



# Burden of chronic hepatitis B and C infections in 2015 and future trends in Japan: A simulation study

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## Summary

**Background** Determining the number of chronic hepatitis B (HBV) and C virus (HCV) infections is essential to assess the progress towards the World Health Organization 2030 viral hepatitis elimination goals. Using data from the Japanese National Database (NDB), we calculated the number of chronic HBV and HCV infections in 2015 and predicted the trend until 2035.

**Methods** NDB and first-time blood donors data were used to calculate the number of chronic HBV and HCV infections in 2015. A Markov simulation was applied to predict chronic infections until 2035 using transition probabilities calculated from NDB data.

**Findings** The total number of chronic HBV and HCV infections in 2015 in Japan was 1,905,187–2,490,873 (HCV:877,841–1,302,179, HBV:1,027,346–1,188,694), of which 923,661–1,509,347 were undiagnosed or diagnosed but not linked to care (“not engaged in care”), and 981,526 were engaged in care. Chronic HBV and HCV infections are expected to be 923,313–1,304,598 in 2030, and 739,118–1,045,884 in 2035. Compared to 2015, by 2035, the number of persons with HCV not engaged in care will decline by 59.8 – 76.1% and 86.5% for patients in care. For HBV, a 47.3 – 49.3% decrease is expected for persons not engaged in care and a decline of 26.0% for patients engaged in care.

**Interpretation** Although the burden of HBV and HCV is expected to decrease by 2035, challenges in controlling hepatitis remain. Improved and innovative screening strategies with linkage to care for HCV cases, and a functional cure for HBV are needed.

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**Keywords:** Bepatitis B; Gepatitis C; Prediction; Markov model; Japan

*Abbreviations:* AC, asymptomatic carrier; CH, chronic hepatitis; C-LC, compensated liver cirrhosis; DAA, direct-acting antiviral; D-LC, decompensated liver cirrhosis; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; ICD, International classification of diseases; IFN, interferon; LC, liver cirrhosis; MHLW, Ministry of health labour; NA, nucleos(t)ide analogues; MTCT, mother-to-child transmission; NDB, national database, SVR, sustained virologic rate, WHO, World Health Organization

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### Research in context

#### *Evidence before this study*

In 2000, the total number of people chronically infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) in Japan was 3.01–3.66 million. This number decreased to 2.09–2.84 million in 2011. It is essential to assess the change in the number of chronic infections and the progress towards the World Health Organization (WHO) goal of eliminating viral hepatitis as a public health threat by 2030, compared to 2015. We searched Pubmed for published articles reporting the total number of chronic HBV and HCV infections in Japan in 2015 and/or predicting the trends until 2030. Our search found no research articles reporting such information or indicating the likelihood of Japan to achieve the WHO targets.

#### *Added value of this study*

This study provides updated information on the number of people infected with HBV and HCV in Japan in 2015 and forecasts the future number of chronic infections until 2035. We used actual data from the Japan National Database (NDB) to calculate the number of chronic infections in 2015. The NDB is an exhaustive valuable database for health policymaking and research. The use of this database enables to obtain an accurate picture of the burden of HBV and HCV in Japan. Using the number of chronic infections in 2015 as a baseline and simulation parameters from first-time blood donors and official population statistics, we projected the number of chronic infections in 2030 and 2035. We found that chronic HBV and HCV infections will significantly decrease, but challenges in controlling hepatitis will remain.

#### *Implications of all the available evidence*

Although our findings show that Japan is making progress towards the elimination of viral hepatitis, efforts should be made to identify undiagnosed HCV cases and link them to care with highly effective direct-acting antivirals. Improved screening and innovative approaches for identifying persons infected with chronic HCV are recommended. For HBV, it is essential to develop new therapies that allow for a complete cure.

### Introduction

The World Health Organization (WHO) estimates that 296 million people were living with chronic hepatitis B infection, and 58 million people had chronic hepatitis C infection worldwide, representing 4.4% of the world population in 2019.<sup>1</sup> As a result, in 2016, the WHO set a target for eliminating viral hepatitis by 2030.<sup>2</sup> The implementation of the hepatitis B vaccine at birth and the approval of potent nucleos(t)ide analogues (NA) and

direct-acting antivirals (DAA) have made the elimination of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections possible. However, despite these advances, viral hepatitis remains a major cause of death globally, raising concern about the satisfactory prevention and management of cirrhosis and hepatocellular carcinoma (HCC).

Japan has a long history of combatting viral hepatitis. The routes of HBV infection used to be horizontal transmission and mother-to-child transmission (MTCT). After World War II, improved hygiene and the introduction of disposable devices in medical institutions are estimated to have reduced the rate of horizontal transmission of various blood sources, including HBV and HCV.<sup>3</sup> As a result of the decline in cases of HBV infection due to horizontal transmission, it is estimated that in the population born in the early 1980s, the majority of cases of chronic HBV infection may be due to MTCT.<sup>4</sup>

Therefore, since 1986, a nationwide project for the prevention of MTCT of HBV has been implemented, with the screening of all pregnant women for hepatitis B surface antigen (HBsAg) and the administration of hepatitis B vaccine and Hepatitis B immune globulin (HBIG) to children born to women testing positive for HBsAg.<sup>5,6</sup> Using data from the prefectures where the strategy was piloted, the prevention rate was found to be over 90%, and has been maintained until now.<sup>7,8</sup> The rate of chronic infections in infants was 0.26% in 1985, before the implementation of the project, and decreased to 0.024% in 1995.<sup>6</sup> The project is running under the universal health insurance system for about 36 years, and more than 98% for children born to HBsAg-positive pregnant women benefited from the prophylaxis.

To further control HBV and HCV infections, viral hepatitis screening has been introduced in the resident health checkups since 2002.<sup>9</sup> Since 2008, all patients who submit a subsidy application to the government can receive treatment by NAs, DAAs, or interferon (IFN) at a reduced cost.<sup>9</sup> Also, Japan has implemented a national action plan to combat viral hepatitis in 2010, which provides comprehensive support for patients in testing, treatment, and care. Under this plan, individuals with chronic HBV or HCV are referred to dedicated health facilities for viral hepatitis management. Furthermore, in 2016, universal vaccination against hepatitis B has been expanded to cover all infants.<sup>10</sup> Thus, Japan is expected to become one of the leading countries to achieve viral hepatitis elimination within the next decade.

To assess the effectiveness of countermeasures and the progress towards controlling HBV and HCV, it is essential to keep track of the number of infections.<sup>1</sup> In 2000, the total number of people chronically infected with HBV or HCV in Japan was 3.01–3.66 million.<sup>11</sup> In 2011, this number was estimated to be 2.09–2.84 million, representing a decrease of approximately one million from the 2000 estimates.<sup>11</sup>

This study aimed to calculate the number of chronic HBV and HCV infections in 2015 in Japan, using the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) and countrywide statistics. Subsequently, based on the number of chronic infections in 2015, a Markov model was applied to predict the infection burden until 2035.

## Methods

### Source of data

**National database of health insurance claims and specific health checkups of Japan (NDB).** Japan has a national health coverage system where all residents must join the health insurance system.<sup>12</sup> Insurance claims and health checkups from all hospitals and clinics in Japan are recorded into the NDB, which contains demographics, diagnosis, medical practice, and drug prescription information of all patients.<sup>12</sup> The NDB is one of the most comprehensive national databases globally and is used for health policymaking and research. Diagnostic data in the NDB are classified using the International Classification of Diseases version 10 (ICD-10) codes. We requested and obtained data with ICD-10 codes related to liver diseases between April 2012 and March 2016: B15 – B19 (viral hepatitis), C15 – C26 (malignant neoplasms of digestive organs), D10 – D36 (benign neoplasms), D37 – D48 (neoplasm of unknown or unspecified nature), K70 – K77 (liver disease), K80 – K87 (disorders of the gallbladder, biliary tract, and pancreas), and K90 – K93 (other diseases of the digestive system). A total of 25.9 billion medical records, 3.5 billion Diagnostic Procedure Combination (DPC) records, and 9.8 billion prescription records with at least one disease name related to liver diseases (total of 25,212,790 patients) were provided by the Japan Ministry of Health Labor and Welfare (MHLW) to our research group, the Epidemiological Research Group on the Burden of Viral Hepatitis and Measures for its Elimination (VH-Epi group).

**First-time blood donors.** In Japan, blood donation is completely voluntary and supplied by the Japanese Red Cross Society (JRC). Blood donation is authorised for people aged 16–69 years old. Before donating blood, all donors are asked to complete a questionnaire about their lifestyle, personal and family health history and are examined by a licensed physician. Individuals with a high risk of transfusion-transmitted diseases, including hepatitis B and C, are temporarily or permanently deferred from donating. First-time donors are not compensated and donate blood voluntarily to benefit those in need. Therefore, first-time blood donors are considered a healthy population, and hepatitis virus prevalence

in this group is close to the actual prevalence in the general population without disease.<sup>13</sup> Sex and age-specific prevalence of HBV and HCV infections among 358,291 first-time blood donors in 2015 were provided to the VH-Epi group by the JRC.

**Issued records of application for government-subsidised medical expense of hepatitis treatment.** Since 2008, the Japanese government subsidises treatment for people diagnosed with chronic hepatitis B and C infections.<sup>9</sup> The subsidy policy started with IFN and was later extended to NAs and DAAs. To benefit from this subsidy, patients have to submit an application to the local government. Data on government-subsidised medical expenses for hepatitis treatment are publicly available.<sup>14</sup> In this study, we used data from 2008 to 2015.

**Vital statistics in Japan.** Vital statistics in Japan are health statistics issued annually by the MHLW. This publicly available database contains national data on the burden of diseases in Japan.<sup>15</sup>

**Population census.** Population census has been conducted every five years since 1920 and covers the whole territory of Japan. We used the census data of 2000, 2005, 2010 and 2015.<sup>16</sup>

### Six groups of chronic infections

Persons living with chronic HBV or HCV infections were classified into six groups: undiagnosed, diagnosed but not linked to care, patients engaged in care, newly infected, cured, and deaths.

### Procedure for the calculation of the number of chronic infections in 2015

**Undiagnosed.** The number of undiagnosed individuals was based on HBsAg and HCV antibody (Anti-HCV) positivity rates by sex and age group in the first-time blood donors in 2015 and the population census in 2015.<sup>17</sup> The sex- and age-specific prevalence of HBV and HCV in first-time blood donors is presented in Supplementary Table S1. We assumed that 70% of individuals testing positive for anti-HCV were chronically infected with HCV, and all individuals testing positive for HBsAg were infected with HBV.<sup>18</sup> In Japan, the rate of chronic infections peaks among baby boomers for HBV and among the elderly for HCV. Therefore, the number of undiagnosed cases in those under 16 years was calculated using HBV and HCV prevalence in the 16–19 age group. Similarly, the number of undiagnosed people

over 65 years was approximated by HBV and HCV positivity rates in the 50–65 age group.

**Diagnosed but not linked to care.** Individuals diagnosed but not linked to care were defined as people who tested positive for chronic hepatitis infection and were not linked to care. We first calculated the total number of chronic infections in 2015 by adding new chronic infections since 2000 to the previously published number of chronic infections in 2000 and subtracting individuals who achieved SVR and those who died. Then, the number of people diagnosed but not linked to care in 2015 was calculated by subtracting undiagnosed and patients engaged in care from the total number of chronic infections in 2015.

**Patients engaged in care.** From the crude NDB data on liver disease, we extracted all records related to HBV or HCV infection and the type of treatment received. We implemented a methodology to ensure the reliability of the extracted data. The number of patients engaged in care, whether on treatment or clinical monitoring only, was characterized by sex, age group, liver disease status, and type of treatment. The complete procedure for calculating the number of patients engaged in care is presented in Supplementary Figure S1.

**New infections from 2000 to 2015.** The number of new HCV infections was calculated based on the sex- and age-specific incidence rate among blood donors in 1994–2004<sup>19</sup> and 2008–2013<sup>20</sup> cohorts. We applied this rate to the sex- and age-specific population in Japan in 2000, 2005, and 2010 to identify the number of new HBV and HCV infections between 2000 and 2015. New chronic HCV infections were assumed to account for 70% of all new infections.<sup>18</sup>

For HBV, new chronic infections are considered rare due to the successful implementation of countermeasures for preventing MTCT since 1986, and the low rate of progression to chronicity if infected in adulthood.<sup>5–8</sup> It is estimated that there were only 47 (95% CI: 0–145) cases of HBV MTCT in 2016 nationwide.<sup>21</sup> However, even though MTCT is rare, there is still a possibility of infection in utero,<sup>22</sup> or in the family (horizontal infection), including father-to-child infection in early childhood.<sup>23</sup> Therefore, based on the number of mother-to-child infections (0–145 cases per year), and adding a few cases of horizontal infections, the number of new chronic HBV infections was assumed to be 0–200 cases per year.

**Patients cured from 2000 to 2015.** Cure was defined as the achievement of sustained virologic response (SVR) in HCV-treated patients. The number of

individuals cured was calculated based on the government-subsidized medical claims for hepatitis treatment and the SVR rate following HCV treatment. SVR rates were assumed to be 60% after interferon (IFN) therapy, 70% after triple therapy (Pegylated IFN-Ribavirin-protease inhibitor), and 95% after DAA therapy.<sup>18</sup> For HBV, we did not consider a virologic cure (viral eradication).

**Deaths from 2000 to 2015.** The same methodology as previously reported was used for the cumulative number of deaths.<sup>11</sup> Briefly, the probabilities of death in 2000, 2005 and 2010 were calculated by dividing the number of deaths from all causes by the population for each year. Then, these probabilities were successively applied to the number of persons with chronic infections each year to obtain the number of deaths per year.<sup>15</sup> However, it is reported that persons with chronic HBV or HCV infections have an excess all-cause mortality rate compared to the general population.<sup>24–26</sup> On the other hand, it is also reported that all-cause mortality rate of individuals with inactive chronic HBV infection is similar to that of the general population.<sup>27</sup> Considering these parameters, we adjusted the number of deaths, assuming a relative risk of all-cause death of 1.0 – 1.4 for HBV, and 1.0 – 2.0 for HCV.

#### Prediction of the number of chronic infections until 2035

Based on the burden of HBV and HCV infections in 2015, we performed a mathematical simulation using the Markov model to predict the trend in the number of chronic infections until 2035.

**Transition pathway of liver disease.** To construct the liver disease transition pathway for both HBV and HCV, we stratified the individuals chronically infected with HBV or HCV into two groups: (i) undiagnosed and diagnosed but not linked to care, that is “not engaged in care” and (ii) patients engaged in care. We further subdivided the patients engaged in care between those on treatment and those receiving clinical monitoring only. Four liver disease states were considered. The definitions of these liver disease states for HBV were the same as previously reported<sup>28</sup>:

- Asymptomatic carriers (AC): patients with ALT less than 35 IU/L for one year and no abnormal findings on medical imaging,
- Chronic Hepatitis (CH): patients with ALT greater than 35 IU/L for one year and no abnormal findings on medical imaging,
- Liver Cirrhosis (LC): clinical diagnosis according to the guidelines of the Japan Society of Hepatology (medical imaging),

- Hepatocellular Carcinoma (HCC). clinical diagnosis according to the Japan Society of Hepatology (medical imaging).

For HCV, we used the following categories, as described by Yamasaki et al.<sup>29</sup>:

- AC: patients with an alanine aminotransferase ALT level below 35 IU/L and HBV viral load less than 4.0 log IU/mL, but without liver cirrhosis,
- CH: patients with an ALT level greater or equal to 35 IU/L and HBV viral load greater or equal to 4.0 log IU/mL, but without liver cirrhosis,
- LC: patients with one or more of the following criteria: i) aspartate aminotransferase (AST)-to-platelet ratio index greater or equal to 1.4 (AST level 80 IU/L or less), ii) fib-4 index value greater or equal to 3.6, iii) platelet count less than or equal to 130,000, or iv) esophageal or gastric varices at endoscopy,
- HCC: diagnosis based on liver biopsy or laparoscopy.

In the case of patients on treatment, we further divided liver cirrhosis patients into two groups by their status of compensated (C-LC) or decompensated (D-LC) (Figure 1). Thus, the transition pathway took into account within-group and between-group transitions.

- HCV (Figure 1A): The disease pathway starts with uninfected subjects who become newly infected and move to the liver disease transition cycle among undiagnosed and diagnosed but not linked to care. Some may be screened for HCV and linked to care, thus moving to the transition cycle among patients on clinical monitoring. A number of patients may receive treatment by antivirals (DAA or IFN) or hepatoprotective drugs (such as ursodeoxycholic acid or glycyrrhizic acid), and some may achieve SVR. Despite the treatment, a few subjects who achieve SVR may still develop HCC. Death was the final stage and was separated into liver-related deaths and other causes of death. Each liver disease states were mutually exclusive and collectively exhaustive.
- HBV (Figure 1B): The design of the HBV transition pathway followed the same structure as for HCV. However, no virologic cure was assumed.

**Transition probabilities used for the Markov simulation.** The 1-year probabilities of change in liver state for undiagnosed and diagnosed but not linked to care were the same as in our previously published research (Supplementary Table S2 for HCV and Table S3 for HBV). These probabilities were based on long-term

observation of individuals diagnosed with HBV or HCV after blood donation or community health screening.

The transition probabilities for patients either on treatment or clinically monitored were calculated based on the NDB data and stratified by age, sex, and treatment type (Supplementary Tables S4 and S5).

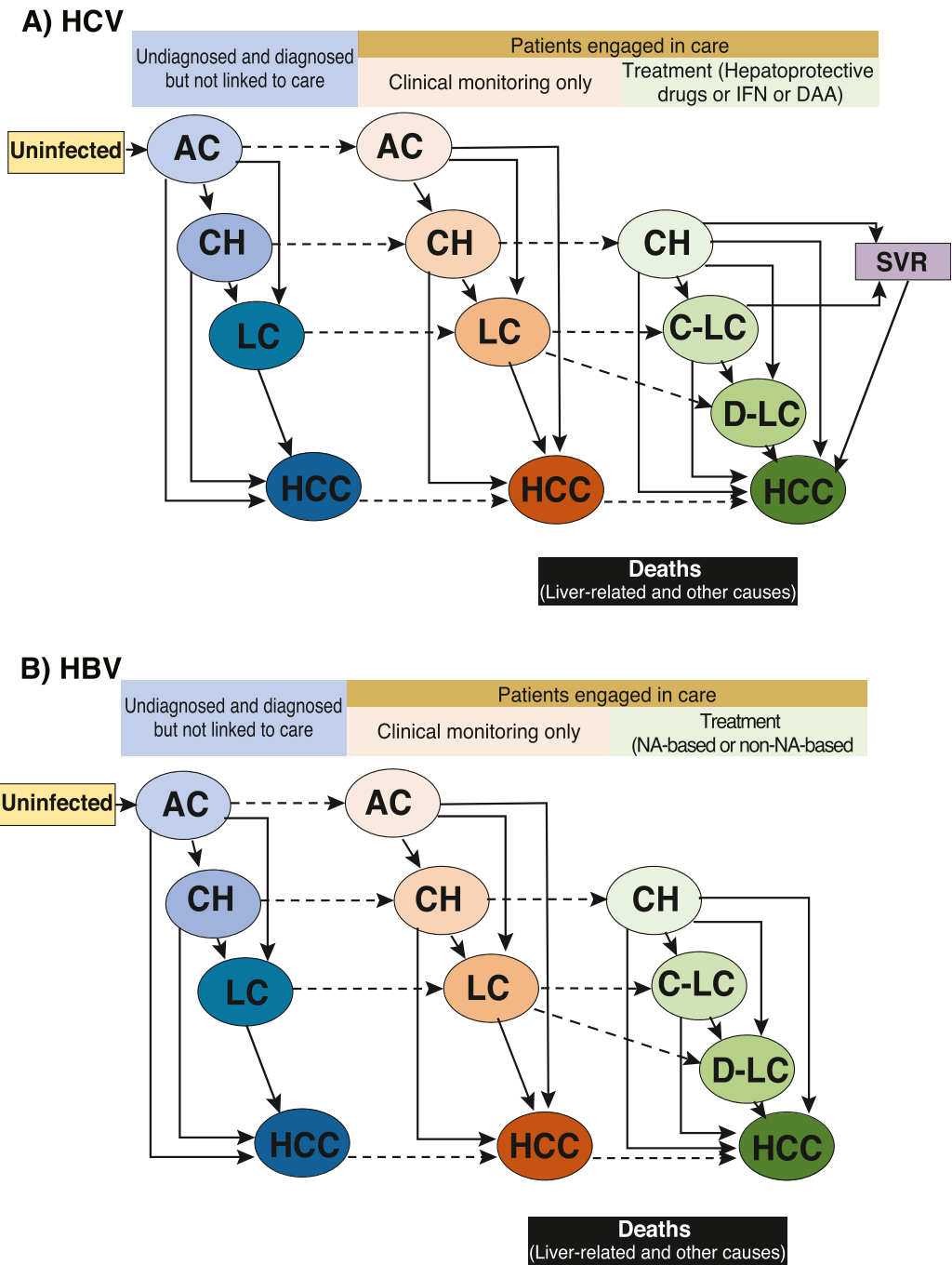
**Parameters for predicting HBV and HCV trends until 2035.** The parameters used for our simulation are shown in Table 1.

We set the following parameters for the simulation of HCV:

- Newly diagnosed: 5,000 per year, based on the number of people screened by the health promotion project (1,000,000), the rate of chronic HCV infection (1%),<sup>5,9,30</sup> according to the MHLW guidelines on HCV screening procedure using a combination of quantitative anti-HCV test and nucleic acid amplification tests, and the rate of medical consultation for those screened positive (50%).<sup>31,32</sup>
- Initial HCV treatment: based on the NDB data, the initial treatment distribution among patients with chronic hepatitis was 67.6% for hepatoprotective drugs, 30.7% for DAAs, and 1.7% for IFN. Among patients with compensated liver cirrhosis, the calculated proportions were 71.6% for hepatoprotective drugs, 27.6% for DAAs, and 0.9% for IFN. Until 2019, the Japanese Society of Hepatology guidelines for the management of hepatitis C was not recommending antiviral treatment for patients with decompensated liver cirrhosis or HCC.<sup>33</sup> Therefore, we assumed that these patients were treated by hepatoprotective drugs only.
- SVR rates for each treatment type: 0% for hepatoprotective drugs, 95% for DAAs, and 50% for IFN.<sup>18</sup>
- Mortality due to decompensated liver cirrhosis and liver cancer: 15.1% and 15.4%, respectively.<sup>34</sup>
- Proportions of compensated and decompensated liver cirrhosis: 53.4% and 46.6%, respectively, based on the NDB data.
- 1-year incidence rate of liver cancer after SVR: 0.3% for SVR after chronic hepatitis and 1.1% for SVR after compensated cirrhosis.<sup>33</sup>

The following parameters were applied to the simulation of HBV:

- Newly diagnosed: 5,000 per year, using the same assumptions as for HCV, based on the number of people screened by the health promotion project and the test positivity and consultation rates.
- Initial HBV treatment: based on the NDB data, 77,714 patients were treated with NAs and 70,002 with hepatoprotective or anticancer drugs in 2015.



**Figure 1.** Transition pathway of liver disease. This figure shows the transition pathway of liver disease for HCV (Figure 1A) and HBV (Figure 1B) based on the natural history of liver disease [Asymptomatic carriers (AC), Chronic Hepatitis (CH), Liver Cirrhosis (LC), and Hepatocellular Carcinoma (HCC)] and classified into groups of undiagnosed and diagnosed but not linked to care, and patients engaged in care (on treatment or clinical monitoring only). Dashed lines represent changes between the groups, and straight lines notify the progression in liver disease. Death is the absorbing state and is classified into liver-related deaths and deaths from other causes.

The distribution of medication type at HBV treatment initiation was assumed to be 50% for NAs and hepatoprotective or anticancer drugs.

- Annual NA initiation rate among individuals previously treated with hepatoprotective or anticancer drugs: 12.49% for chronic hepatitis, 13.24% for

	HCV	HBV	Note
<b>Chronic infections in 2015</b>			
Undiagnosed and diagnosed but not linked to care			
AC	94,678–258,485	721,461–791,010	Based on the number of undiagnosed in 2011 <sup>11</sup>
CH	138,992–379,467	37,87–41,523	Based on the number of undiagnosed in 2011 <sup>11</sup>
LC	2,890–7,891	10,344–11,341	Based on the number of undiagnosed in 2011 <sup>11</sup>
HCC	1,153–3,147	12,305–13,491	Based on the number of undiagnosed in 2011 <sup>11</sup>
Patients clinically monitored			
AC	0	48,568	Calculated based on NDB data
CH	163,080	102,061	Calculated based on NDB data
C-LC	8,005	3,625	Calculated based on NDB data
DC-LC	3,867	1,377	Calculated based on NDB data
HCC	6,251	2,738	Calculated based on NDB data
Patients on treatment			
CH	315,343	129,033	Calculated based on NDB data
C-LC	40,894	10,970	Calculated based on NDB data
DC-LC	35,429	7,713	Calculated based on NDB data
HCC	80,320	22,252	Calculated based on NDB data
<b>New chronic infections</b>	70% of new infections reported by Uchida et al. <sup>20</sup>	0-200	Based on the incidence rates among blood donors
<b>Transition probabilities</b>			
Undiagnosed and diagnosed but not linked to care	Supplementary Table S2	Supplementary Table S3	Transition probabilities among the general population
Patients clinically monitored only	Supplementary Table S4	Supplementary Table S5	Calculated based on NDB data
Patients on treatment	Supplementary Table S4	Supplementary Table S5	Calculated based on NDB data
<b>Screening</b>			
Number of people screened	1,000,000	1,000,000	Based on Regional Public Health and Health Promotion Services reports <sup>31,32</sup>
Positivity rate	1%	1%	Based on Regional Public Health and Health Promotion Services reports <sup>31,32</sup>
Linkage to care rate (for positive individuals)	50%	50%	Based on Regional Public Health and Health Promotion Services reports <sup>31,32</sup>
<b>Distribution of liver disease state at diagnosis</b>	Same as Tanaka et al. <sup>6</sup>	Same as Tanaka et al. <sup>4</sup>	Based on the distribution of liver disease state among undiagnosed individuals
<b>Proportion of D-LC among LC patients</b>	46.4%	41.3%	Calculated based on NDB data
<b>Proportion of C-LC among LC patients</b>	53.6%	58.7%	Calculated based on NDB data
<b>Distribution of the type of treatment</b>	Calculated	Calculated	Calculated based on NDB data
<b>HCC incidence after SVR</b>			
CH	0.3%	NA	JSH guidelines on HCV <sup>33</sup>
C-LC	1.1%	NA	JSH guidelines on HCV <sup>33</sup>
D-LC	0%	NA	JSH guidelines on HCV <sup>33</sup>
HCC	0%	NA	JSH guidelines on HCV <sup>33</sup>
<b>Deaths</b>			
Liver-related deaths			
D-LC	15.1%	22.2%	MHLW report <sup>34</sup>
HCC	15.4%	12.6%	MHLW report <sup>34</sup>
Other causes of death			
			Vital statistics in Japan <sup>15</sup>

**Table 1: Baseline data for the 2015–2035 prediction of HBV and HCV trends.**

AC, asymptomatic carrier; CH, chronic hepatitis; LC, liver cirrhosis; HCC, hepatocellular carcinoma; C-LC, compensated liver cirrhosis; D-LC, decompensated liver cirrhosis; HCV, hepatitis C virus; HBV, hepatitis B virus; NDB, national database; SVR, sustained virologic rate; JSH, Japanese Society of Hepatology; NA, not applicable

compensated liver cirrhosis, and 6.32% for decompensated liver cirrhosis, based on the NDB data.

- Mortality due to decompensated liver cirrhosis and liver cancer: 22.2% and 12.6%, respectively.<sup>34</sup>
- Initial proportions of compensated and decompensated liver cirrhosis: 58.7% and 41.3%, respectively, based on the NDB data.

**Sensitivity analysis**

We performed a one-way sensitivity analysis to assess the influence of parameters on the predicted number of HBV and HCV chronic infections in 2030 and 2035. For HCV: incidence rate among blood donors (1 to 5 times the base value), newly diagnosed cases (2,500–7,500 per year), receiving rate of DAA among CH patients (15–90%), receiving rate of DAA among C-LC patients (15–90%). For HBV, the sensitivity analysis considered a number of newly diagnosed cases varying between 2,500 and 7,500.

**Ethics considerations**

Data from the NDB were obtained in accordance with the Guidelines for the Provision of Information on Receipt and Specified Health Examination established by the MHLW (approval number MHLW-H-0722-13).

Before donating blood, all donors signed an informed consent form stating that their laboratory test results could be used for research purposes. The ethics committee for epidemiological research of Hiroshima

University waived the requirement for further consent (approval number E-1082).

All study procedures were performed following the applicable regulations and guidelines.

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**Results**

**Number of chronic infections in 2015**

The calculated number of chronic HBV and HCV infections in 2015 was 1,905,187–2,490,873, of which 877,841–1,302,179 were HCV and 1,027,346–1,188,694 were HBV. Based on the calculation, HCV accounted for 46.1–52.3% of the total number of chronic infections, and HBV accounted for 47.7–53.9%. The number of undiagnosed, diagnosed but not linked to care and patients engaged in care in 2015, as well as new infections, patients cured, and deaths between 2000 and 2015, are shown in Table 2 and Figure 2.

**Trends in the number of chronic infections until 2035**

Table 3 and Figure 3 show the predicted number of chronic HBV and HCV infections until 2035. A decrease

	HCV	HBV	HBV and HCV
<b>In 2015</b>			
Total	877,841–1,302,179	1,027,346–1,188,694	1,905,187–2,490,873
Undiagnosed	224,652	452,107–455,099	676,759–679,751
Diagnosed, not linked to care	0–424,338	246,902–405,258	246,902–829,596
Patients engaged in care	653,189	328,337	981,526
On treatment	471,986	169,968	641,954
Direct-Acting Antivirals	108,073	-	108,073
Interferon	5,602	*	5,602
Nucleos(t)ide analogues	-	77,714	77,714
Others	358,311	92,254	450,565
Clinical monitoring only	181,203	158,369	339,572
<b>2000–2015</b>			
New infections in 2000–2015	34,667	38,856–41,848	73,523–76,515
New chronic infections in 2000–2015	24,267	0–2,992†	24,267–27,259
New chronic infections in 2015	167	0–200†	167–367
Viral eradication in 2000–2015 ‡	340,000–500,000	0	340,000–500,000
Deaths in 2000–2015	328,319–1,154,084	207,433–394,870	535,752–1,548,954

**Table 2: Distribution of chronic HBV and HCV infections in 2015.**

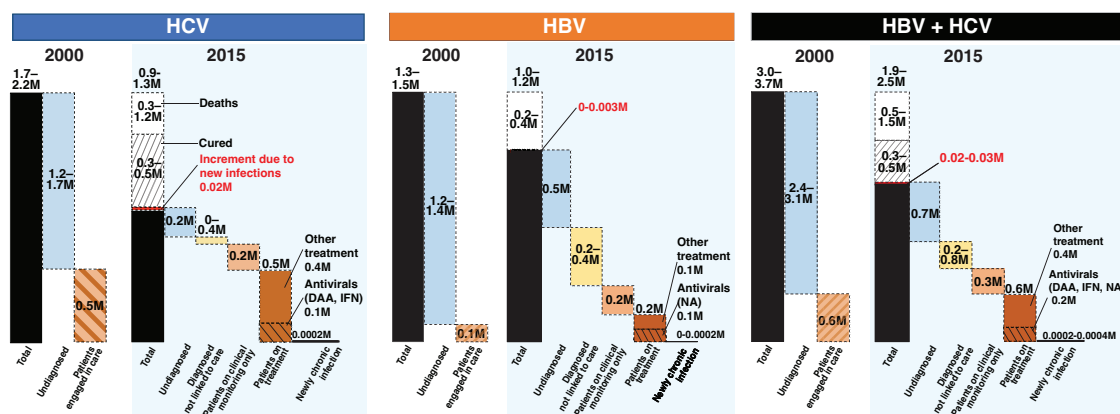
HBV, Hepatitis B virus; HCV, Hepatitis C virus,

†Regarding the number of new cases of chronic HBV infections, cases of HBV mother-to-child transmission are rare due to the effect of Hepatitis B vaccine measures at birth and infancy. In addition, HBV infection in adulthood is rarely chronic except for genotype A.

‡Viral eradication for HCV is defined as the achievement of SVR after treatment. To date, no treatment allows the eradication of HBV.

\* For HBV, few patients are treated with interferon and were combined in the others category group, with hepatoprotective and anticancer drugs.





**Figure 2.** Breakdown of the number of chronic HBV and HCV infections in Japan in 2000 and 2015. Distribution of the number of persons living with chronic HBV and HCV infections in 2015 compared to previously published results in 2000.<sup>11</sup> In 2015, chronic HBV and HCV infections were classified into two groups (undiagnosed and patients engaged in care), whereas in 2015 they were classified into six groups: undiagnosed, diagnosed but not linked to care, patients engaged in care (on clinical monitoring only or treatment), newly infected, cured, and deaths.

in chronic infections is expected over the next 20 years for HBV and HCV, with a faster decrease for HCV.

In 2030, the number of individuals undiagnosed for HCV and those diagnosed but not linked to care (living with chronic HCV and not engaged in care) is expected to be 92,308 – 357,068. As for HCV patients engaged in care, the number of persons is expected to be 119,457 – 119,472. Concerning HBV, 442,430 – 558,939 people are expected to be not engaged in care, and 269,119 patients will be engaged in care.

Compared to 2015, it is expected that by 2035, the number of persons not engaged in care for HCV will decline by 59.8 – 76.1% and 86.5% for patients engaged in care. For HBV, a 47.3–49.3% decrease in persons not engaged in care is expected, along with a 26.0% decrease for patients engaged in care. The breakdown of the trend in the number of patients engaged in care by type of treatment is shown in Supplementary Table S6. The age- and sex-specific total number of chronic infections from 2015 to 2035 is presented in Supplementary Table S7.

### Trend in the specific number of chronic infections by disease state

The number of chronic HBV and HCV infections is expected to decrease yearly (Figure 3). For HCV, although chronic hepatitis will account for most HCV-liver disease states, the number of chronic hepatitis is expected to significantly decrease over the next 20 years (Figure 3A). As for HBV, the number of asymptomatic carriers will still account for more than half of the total number of chronic infections in 2035 (Figure 3B).

### Sensitivity analysis

The results of the sensitivity analyses are presented in Supplementary Figure S2. The factors most influencing the

number of chronic HCV infections in 2030 and 2035 are the rates of new infection and diagnosis. Indeed, if HCV incidence rate is five times higher than our base value, 520,101 persons will be chronically infected in 2030 and 401,030 in 2035. On the other hand, if the number of newly diagnosed cases is 7,500 per year, chronic infections will be 456,027 in 2030 and 323,971 in 2035. For HBV, if the number of newly diagnosed cases is 7,500 per year, the projected number of chronic infections in 2030 and 2035 will be 828,031 and 694,450, respectively.

### Discussion

Using actual data from the NDB, we calculated the number of chronic HBV and HCV infections in 2015 and predicted the trend until 2035.

Our previous report on the total number of chronic HCV infections was 1,694,954–2,194,954 in 2000 and 983,879–1,583,879 in 2011.<sup>11</sup> In the present study, the total number of chronic HCV infections decreased to 877,841–1,302,179. For HBV, the total number decreased from 1,317,752–1,467,752 in 2000, to 1,118,627–1,268,627 in 2011, 1,027,346–1,188,694 in 2015. Our prediction model showed that this decreasing trend will continue until 2035, and the number of persons chronically infected will gradually decrease due to the increase in the number of deaths on the one hand and as a result of the countermeasures on the other hand.

In Japan, hepatitis virus testing under the geriatric health program for the entire population started in 2002, and hepatitis virus testing is still being conducted under the health promotion program. Nationwide surveys on hepatitis virus testing rates were conducted in 2011 and 2017.<sup>5</sup> Over these six years, HCV testing rate increased from 47.9% to 61.6%, and that of HBV

Year	HCV			HBV			HBV and HCV		
	Undiagnosed and diagnosed but not linked to care	Patients engaged in care	Total	Undiagnosed and diagnosed but not linked to care	Patients engaged in care	Total	Undiagnosed and diagnosed but not linked to care	Patients engaged in care	Total
2015	224,652–648,990	653,189	877,841–1,302,179	699,009–860,357	328,337	1,027,346–1,188,694	923,661–1,509,347	981,526	1,905,187–2,490,873
2020	182,690–564,730	270,566–270,567	453,256–835,297	616,921–764,794	310,462	927,383–1,075,256	799,611–1,329,524	581,028–581,029	1,380,639–1,910,553
2025	136,417–461,629	167,803–167,808	304,220–629,437	531,181–664,123	291,647	822,828–955,769	667,598–1,125,752	459,450–459,455	1,127,048–1,585,206
2030	92,308–357,068	119,457–119,472	211,765–476,540	442,430–558,939	269,119	711,548–828,058	534,738–916,007	388,576–388,591	923,313–1,304,598
2035	53,698–261,153	88,128–88,158	141,826–349,311	354,289–453,569	243,003	597,292–696,573	407,987–714,722	331,131–331,162	739,118–1,045,884

**Table 3: Trend in the number of HBV and HCV undiagnosed, diagnosed but not linked to care, and patients engaged in care from 2015 to 2035.**

HBV, Hepatitis B virus; HCV, Hepatitis C virus.

increased from 57.7% to 71.0%.<sup>17</sup> However, in 2015, the number of persons not engaged in care, either undiagnosed or diagnosed but not linked to care, was 224,652–648,990 for HCV and 699,009–860,357 for HBV. Our simulation results show that more than 50,000 HCV- and 300,000 HBV-infected individuals will still be undiagnosed or diagnosed but not linked to care in 2035. Finding undiagnosed cases is one of the main challenges for eliminating HCV. Innovative screening strategies are needed for early diagnosis and linkage to care. Artificial intelligence (AI) applied to population health records has been suggested to assist in identifying undiagnosed persons, especially those with a high-risk of infection, and reduce false-positive results.<sup>35</sup> As the NDB is a comprehensive database, the use of AI can help identify undiagnosed cases and link them to care.

The number of HCV patients engaged in care is expected to continue to decrease more substantially compared to HBV. This decreasing trend could be partly explained by countermeasures against HCV and advances in treatment, including widespread screening, improved access to anti-HCV treatment, and high rates of SVR achievement after treatment. Indeed, the management of HCV infection has improved substantially with the introduction of interferon-free Direct Acting Antivirals (DAA) in 2014, which have few side effects and an SVR rate of 95% or higher regardless of the genotype.<sup>33,36</sup> Treatment algorithms are now very simple for patients. However, although the Japanese government subsidises treatment for people who request it, some infected persons are still not linked to care and remain untreated despite being diagnosed.<sup>5</sup> The main reasons for not attending hospitals for care include time constraints and unawareness of the progression of the infection to liver cancer.<sup>31</sup> This highlights the importance of awareness-raising and re-engagement in care for the control of HCV infection.

Although an overall decrease in the total number of chronic HBV infections is anticipated, the number of HBV patients engaged in care is expected to decrease slowly. To date, no HBV treatment achieves a virologic cure, and the anticipated decrease in the number of patients is thought to be caused by mortality. Therefore, new therapies against HBV that allow a complete cure with viral eradication and decreased risk of progression to HCC are needed. Promising drugs under investigation, alone or in combination, offer hope of finding a cure for HBV patients.<sup>37</sup>

In 2016, WHO advocated for eliminating hepatitis infections, expressed as a 95% reduction in HBV incidence, an 80% reduction in HCV incidence and a 65% reduction in mortality by 2030, with respect to the baseline situation in 2015.<sup>2</sup> Based on our estimations, a 46.1–60.5% reduction in HBV and HCV mortality is projected in 2030. However, the WHO relative targets disadvantage countries like Japan with an ageing population and a low prevalence of HBV and HCV before

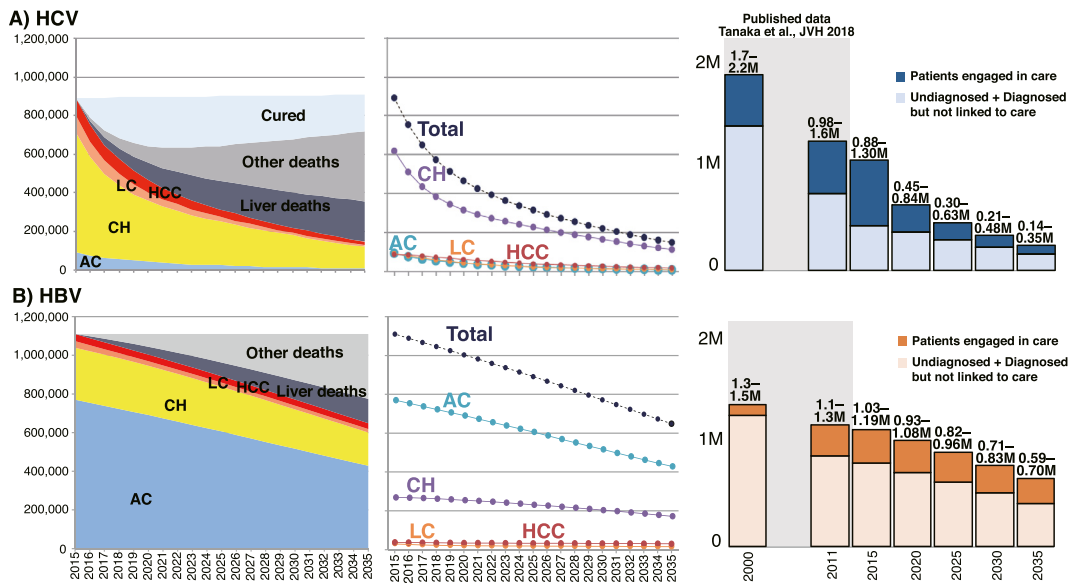


FIGURE 3 Trends in chronic HBV and HCV infections between 2015–2035 by simulation

**Figure 3.** Trends in chronic HBV and HCV infections between 2015 and 2035 by simulation. Simulation of the dynamics of chronic HCV (Figure 3A) and HBV (Figure 3B) infections between 2015 and 2035, based on Markov model. Left and middle graphs show the lower estimates of the cumulative number of chronic infections (left) and the distribution of chronic infections by liver disease state (middle). Right graphs represent the trend in the number of undiagnosed, diagnosed but not linked to care, and patients engaged in care until 2035, compared to previously published results in 2000 and 2011.<sup>11</sup>

2015.<sup>38</sup> Recently, the WHO issued new guidelines recommending the use of absolute impact targets along with programmatic targets.<sup>39</sup> The use of these targets will better assist in assessing Japan's progress towards eliminating viral hepatitis.

We assumed that new chronic HBV infections in Japan are rare, considering the successful implementation of the selective countermeasures for preventing MTCT and the low rate of horizontal infections (although father-to-child and in-utero infections are possible).<sup>6,7,22,23</sup> The situation is different in countries with high endemicity. For instance, in Taiwan, where the prevalence of HBsAg was high (>8%), a selective prevention approach was first used in 1984, with vaccination of infants born to HBsAg-positive mothers, and administration of HBIG to those born from mothers positive to HBeAg. Then, in 1986, the vaccination was extended to all children, irrespective of the mother's HBV status, leading to a dramatic decrease in the HBV prevalence and incidence of HCC in Taiwan.<sup>41</sup> This highlights that in countries with high endemicity, especially in the Western Pacific Region, prevention of both vertical and horizontal HBV transmission is required to reduce the incidence of chronic HBV infections.<sup>6</sup> However, there is still a risk of immunoprophylaxis failure with HBV genotype C and in women with high HBV viral load.<sup>42</sup> To further assist countries in achieving the elimination of MTCT of HBV, WHO has issued guidelines recommending the use of antivirals during

pregnancy for HBV-infected women with high DNA level (>200,000 IU/mL) or HBeAg-positive, in addition to three-dose hepatitis B vaccination in all infants (including timely birth dose), and HBIG to those born from HBsAg-positive mothers if available.<sup>40</sup>

This study is limited by several factors. First, the simulation parameters were assumed to be constant and did not consider future improvements in HBV treatment or hepatitis and liver cancer policies that may be introduced. Therefore, the future burden of hepatitis virus could be lower than our predictions. Also, the number of chronic HBV infections was estimated to be rare, based on studies discussing HBV transmission routes in Japan and the effectiveness of the countermeasures to prevent MTCT of HBV. If the number of chronic HBV infections changes due to various circumstances (such as a war), it is necessary to reconsider the calculation. Second, the Markov model did not take into account the lost to follow-up among those engaged in care. Third, the prevalence of HBV and HCV in the general population was approximated based on the prevalence of HBV and HCV among first-time blood donors. First-time blood donors undergo a pre-screening for hepatitis infection, which may underestimate the actual prevalence. However, although the pre-screening questionnaire asks about piercings, tattoos, injecting drug use, and sexual contact with chronically infected persons, more than 60% of new HCV cases reported during infectious disease surveillance from 1999 to 2009

have no known cause.<sup>43</sup> Therefore, although this is an underestimate, it is reasonable to approximate the prevalence in the general population by the prevalence in first-time blood donors. Forth, the proportions of DAA therapy among HCV patients with CH and C-LC were based on actual data from the NDB in 2015. The rate of DAA use is likely to increase over the coming years. Sensitivity analysis showed that if the rate of DAA therapy in patients with CH increases to 90%, the total number of people with chronic HCV will be 465,304 in 2030, and 339,602 in 2035. It is worth noting that given the restrictive measures implemented by the Japanese government in response to the COVID-19 pandemic, the rate of hospital visits and DAA treatment could be affected, which would negatively impact the future number of chronic infections.

In conclusion, although the number of chronic HBV and HCV infections in Japan is expected to decrease, challenges in controlling hepatitis remain. Along with the control strategies already in place, achieving the WHO goal of eliminating hepatitis will require improved and innovative screening approaches and linkage to care of people infected with HCV and new therapies that allow for a complete cure of HBV.

### Data sharing statement

The dataset used and analyzed in the current study is available from the corresponding author on reasonable request.

### Contributors

JT, TA, AK, MOhi conceived and designed the study and the data analysis concept. JT, MS, MOha acquired the data. TA, AK, MOhi, MW, AS analysed the data. JT, TA, SO, MW, MS, MOha interpreted the data. SO, TA, JT, TK, MOha, LH drafted the manuscript. All authors read and approved the final version of the manuscript.

### Declaration of interests

The authors declare no conflict of interest.

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The Liver Meeting in Washington (USA) in 2016, and at the 24th International Symposium on Hepatitis C virus and Related Viruses (HCV2017) in Massachusetts (USA) in 2017.

### Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100428.

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