Japan should accelerate measures to achieve WHO 2030 hepatitis C elimination targets as it will provide significant clinical and economic benefits

Hepatitis Elimination Project at the Institute for New Era Strategy (INES) (stopkanen.net)

EXECUTIVE SUMMARY

- In 2016, the WHO General Assembly adopted a strategy to eliminate viral hepatitis by 2030.
- While previous modeling has indicated that Japan is on track to achieve the WHO elimination targets, recent treatment data shows the number of patients treated annually continues to decline, and as a result achieving the targets may be more challenging than expected.
- To achieve the WHO targets, Japan needs to expand hepatitis C screening and link a larger number of positive patients to treatment.
- Our modeling demonstrates that raising screening and treatment rates to the levels required to achieve the WHO targets will prevent 99,799 unnecessary liver-related deaths and generate 1.3 trillion Japanese Yen in healthcare system savings between 2020 and 2040.

BACKGROUND

In May 2016, the World Health Organization (WHO) General Assembly unanimously adopted a strategy to eliminate viral hepatitis by 2030 and declared the need to aggressively implement policy measures to control hepatitis across the globe. The WHO set specific targets to evaluate progress towards the global elimination of hepatitis C: the incidence of hepatitis C virus infections is to be reduced by 80%, hepatitis C-related mortality by 65%, 90% of cases of hepatitis C diagnosed, and 80% of eligible people with chronic hepatitis C treated (Table 1).[1]

A major strategy to achieving these targets is expanding access to highly effective direct-acting antiviral (DAA) therapies. DAA therapies have been proven a clinically effective[2] and cost-effective intervention for the treatment of hepatitis C.[3] It is now possible to eliminate HCV more quickly and reliably, with shorter treatment durations and more effective therapies.

In Japan, as of the year 2000 there were an estimated 1.9 to 2.3 million chronic hepatitis C virus infections.[4] This number has been reduced by the introduction of novel HCV treatments, particularly with the introduction of DAA therapies in 2014. Globally, Japan is one of a few countries providing nearly unrestricted access to DAA therapies. Under Japan's Basic Act on Hepatitis Measures, national and local governments provide financial support for screening and treatment costs. Maximum out-of-pocket costs are capped at between approximately 10,000 and 20,000 monthly Japanese Yen.[5]

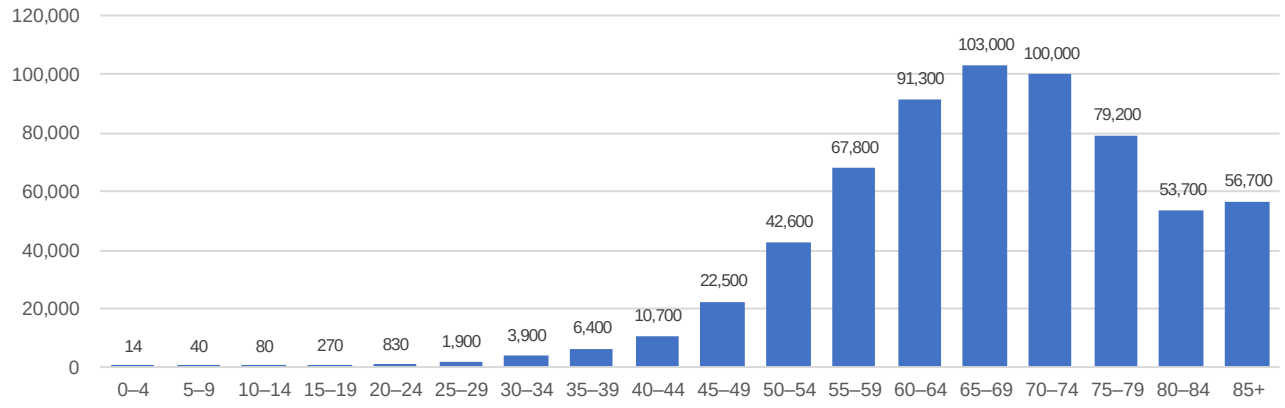
While previous modelling has indicated that Japan is on track to achieve the WHO elimination targets in 2027, this was based on maintaining the same levels of screening and treatment indefinitely.[6] Recent treatment data suggests that Japan is actually experiencing a 17% drop in the number of patients treated annually.[7] As a result achieving the WHO elimination targets in Japan by 2030 may be more challenging than initially anticipated.

Table 1. WHO targets to achieve hepatitis elimination by 2030

Impact Targets	2030 Targets
Incidence: New cases of chronic hepatitis C	80% reduction (in HCV)
Mortality: Viral hepatitis C-related deaths	65% reduction
Screening: Viral hepatitis C diagnosis	90%
Treatment: Viral hepatitis C	80%

*When compared to the corresponding levels in 2015.

Figure 1. Estimated number of HCV infections by age group as of 2020 (modeled)



In our research, we collated recent data on hepatitis C screening and treatment in Japan across several datasets. We then applied mathematical modeling to determine progress towards the 2030 WHO elimination targets, evaluating the clinical and economic impact of accelerating efforts to achieve elimination at the national level.

Table 2. Screening and treatment related costs

Type	Variable	Cost	Source
Diagnosis	Anti-HCV	2,520	Japan Medical Fee Schedule (April 2020)
Diagnosis	RNA test	5,870	
Diagnosis	Genotyping	3,710	
Diagnosis	Staging/liver biopsy/fibroscan	**	
Pre-SVR	F0 ~ F3*	345,300	Ishida and Yotsuyanagi [8]
Pre-SVR	Compensated cirrhosis*	478,600	
Pre-SVR	Decompensated cirrhosis*	706,600	
Pre-SVR	HCC*	1,992,800	
Pre-SVR	Liver transplant*	14,995,200	
Pre-SVR	Liver transplant – subsequent years*	2,019,000	
Post-SVR	History of F0 ~ F3*	57,186	McEwan et al. [9]
Post-SVR	History of compensated cirrhosis*	124,439	

*Annual costs per patient.
**There was not sufficient evidence to determine the average cost of liver staging in Japan.

DAA Treatment Cost	Estimated Cost
Weighted Average of Available Therapies*	JPY 3,930,891

*DAA therapies with less than 0.5% market share were excluded from this analysis due to overall low utilization.
*For products with a variable treatment duration, actual duration was estimated on data extracted from the MDV claims database. For products with only a single duration the approved treatment duration was used.
*Patient share was estimated based on market share data for the 6-month period from July 2019 to December 2019.

METHODS

Disease Prevalence

As of 2000, there were an estimated 1.9 to 2.3 million people infected with hepatitis C in Japan.[4] Most of these infections were due to medical procedures conducted prior to 1980, when the use of disposables was not widespread in clinical practice, and as a result of contaminated blood transfusions prior to regular hepatitis C testing. As a result, the highest prevalence of hepatitis C is seen in those over age 60.

Based on the current demographics of Japan, historical estimates of hepatitis C infection rates, and recent treatment trends, we modeled the total HCV infections by age group (see section on model projections).[11] While there has been a significant reduction in total number of cases over the past 10 years, as of 2020 there are still approximately 641,000 people infected with HCV. Of these cases, more than 157,000 are under age 60 and 530,000 under age 80 (Figure 1). Furthermore, according to model estimates, more than 70% of these patients, nearly 486,000, have already been diagnosed.[11]

Screening & Treatment Related Costs

Direct costs associated with the screening and treatment of hepatitis C were estimated based on previously published literature for pre-SVR[8] and post-SVR treatments,[9] and the most recent data from Japan's

schedule of medical fees. The approximate cost of treatment with DAA therapies was estimated as a weighted average of available treatment options. Calculations were based on the respective National Health Insurance list prices as of April 2020 for available DAA therapies and the 6-month market share average from July 2019 to December 2019 (Table 2).

Extra-Hepatic Manifestation (EHM) Costs

It is well known that chronic hepatitis C leads to cirrhosis and hepatocellular carcinoma. However, chronic hepatitis also leads to a series of systemic disorders and diseases that can have even greater health consequences than liver disease itself. These disorders are called extra-hepatic manifestations (EHM) and cover a wide range of conditions, from kidney damage to diabetes, and even neuropsychiatric changes and increased cardiovascular morbidity. In this study, we incorporate EHM costs based on a 2019 study in which EHM costs were estimated based on an analysis of the Medical Data Vision (MDV) claims database. Annual EHM costs were estimated at 1,405,787 Japanese Yen for Pre-SVR patients and 421,624 Japanese Yen for Post-SVR.[10]

Table 3. Scenarios simulated in our mathematical model

Scenario	Diagnosis Input	Treatment Input
[1] Current situation (based on recent treatment trends)	10,074 in 2020, annual reduction of 14.3% thereafter	21,063 in 2020, annual reduction of 17% thereafter*
[2] No treatment (e.g., discontinuing treatment of HCV with DAA or interferon therapies)	10,074 in 2020, annual reduction of 14.3% thereafter	No treatment**
[3] Achieve elimination by 2030	19,765**	46,422** (reduced to 0 after all patients are treated)
[4] Moderate diagnosis and treatment levels	10,074 (maintain 2020 levels)	24,945** (average of patients treated annually in 2019 & 2020)

*Reduction rate has been estimated by AbbVie based on the actual reduction in number of treated patients between 2019 and 2020 and the input of clinical experts.
**The new diagnosis & treatment levels are applied from 2021.

WHO Elimination Targets in Japan

The WHO has set very specific elimination targets (Table 1). In Japan, due to all-cause and liver-related mortality among the hepatitis C-infected population, caused by an elderly population, we have excluded the WHO targets for diagnosis and treatment in line with previous publications.[6] We believe the evaluated targets of incidence and liver-related mortality alone represent the most clinically meaningful outcomes for patients.

Model Projections

This study utilizes the Impact of Inaction (IOI) tool, a Markov model developed to measure the clinical and economic impact of expanding diagnosis and antiviral treatment of HCV infection in a population.[11] The model was populated with demographic and epidemiological inputs, with historical incidence calibrated to reported prevalence of chronic HCV in Japan. The IOI tool has been previously published in several countries at the national and provincial level, including in France,[12] Germany,[13] and four Canadian provinces.[14]

Future incidence is assumed to be a linear function of overall prevalence. Future diagnosis and treatment levels were estimated based on recent trends in diagnosis and treatment. We allocate treatments proportionally: e.g., if there are more HCV-infected 40–49-year-olds than 30–39-year-olds, more treatments will be allocated towards the 40–49-year-olds. To model the impact of various policy actions, four scenarios were developed over a period of 21 years (2020 - 2040) allowing us to evaluate the clinical and economic implications of future diagnosis and treatment levels (Table 3). The model assumes a 2.0% discount rate in estimating the economic impact of proposed policy measures.

RESULTS

The four scenarios (Table 3) were input into the model to evaluate the clinical and economic implications of accelerating or decelerating efforts to achieve the WHO 2030 elimination targets.

Figure 2. Scenarios simulated in our mathematical model demonstrating the associated clinical outcomes with changes to diagnosis and treatment levels

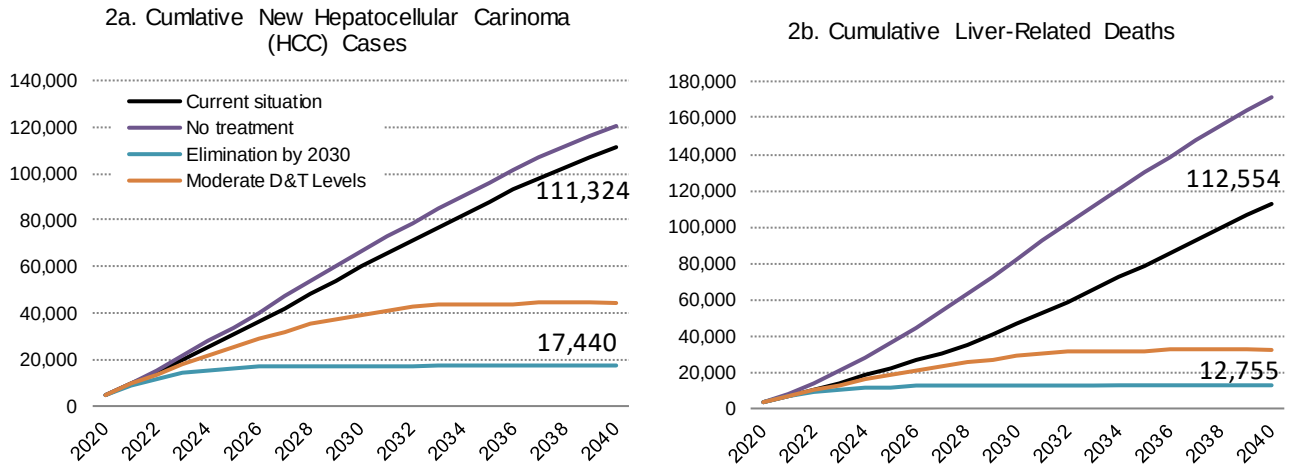
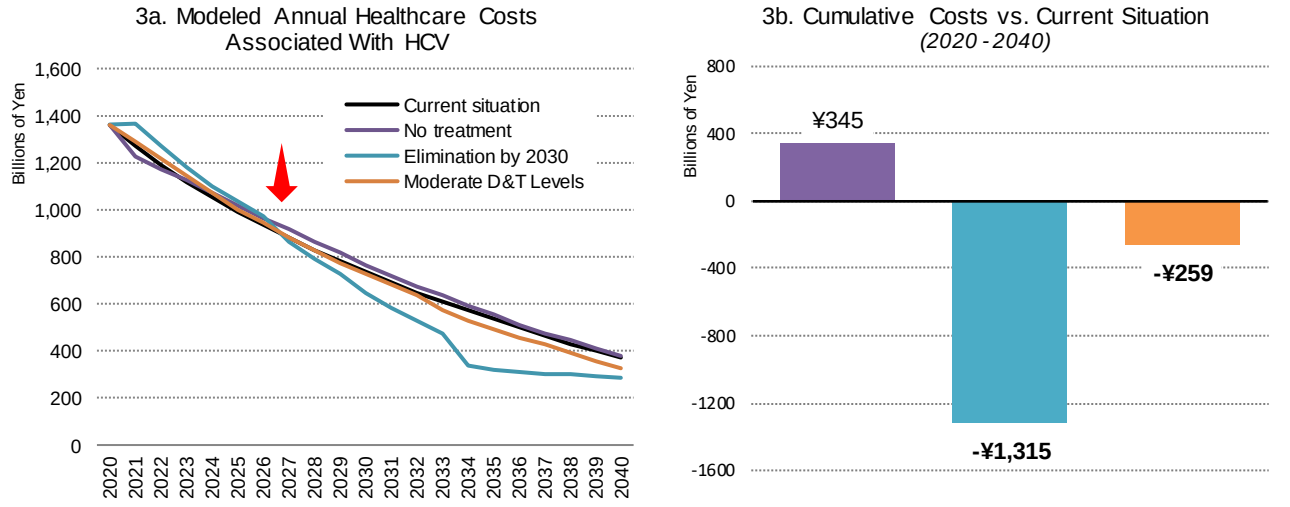


Figure 3. Scenarios simulated in our mathematical model demonstrating economic impact of changes to diagnosis and treatment levels in comparison to the current situation



Clinical Implications

Between 2020 and 2040, accelerating elimination by raising diagnosis and treatment levels would generate significant clinical benefits. Comparing the current situation with the necessary diagnosis and treatment levels to achieve elimination by 2030, there are 93,884 fewer new HCC cases and 99,799 fewer liver-related deaths (Figure 2).

Economic Implications

There are also direct economic benefits of accelerating elimination. While the total economic burden associated with HCV is on a downward trend due to the overall reduction in number of patients, increasing diagnosis and treatment levels could generate even further savings. As shown in figure 3a, while there is an initial increase in annual costs associated with expanding screening and treatment, the elimination by 2030 and moderate D&T level scenarios become cost-saving on an annual basis in 2027 and 2028, respectively. Furthermore, the same two scenarios reach their break-even points on a cumulative basis in 2032 and 2034, respectively, becoming overall cost-saving interventions. The more aggressive scenario, elimination by 2030, would most greatly

contribute to reduced hepatitis C-related healthcare expenditure between 2027 and 2040.

Accelerating efforts to achieve the WHO 2030 targets could generate up to 1.3 trillion Japanese Yen in healthcare system savings between 2020 and 2040, not to mention the broader economic benefits of greater workforce productivity. Even on the lower end, maintaining moderate diagnosis and treatment levels could result in nearly 259 billion Japanese Yen in healthcare system savings. Conversely, stopping treatment would raise costs by 345 billion Yen. There is a clear economic benefit to accelerating elimination—one that would continue to be realized for decades to come (Figure 3).

DISCUSSION & POLICY RECOMMENDATIONS

Despite current efforts to address hepatitis C treatment, our modelling demonstrates that Japan may not be on track to achieve the WHO 2030 elimination targets if diagnosis and treatment rates continue to decline. Accelerating elimination has direct and indirect benefits and would contribute to the sustainability of Japan's universal healthcare system.

The Government of Japan has plans to update its Basic Act on Hepatitis Measures within the next couple of years. The most recent update was in 2016, just atter the introduction of the first DAA therapies. The next revision offers an important opportunity for Japan to re-evaluate its progress towards achieving the WHO 2030 elimination targets and reflect the paradigm shift DAA therapies have made in the treatment of hepatitis C. There are several important measures that should be introduced or expanded to accelerate efforts to achieve elimination. This is a crucial moment for Japan to lead the world in achieving the WHO hepatitis C elimination targets.

Screening

- Through appropriate law revisions, the Government of Japan (GOJ) should implement mandatory hepatitis screening tests as part of annual health check-ups or special health check-ups targeting those over 40 years old.
- Referencing the WHO Framework on hepatitis elimination, the GOJ should establish effective processes to identify high-risk subpopulations, such as people who inject drugs and prisoners, and carry out comprehensive HCV screening and treatment programs for these high-risk individuals to reduce the risk of transmission to non-infected individuals.
- The GOJ should explore opportunities to simplify the patient journey, particularly in screening. Specifically, the GOJ should consider:
    - Conducting RNA testing by general physicians (not just specialists).
    - Expanding options for point-of-care RNA testing.
    - Conducting initial screening by RNA test in high-risk populations and simultaneous anti-body/RNA testing in all other patients.
    - Pooled RNA testing for screening large numbers of patients simultaneously.

Treatment & Linkage to Care

- In collaboration with each prefectural government, the GOJ should arrange efficient systems that enable HCV positive carriers identified through hepatitis screening tests to access information on the latest available treatment options in their area for eradicating the HCV effectively and efficiently.
- Further, the GOJ should achieve the goals of promoting hepatitis viral testing and expanding access to hepatitis curable treatments by establishing a medical system that works collaboratively not only with primary care physicians, but also with local governments and hepatic disease center hospitals.
- While thousands of patients are screened for hepatitis C during annual health check-ups, many are not linked to care. The GOJ should encourage stronger efforts to link positive patients to care with appropriate follow up following annual health checks.

Funding

- The GOJ should continue to secure enough budget for executing comprehensive approaches toward HCV eradication.
- The GOJ should consider further simplifying the patient journey, expanding access to the HCV treatment subsidy program beyond specialists in areas where an unmet need to access care exists.

[1] World Health Organization. Global health sector strategy on viral hepatitis 2016–2021. Towards ending viral hepatitis. Geneva: WHO, 2016. https://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/ (Accessed June 2020).

[2] Lamb, Y.N. Glecaprevir/Pibrentasvir: First Global Approval. Drugs 77, 1797–1804 (2017). https://doi.org/10.1007/s40265-017-0817-y

[3] Kawaguchi I, Chayama K, Gonzalez YS, et al. A Cost-Effectiveness Analysis of Glecaprevir/Pibrentasvir Versus Existing Direct-Acting Antivirals to Treat Chronic Hepatitis C in Japan. Adv Ther. 2020;37(1):457-476. doi:10.1007/s12325-019-01166-3

[4] Estimated from the 2004 Health, Labour, and Welfare Science Research Grant "Emergency measures for overcoming hepatitis" (Yoshizawa group). Accessed 26 October 2020. https://www.kanen.org/about/kensa/#nav_subcategory

[5] Basic guidelines for promotion of control measures for hepatitis. MHLW. https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/pdf/hourei-27.pdf (Accessed June 2020).

[6] Razavi H, Gonzalez Y, Yuen C, Cornberg M. Global timing of hepatitis C virus elimination in high-income countries. Liver Int. 2020;40(3):522-529. doi: 10.1111/liv.14324.

[7] Reduction rate has been estimated by AbbVie based on the actual reduction in number of treated patients between 2019 and 2020 and the input of clinical experts.

[8] Ishida H, Yotsuyanagi H. Examination of the cost-effectiveness of the standard of care for chronic HCV treatment [In Japanese only]. Research on medical economic evaluation of various measures related to viral liver disease: MHLW, 2014. Report No.: 20133004B: Cat No.: 20133004B007-20133004B0010: Pages: 127–192. https://mhlw-grants.niph.go.jp/niph/search/NIDD00.do?resrchNum=201333004B. Accessed 3 Nov 2019.

[9] McEwan P, Ward T, Webster S, et al. Estimating the long-term clinical and economic outcomes of daclatasvir plus asunaprevir in difficult-to-treat Japanese patients chronically infected with hepatitis C genotype 1b. Value Health Reg Issues. 2014;3(Supplement C):136–45.

[10] Yamazaki, K., Macaulay, D., Song, Y. et al. Clinical and Economic Burden of Patients with Chronic Hepatitis C with Versus Without Antiviral Treatment in Japan: An Observational Cohort Study Using Hospital Claims Data. Infect Dis Ther. 2019;8(2):285-299. doi: 10.1007/s40121-019-0234-5.

[11] Access to the Input of Inaction tool was provided to INES by AbbVie GK.

[12] De Ledinghen V, et al. SAT-259-Achieving accelerated elimination of hepatitis C virus infection by 2025: A case study in France. 2019. doi: 10.1016/S0618-8278(19)31492-6

[13] Cornberg M, et al. A tool to measure the impact of inaction towards elimination of hepatitis C virus: A case study in Germany. 2018. doi: 10.1016/S0168-8278(18)30560-9

[14] Annual Meeting of the Canadian Association for the Study of the Liver (CASL), the Canadian Network on Hepatitis C (CANHEPC) and the Canadian Association of Hepatology Nurses (CAHN) 2020 Abstracts. 2020. doi: 10.3138/canlivj.3.1.abst