyed by qualitative interviews with HMCCs, working supervisors and colleagues of HMCCs in 2018 (*12*). A total of 124 healthcare professionals were interviewed and various issues were recognized. We then conducted a quantitative self-evaluation survey in all 47 prefectures. HMCCs were divided into four segments in accordance with their degree of activity as a HMCC and degree of self-awareness as a HMCC. Regardless of the self-awareness as a HMCC, HMCCs with professions and backgrounds showed high activity levels. We generated a movie of their activities (*16*) and compiled the important points into a reference book (*17*). The survey also revealed several issues regarding underutilization in the segments with low activity caused by no opportunity for HMCC activity, not knowing what they can do as an HMCC, not having the knowledge and methods for HMCC activity, and being denied permission for HMCC activity by the institution. The degree of activity tended to be low when the HMCC activity was not recognized by the prefectural government, supervisor, and physicians. In contrast, active HMCCs were well recognized and appreciated by supervisors, hepatologists, and patients in their institutions, and were given further opportunities for HMCC activity. These results suggest that recognition of HMCCs by others is associated with increasing activity of HMCCs. Our research group created leaflets for each prefecture to help supervisors and patients understand the importance of HMCC activity (*18*).

Overseas expansion of HMCCs

Similar to Japan, Mongolia has a high mortality rate of liver cancer, and the major etiology of liver cancer is chronic hepatitis C (*19,20*). It is estimated that 52,500 patients need anti-hepatitis C therapy (*21*). The total number of medical workers in Mongolia is insufficient, and the individual medical workers have inadequate knowledge about hepatitis C (*22*). Therefore, there is a need for an awareness program for patients with hepatitis and an educational program for medical workers. Since 2016, we have been exchanging opinions and information about viral hepatitis with the members of the Ministry of Health in Mongolia. In December 2018, we educated 150 medical workers as the first HMCCs in Tuv province, Mongolia. The HMCCs training program was officially supported by the Mongolian government. To our knowledge, there is no similar human resource development program like the HMCCs training program supported by government in other countries except in Japan and Mongolia. Further training sessions were scheduled in other provinces of Mongolia in 2020. However, it was postponed due to the recent COVID-19 pandemic. We are planning to support the Mongolian HMCCs training activity on the web. Overseas expansion of the Japanese HMCC training program will contribute to improve the hepatitis care system and decrease the mortality rate of liver cancer in Mongolia and other countries.

Conclusion

There have been marked developments in the diagnosis and treatment of viral hepatitis, cirrhosis, and liver cancer. In accordance with the World Health Organization's target of hepatitis C elimination by 2030 (*23*), there has been a worldwide expansion of hepatitis screening tests and encouragement of patients with positive results to undergo treatment. The training and effective utilization of HMCCs in Japan is a promising way to decrease the prevalence and mortality of liver disease.

Acknowledgements

This work was conducted as part of research by the Hepatitis of Ministry of Health, Labour and Welfare in Japan and was supported by grants for Research on Hepatitis of Ministry of Health. We would like to thank the researchers working on our research project entitled "Validation and Expansion of Strategies to Control Hepatitis through Screening, Detailed Examination after Screening, and Treatment" and all the staff of the Liver Center and Department of Internal Medicine at Saga University Hospital for their assistance in writing this manuscript.

Funding: This work was conducted as part of research by the Hepatitis of Ministry of Health, Labour and Welfare in Japan and was supported by grants for Research on Hepatitis of Ministry of Health entitled "Validation and Expansion of Strategies to Control Hepatitis through Screening, Detailed Examination after Screening, and Treatment".

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Ministry of Health, Labour and Welfare. Survey of hepatitis screening rates among Japanese citizens, 2012.

https://www.mhlw.go.jp/stf/houdou/2r9852000002gd4j-att/2r9852000002gd60.pdf (accessed July 23, 2021). (in Japanese)
2. Ministry of Health, Labour and Welfare. Material 3 at the 13th meeting of the council for promotion of hepatitis measures. *https://www.mhlw.go.jp/file/05-Shingikai-10905750-Kenkoukyoku-Kanentaisakusuishinshitsu/0000075723.pdf* (accessed July 23, 2021). (in Japanese)
3. Basic Act on Hepatitis Measures. *http://www.japaneselawtranslation.go.jp/law/detail/?id=1995&vm=04&re=01* (accessed July 23, 2021).
4. Basic guidelines for promotion of control measures for hepatitis, May 16, 2011. *https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/pdf/hourei-17e.pdf* (accessed July 23, 2021).
5. The revised basic guidelines for promotion of control measures for hepatitis, May, 2016. *https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/pdf/hourei-27.pdf* (accessed July 23, 2021). (in Japanese)
6. Oza N, Isoda H, Ono T, Kanto T. Current activities and future directions of comprehensive hepatitis control measures in Japan: The supportive role of the Hepatitis Information Center in building a solid foundation. Hepatol Res. 2017; 47:487-496.
7. MHLW HSB Notification No. 0425004. Notification regarding training and utilization of hepatitis medical care coordinators. April 25, 2017. *https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/pdf/hourei-170425-1.pdf* (accessed July 23, 2021). (in Japanese)
8. Summary of main points across 47 prefectures for hepatitis control. *https://kan-co.net/potal/files/case/questionnaire-results_201901.pdf* (accessed July 23, 2021). (in Japanese)
9. 2018 Annual Report of Health and Labour Sciences Research Grant project, May, 2019. *https://mhlw-grants.niph.go.jp/project/27365/1* (accessed July 23, 2021). (in Japanese)
10. National Center for Global Health and Medicine. Hepatitis Information Center. *http://www.kanen.ncgm.go.jp/index.html* (accessed July 23, 2021). (in Japanese)
11. Ministry of Health, Labour and Welfare. Material 1 at the 2nd annual conference by the Hepatitis Information Center for regional core centers for the management of liver disease. *http://www.kanen.ncgm.go.jp/archive/conference/council/20210122_final_kourou_all.pdf* (accessed July 23, 2021). (in Japanese)
12. Kanto T. Nationwide survey on activities of regional core centers for the management of liver disease in Japan: Cumulative analyses by the Hepatitis Information Center 2009-2019. *http://www.kanen.ncgm.go.jp/archive/conference/council/20200124_kanto_houkoku.pdf* (accessed July 23, 2021). (in Japanese)
13. Kanzaki N, Iwane S, Oeda S, Okada M, Kimura H, Eguchi Y, Fujimoto K. Categorization and characterization of activities designed to help health-care professionals involved in hepatitis care increase their awareness of the disease: The classification of hepatitis medical care coordinators. Intern Med 2019; 58:1825-1834.
14. Ministry of Health, Labour and Welfare. Material 1 at the 24th Meeting of the Council for Promotion of Hepatitis Measures. *https://www.mhlw.go.jp/content/10901000/000576275.pdf* (accessed July 23, 2021). (in Japanese)
15. Enomoto M, Hidaka I, Inoue T, *et al*. Present status of hepatitis medical care coordinators in regional core centers in Japan. Kanzo 2021; 62:96-98.
16. The website for hepatitis medical care coordinator built by the Research on Hepatitis of Ministry of Health, Labour and Welfare in Japan. *http://kan-co.net* (accessed July 23, 2021). (in Japanese)
17. Eguchi Y. The pocket manual for hepatitis medical care coordinator. Published by the Research on Hepatitis of Ministry of Health, Labour and Welfare in Japan. 2018. *https://kan-co.net/potal/files/faq/pocketmanual_A6size_0108.pdf* (accessed July 23, 2021). (in Japanese)
18. Eguchi Y. The guidebook for efforts of hepatitis medical care coordinator "Moshimo series" Published by the Research on Hepatitis of Ministry of Health, Labour and Welfare in Japan, 2018-2019. *https://kan-co.net/potal/files/case/moshimo_vol1.pdf* (accessed July 23, 2021). (in Japanese)
19. Alcorn T. Mongolia's struggle with liver cancer. Lancet. 2011; 377:1139-1140.
20. Znaor A, Chimed T, Laversanne M, Tudev U, Sanjaajamts E, Sandagdorj T, Bray F. The public health challenge of liver cancer in Mongolia. Lancet Gastroenterol Hepatol. 2018; 3: 660-662.
21. World Health Organization, Viral hepatitis in Mongolia: situation and response 2015. *https://apps.who.int/iris/handle/10665/208324* (accessed July 23, 2021).
22. Kim YA, Estevez J, Le A, Israelski D, Baatarkhuu O, Sarantuya T, Narantsetseg S, Nymadawa P, H Le R, Yuen MF, Dusheiko G, Rizzetto M, Nguyen MH. Screening and management of viral hepatitis and hepatocellular carcinoma in Mongolia: results from a survey of Mongolian physicians from all major provinces of Mongolia. BMJ Open Gastroenterol. 2016; 3:e000119.
23. World Health Organization. Global health sector strategy on viral hepatitis 2016-2021: Towards ending viral hepatitis. *https://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf;jsessionid=60A93ADD1A191FF6A0FA823314D24C43?sequence=1* (accessed July 23, 2021).

Received June 16, 2021; Revised July 23, 2021; Accepted September 1, 2021.

Released online in J-STAGE as advance publication September 21, 2021.

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Global Health & Medicine. 2021; 3(5):351-355.
DOI: 10.35772/ghm.2021.01068

MINI-REVIEW

International cooperation on health and medical care for viral hepatitis: 30 years of activities on comprehensive viral hepatitis control of the JICA group training program for developing countries

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Abstract: The National Hospital Organization Kumamoto Medical Center has conducted a group training course for health care workers (HCW) from developing countries on viral hepatitis and its related diseases in cooperation with the Japan International Cooperation Agency, for 30 years. In the first 10 years, the course included acquired immunodeficiency syndrome (AIDS), adult T-cell leukemia/lymphoma (ATL), and hepatitis. Following the discovery of the hepatitis C virus and the genotype of the hepatitis B virus, and development of treatments for hepatitis, viral-related cirrhosis, and cancer, the course was divided into two courses. In 2015, the hepatitis training course was renewed as the "Comprehensive Countermeasure for Virus Hepatitis", which ended its role in February 2018. Between 1998 and 2017, 175 HCW from 43 countries, including 36 participants from Egypt, participated. Between October 11 and 20, 2019, we conducted a follow-up survey of the results of the training and conducted a field visit on hepatitis control in Egypt.

***Keywords*:** international cooperation on health and medical care, Japan International Cooperation Agency (JICA), JICA group training program, comprehensive countermeasure of viral hepatitis, developing county

Introduction

Acquired immunodeficiency syndrome (AIDS) and viral hepatitis are serious global issues. There were an estimated 257 million hepatitis B virus (HBV) carriers worldwide in 2015, and HBV-related deaths occurred in an estimated 887,000 patients mostly from cirrhosis and primary liver cancer in 2016 (*1*). Some countries in South-East Asia and Africa have more than 6.2% and 2.0% of their population as carriers, respectively (*1*), and some have more than 20%, presenting a significant health care challenge. Hepatitis A, which is not seen in epidemic numbers in developed countries, is also common in developing countries. The prevention of hepatitis A virus infection is becoming an important issue internationally as international activities, such as the growth in food imports from those countries, increase.

Hepatitis C is a major cause of acute and chronic hepatic diseases, including liver cirrhosis and primary liver cancer. It is estimated that there are as many as 71 million chronically infected people in the world and around 40 thousand people die from hepatitis C virus (HCV)-related diseases (*1*).

Viral hepatitis is an infection that requires urgent development of global measures; thus, collaboration among the international community is essential to implement infection prevention measures and surveillance initiatives to understand the domestic and international situations of hepatitis outbreaks.

The National Hospital Organization Kumamoto Medical Center (NHOKMC) has conducted a group training course for health care workers (HCW) from developing countries in viral hepatitis and its related diseases in cooperation with the Japan International Cooperation Agency (JICA) for 30 years.

Transition of viral hepatitis group training course

In 1988, the NHOKMC made promoting international cooperation on health and medical care one of the basic policies of the hospital. At the request of the JICA, a group training course was started for developing countries by order of the Honorary Director Isao Arita who headed the WHO Smallpox Eradication Unit in 1977-1985 (*2*). The first training course was "Seminar on Blood Transmitted Diseases: Special reference to AIDS, ATL, and Hepatitis", with former Director Fumio Kawano as the course leader. At that time, only HBV was known as a blood transmitted hepatitis virus. In 1989, HCV was discovered (*3*). Investigation of HCV rapidly progressed to not only virology but also

epidemiology and clinical medicine research such as testing, treatments, and clinical course. The seminar on blood transmitted diseases was expanded to include hematology and hepatology; however, it was considered that there was too much content. Hence, in 1998, two courses using material from the AIDS, ATL, and hepatitis courses were created. The first course leader of the hepatitis course was the late Vice President Keishi Kimura (1998-2003).

We planned and formulated training, facilitated lectures and hospital training, accompanied tours at other facilities, and assisted with action plans for hepatitis control after completing the training (2003-2017). For a total of 30 years, the JICA conducted group training activities on hepatitis protection, and supported the dissemination of knowledge on hepatitis in developing countries and the formulation of hepatitis countermeasures. In 2015, the hepatitis course was finally renewed as the "Comprehensive Countermeasure for Virus Hepatitis" course, which ended its role in February 2018.

In the first year of the course in 2003, on the advice of Honorary Director Isao Arita, we avoided duplication of training contents, covered overall viral hepatitis, and enriched the field training with basic and clinical physicians representing Japan as lecturers (Figure 1, Supplemental Figures S1 and S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=29*). Using the requests and opinions of the trainees at the evaluation meeting at the end of the training, and by learning new diagnostic techniques and treatment methods in the training, we worked to improve our training while reviewing the lecturers and tour facilities. In addition, workshop training was taken from second-type training to active type. We communicated with the trainees, repeated trials and errors, and formulated a training program with high satisfaction. Comparing the data of the evaluation meeting in the first and last years, the program was more highly evaluated in the latter Supplemental Figures S3 and S4 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=29*).

In 2008, Japan worked on comprehensive hepatitis countermeasures, and in December 2009, the Basic Act on Hepatitis Countermeasures was formulated (*4*), which came into effect in January 2010. However, due to the tight national budget, there was a wave of JICA training reductions, and the virus hepatitis course was threatened with closure. In June of the same year, presentation of the necessity of the JICA viral hepatitis course at the Ministry of Foreign Affairs led to its renewal from 2011. However, in 2014, the course was suspended due to the small number of participants, but it was resumed at the request of representatives from Egypt, which had planned to combat hepatitis C as a national project in 2015 until its role ended in February 2018 (Supplemental Figure S5, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=29*) (*5*).

Changes in epidemiology, treatment, and countermeasures for viral hepatitis

During this time, the hepatitis C virus was discovered in 1989 (*3*) and hepatitis E in 1990 (*6*). The genotypes

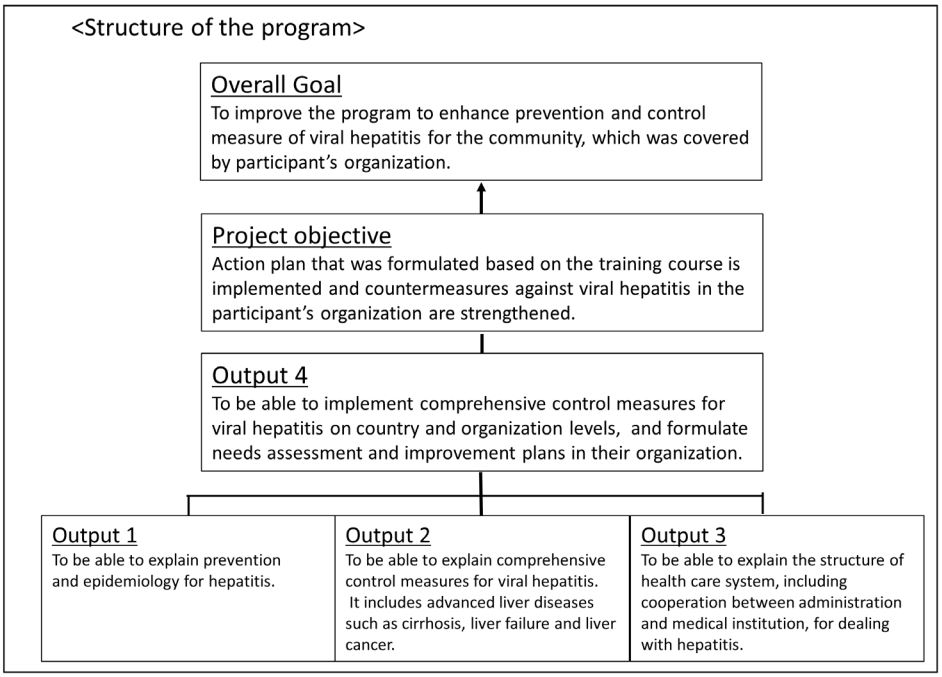

Figure 1. Structure of program. The program consists of six components. Four expected module outputs and project objective, action plan, which was formulated based on the training course is implemented. Overall goal is service for prevention and control measures of viral hepatitis.

of hepatitis B, which have been identified since 1988 (*7*), revealed a difference in clinical features, and the epidemiology of hepatitis has changed significantly (*8*). Furthermore, treatment of viral hepatitis based on these findings, especially advances in interferon (IFN)-based therapy and direct-acting antivirals (DAAs) (*9*) for hepatitis C and nucleic acid analogues (*10*) or pegylated-IFN therapy (*11*) for hepatitis B, were developed. Furthermore, there has been remarkable developments in the management, diagnosis, and treatment of liver cirrhosis and liver cancer caused by viral hepatitis (*12,13*). In 2015, the hepatitis training course was restarted as the "Comprehensive Countermeasure for Viral Hepatitis", which included measures taken by the government in addition to epidemiology, prevention, and treatment.

In 2010, the World Health Organization (WHO) established July 28 as World Hepatitis Day with the aim of preventing the spread of viral hepatitis on a global level, eliminating discrimination and prejudice against patients and infected people, promoting infection prevention, and advocating for the implementation of hepatitis awareness activities, which has increased interest in hepatitis worldwide (*14*). Viral hepatitis is considered the fourth most important infectious disease after the world's three largest infectious diseases (malaria, tuberculosis, and AIDS). More than 500 million people are infected with hepatitis B and C, and hepatitis control is expected to become increasingly important worldwide. In recent years, antiviral treatment has advanced dramatically. Nucleic acid analog treatment for hepatitis B prevents viral reactivation in patients receiving chemotherapy or immunosuppressive drugs, and universal vaccines for infants and children will contribute to a decrease in hepatitis incidence (*15*). Direct-acting antivirals (DAAs) against hepatitis C provide a cure rate of 95% or more within 8-12 weeks treatment. These treatments are being widely carried out in developed and developing countries. The WHO has declared the goal of eliminating viral hepatitis by 2030 (*16*). For this purpose, it is important to treat patients and take comprehensive measures such as infection control that includes resident awareness, picking up infected people, and following up after treatment. This training is in line with that purpose and is expected to help wipe out hepatitis. We have received high evaluations for this course from the trainees who have participated so far.

Between 1998 and 2017, 175 participants from 43 countries participated in this training course. In this period, 36 participants from Egypt participated, 20 of whom participated in the last three years (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=29*) (*17*). Between October 11 and 20, 2019, we conducted a follow-up survey of the results of the training and conducted a field visit on hepatitis control in Egypt (Table 1).

Follow-up survey and hepatitis countermeasure inspection in Egypt

Itinerary

The itinerary on site is Day 1: visit Suez Canal University (Ismailia Province), Day 2: visit two hepatitis centers in Cairo, Day 3: visit Beheira Prefectural Health Department and Hepatitis Center, Day 4: a symposium at the National Institute of Hepatitis and Tropical Medicine (NHTMRI), and Day 5: participation in a three-way meeting between the WHO's Egypt Office, Ministry of Health and Population, and the JICA (Supplemental Figure S6, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=29*).

Results and Proposals

The hepatitis C campaign in Egypt was prepared and implemented from October 2018, almost at the same time as the three-year national training in Egypt (October 2015 to February 2018). This country-by-country

Table 1. Anti-HBV response of TCM and related active compounds in clinical trials

Purpose of follow-up

As a follow-up investigation team from JICA Headquarters

- Investigation on the status of hepatitis, especially hepatitis C, in Egypt.
- Confirmation of achievement of action plan by trainees from Egypt.
- Confirmation of our contribution to Egypt so far and its future role.
- Participation in the meeting with WHO Egypt, Ministry of Health and Population (MoHP) and JICA, which participate in consultation on Egypt hepatitis C elimination certification process.
- Visit to Suez Canal University, which participated in the launch of the third country training of JICA and cooperated in the operation.

Results in follow-up survey

The JICA Headquarters confirmed the following as a follow-up investigation team.

- The action plan of the trainees returning from Egypt is being achieved in a short period of time.
- More than 80% of the country's 100 million people have been tested for hepatitis C in Egypt through a national campaign, and treatment has been initiated for those who test positive (testing and treatment costs are free).
- WHO's global elimination of hepatitis C is targeted for 2030, but Egypt could be a global model, with achievement certified in two years.
- In addition to WHO's support, our previous hepatitis control courses have built a foundation for this.
- What can we cooperate with in the future? If the campaign to eliminate hepatitis B in Africa is carried out mainly in Egypt, we may be able to cooperate in the launch and implementation of JICA third country training.

training contributes greatly to the formulation and implementation of hepatitis C measures. Furthermore, the JICA training that has continued for the past 30 years has contributed to these preparation stages. Based on the long history of the JICA hepatitis group training, the NHOKMC is likely to have made a lot of findings, including formulation of measures to find and solve problems for developing countries and the results obtained in Egypt. In addition, the NHOKMC utilized its research to conduct the JICA training, including advice and participation in third-country training, which was scheduled to be mainly deployed in Egypt as well as other African countries. The training included regular surveys of liver cancer after antiviral therapy and liver cancer from non-communicable diseases (*18*), which are a problem after hepatitis C control.

A follow-up study confirmed the following (Table 1): *i*) action plans for trainees returning to Egypt are being achieved in a short period of time; *ii*) hepatitis C in Egypt has been tested by a National Campaign that tested more than 80% of the 100 million people in a year, and treatment was started for positive patients (19); *iii*) the WHO's global hepatitis C sweep is targeted for 2030, but Egypt could be certified as having achieved this in two years and become a global model (20); *iv*) in addition to the WHO's support, our previous hepatitis control courses have built a foundation for future strategies; and *v*) if the campaign to wipe out hepatitis B in Africa is carried out mainly in Egypt, we may be able to cooperate in the launch and implementation of the JICA in a third country. We will continue to build further relationships with Egypt and the JICA.

Conclusion

In the JICA group training course, we comprehensively guided trainees in many developing countries in the epidemiology, prevention, and treatment of viral hepatitis, including liver cirrhosis and liver cancer, as well as administrative measures. Furthermore, we had the opportunity to think about the problems and issues to be overcome in developing countries. This time, as a follow-up survey, we confirmed the activities after training in Egypt. We have confirmed the activities of trainees who were unable to conduct surveys in Egypt, Mongolia, Myanmar, and other countries using social media. In both cases, they utilized their training to achieve the action plan after their return from Japan, and achieved results. Thirty years of international cooperation on health and medical care in the NHOKMC contributed to the practice of comprehensive counter measures for viral hepatitis in developing countries.

Acknowledgements

We would like to express our heartfelt gratitude to the lecturers who cooperated in the group training, the JICA and the NHOKMC staff, including Honorary Director Isao Arita, Former Director Fumio Kawano, and the late Dr. Keishi Kimura who served as the former leader of the course. Moreover, we would like to express our deepest gratitude for the 16th JICA President's Award that was granted by President Shinichi Kitaoka in October 2020.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. World Health Organization: Global hepatitis report, 2017. *https://www.who.int/publications/i/item/global-hepatitis-report-2017* (accessed July 19, 2021).
2. World Health Organization. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi, ID. Smallpox and its eradication. Geneva. 1988. *https://apps.who.int/iris/handle/10665/39485?locale-attribute=en&* (accessed July 19, 2021). (in Japanese)
3. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science. 1989; 244:359-362.
4. Outline of Basic Act on Measures against Hepatitis. Annual Health, Labour and Welfare Reports: Act No.97, 2009. *https://www.mhlw.go.jp/english/wp/wp-hw4/dl/health_and_medical_services/P62.pdf* (accessed July 19, 2021).
5. El-Akel W, El-Sayed MH, El-Kassas M, El-Serafy M, Khairy M, Elsaeed K, Kabil K, Hassany M, Shawky A, Yosry A, Shaker MK, ElShazly Y, Waked I, Esmat G, Doss W. National treatment program of hepatitis C in Egypt: Hepatitis C virus model of care. J Viral Hepatol. 2017; 24:262-267.
6. Krawczynski K, Bradley DW. Enterically transmitted non-A, non-B hepatitis: identification of virus-associated antigen in experimentally infected cynomolgus macaques. J infect Dis. 1989; 159:1042-1049.
7. Okamoto H, Tsuda F, Sakugawa H, Sastrosoewignjo RI, Imai M, Miyakawa Y, Mayumi M. Typing hepatitis virus by homology in nucleotide sequence: comparison of surface antigen subtypes. J Gen Virol. 1988; 69:2575-2583.
8. Sunbul M. Hepatitis B virus genotypes: global distribution and clinical importance. World J Gastroenterol. 2014; 20:5427-5434.
9. Kumada H, Suzuki Y, Ikeda K, *et al.* Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. Hepatology. 2014; 59:2083-2091.
10. Chang TT, Gish RG, de Man R, *et al.* A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med. 2006; 354:1001-1010.
11. Marcellin P, Lau GK, Bonino F, *et al.* Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAgnegative chronic hepatitis B. N Engl J Med. 2004; 16:1206-1217.
12. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases.

Hepatology. 2017; 65:310-335.
13. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, Roberts LR, Heimbach JK. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 Practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018; 68:723-750.
14. Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report. World Hepatitis Day — July 28, 2011. *https://www.cdc.gov/mmwr/pdf/wk/mm6028.pdf* (accessed July 19, 2021).
15. Zhao H, Zhou X, Zhou Y-H. Hepatitis B vaccine development and implementation. Hum Vaccin Immunother. 2020; 16:1533-1544.
16. World Health Organization. Combating hepatitis B and C to reach elimination by 2030. Advocacy brief. *https://apps.who.int/iris/handle/10665/206453?locale-attribute=en&* (accessed July 19, 2021).
17. Kawano F, Sugi K, Kiyokawa T, Hidaka M, Higashi K, Hashimoto N, Miyazaki H, Tsukamoto A, Kimura K. International cooperation on health and medical care in the National Hospital Organization Kumamoto Medical Center. Iryo. 2005; 59:289-294. (in Japanese)
18. Tateishi R, Uchino K, Fujiwara N, *et al.* A nationwide survey on non-B, non-C hepatocellular carcinoma in Japan. J Gastroenterol. 2019; 54:367-376.
19. Waled I, Esmat G, Elsharkawy A, *et al.* Screening and treatment program to eliminate hepatitis C in Egypt. N Engl J Med. 2020; 382:1166-1174.
20. World Health Organization. Accelerating access to hepatitis C diagnostics and treatment: overcoming barriers in low-and middle-income countries. Global progress report 2020. *https://www.who.int/publications/i/item/9789240019003* (accessed July 19, 2021).

Received June 7, 2021; Revised July 19, 2021; Accepted September 2, 2021.

Released online in J-STAGE as advance publication September 21, 2021.

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Print ISSN: 2434-9186 Online ISSN: 2434-9194

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Global Health & Medicine

Volume 1, Number 1
October, 2019

www.globalhealthmedicine.com