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Total Numbers of Undiagnosed Carriers of Hepatitis C and B Viruses in Japan Estimated by Age- and Area-Specific Prevalence on the National Scale

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Key Words
Hepatitis C virus · Hepatitis B virus · Blood donors · Liver cirrhosis · Hepatocellular carcinoma · Healthcare · Japan

Abstract
Objective: To estimate total numbers of undiagnosed carriers of hepatitis C virus (HCV) and hepatitis B virus (HBV) in Japan. ***Methods:*** Area- and age-specific prevalence of HCV as well as HBV was determined in the first-time blood donors [20–39 years (n = 2,429,364)] and examinees of periodical health check-ups [40–74 years (6,204,968 for HCV and 6,228,967 for HBV)] in Japan. Prevalence in adolescents [5–19 years (79,256 for HCV and 68,792 for HBV)] was determined in a single prefecture, and that of HCV in the elderly (≥75 years) was estimated by the exponential model. HBV infection was determined by the detection of hepatitis B surface antigen, and HCV infection by either the algorithm or assuming persistent infection in 70% of the individuals with antibody to HCV. ***Results:*** Of the total population of 127,285,653 in 2005, 807,903 (95% CI 679,886–974,292) were estimated to be infected with HCV at a carrier rate of 0.63%, and 903,145 (837,189–969,572) with HBV at that of 0.71%. ***Conclusion:*** Accurate estimation of undiagnosed HCV and HBV carriers in the general population would help to predict the future burden of liver disease, and take appropriate measures for improving healthcare.

Introduction

Hepatitis C virus (HCV) and hepatitis B virus (HBV) are estimated to infect 170 and 350 million people over the world, respectively [1, 2]. Most infections with HCV or HBV do not induce clinical liver disease, while ~30% of them develop severe liver disease such as cirrhosis and hepatocellular carcinoma [3, 4]. Hence, there is a pressing need to identify the individuals who have undiagnosed HCV or HBV infection, and take effective measures for terminating viral infections and preventing the progression of liver disease.

For management of persistent HCV and HBV infections in a given country, it is necessary to know their exact numbers for assessing medical and financial needs in the foreseeable future. Prevalence of undiagnosed HCV or HBV

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infection has been estimated by survey of blood donors in Japan [5] and a representative population in the USA [6].

In the present study, area- and age-specific prevalence of HCV or HBV infection was determined in 8 jurisdiction areas of the Japanese Red Cross Blood Center. Then, the total numbers of undiagnosed HBV and HCV infections were estimated by compiling the results in the first-time blood donors and examinees of the periodical health check-up program. Of the 127,285,653 Japanese registered in 2005, 807,903 (0.63%) were estimated to be infected with HCV and 903,145 (0.71%) with HBV.

Materials and Methods

Japanese Population

Japan is divided into 8 areas, along its north-to-south axis, according to jurisdiction of the Japanese Red Cross Blood Center, into Hokkaido, Tohoku, Kanto, Hokuriku/Tokai, Kinki, Chugoku, Shikoku and Kyushu. Populations in 5-year age groups in each jurisdiction area were obtained from the registry at the National Census 2005.

First-Time Blood Donors

During 6 years from January 2001 to December 2006, 3,748,422 individuals (aged 16–64 years) donated whole blood or apheresis products for the first time, and their sera were tested for markers of HCV and HBV infections. Ongoing HCV infection was estimated by assuming the detection of HCV RNA in 70% of individuals with the antibody to HCV (anti-HCV), in accordance with a previous report [5].

Examinees of Hepatitis Virus Infections

Since the fiscal year 2002 in Japan, individuals who turned 40, 45, 50, 55, 60, 65 and 70 years were offered to take tests for hepatitis viruses at periodical health check-ups by a 5-year national project. During 5 years through 2006, 6,204,968 individuals received tests for HCV and 6,228,967 for HBV, corresponding to ~30% of the eligible Japanese, and their area- and age-specific prevalence of HCV or HBV infection was determined.

School Children and Adolescents

In the Iwate prefecture located in the north of Japan, biochemical markers of diseases dependent on the lifestyle were examined in children and adolescents at the entrance to schools. Their serum samples had been stored frozen, and were tested for markers of hepatitis virus infections. Carrier rates of HCV and HBV among them were calculated, with their ages adjusted to those in 2005; infants aged <5 were represented by the children aged from 5 to 9 years. Designs and procedures of this investigation were approved by the Ethics Committee of Hiroshima University.

Simulation of HCV and HBV Infections in the Elderly

By its age-specific profile, the prevalence of HCV was deduced to be an exponential function of the age. Accordingly, age-specific prevalence of HCV in the individuals aged ≥75 years was simulated by an exponential function model; it was constructed on the prevalence of HCV in each age group ≥50 years.

The formula was constructed as:

$$\log y(x) = a + bx$$

where x is the 5-year age code, $y(x)$ is an estimator of HCV prevalence in x, and a and b are coefficients.

The equation is transformed into:

$$y(x) = e^a e^{bx}$$

in which e^a represents the HCV prevalence when $x = 0$ (in the group aged 0–4 years), since $y(0)$ is equal to e^a. By replacing x for $x + 1$ in the above equation, it is converted to $y(x + 1) = e^a e^{b(x+1)}$.

Then, the following equation can be constructed:

$$y(x + 1) = e^b y(x)$$

where e^b is the slope of HCV prevalence increasing with age. Thus, the HCV prevalence is multiplied by a factor e^b for an increment of the age code by 1.

The simulation model was applied to estimate age-specific prevalence of HCV in each of 8 areas in the individuals ≥75 years.

Prevalence of HBV in the individuals ≥75 years was represented by that in those aged 70–74 years, since it stayed constant from 65 through 75 years.

Markers of Hepatitis Virus Infections

In blood donors, anti-HCV was determined by passive hemagglutination of the second generation with commercial assay kits (HCV PHA; Abbott Laboratories, North Chicago, Ill., USA) with a cutoff limit set at 2^5, as well as by particle agglutination with commercial assay kits (HCV PA Test-II; Fujirebio, Inc., Tokyo, Japan). HBsAg was determined by reversed passive hemagglutination with reagents prepared by the Japanese Red Cross.

In examinees of periodical health check-ups, ongoing HCV infection was determined by the algorithm with anti-HCV and HCV RNA [7]. Anti-HCV was determined by passive hemagglutination of the second generation with commercial assay kits (HCV PHA; Abbott Laboratories), and since 2002, it was determined by enzyme immunoassay with commercial assay kits (AxSYM HCV Dinapack-III; Abbott Laboratories). Samples with high anti-HCV titers contain HCV RNA, and therefore, only those with low and middle titers were examined for HCV RNA. HBsAg was determined by reversed-passive hemagglutination with commercial assay kits (Institute of Immunology Co., Ltd, Tokyo, Japan).

Statistical Analyses

Statistical analyses for the evaluation of R^2 values were performed with JMP 8.0 (SAS Institute, Inc., Cary, N.C., USA) and DeltaGraph 5.5 (RedRock Software, Inc., Salt Lake City, Utah, USA). A p value > 0.05 was considered significant.

Results

Age-Specific Prevalence of HCV in the First-Time Blood Donors and Examinees of Periodical Health Check-Ups

Figure 1 illustrates age-specific prevalence of HCV in the first-time blood donors (aged 15–69 years in 2005) and examinees of periodical health check-ups (39–73 years in 2005); 70% of individuals with anti-HCV were considered

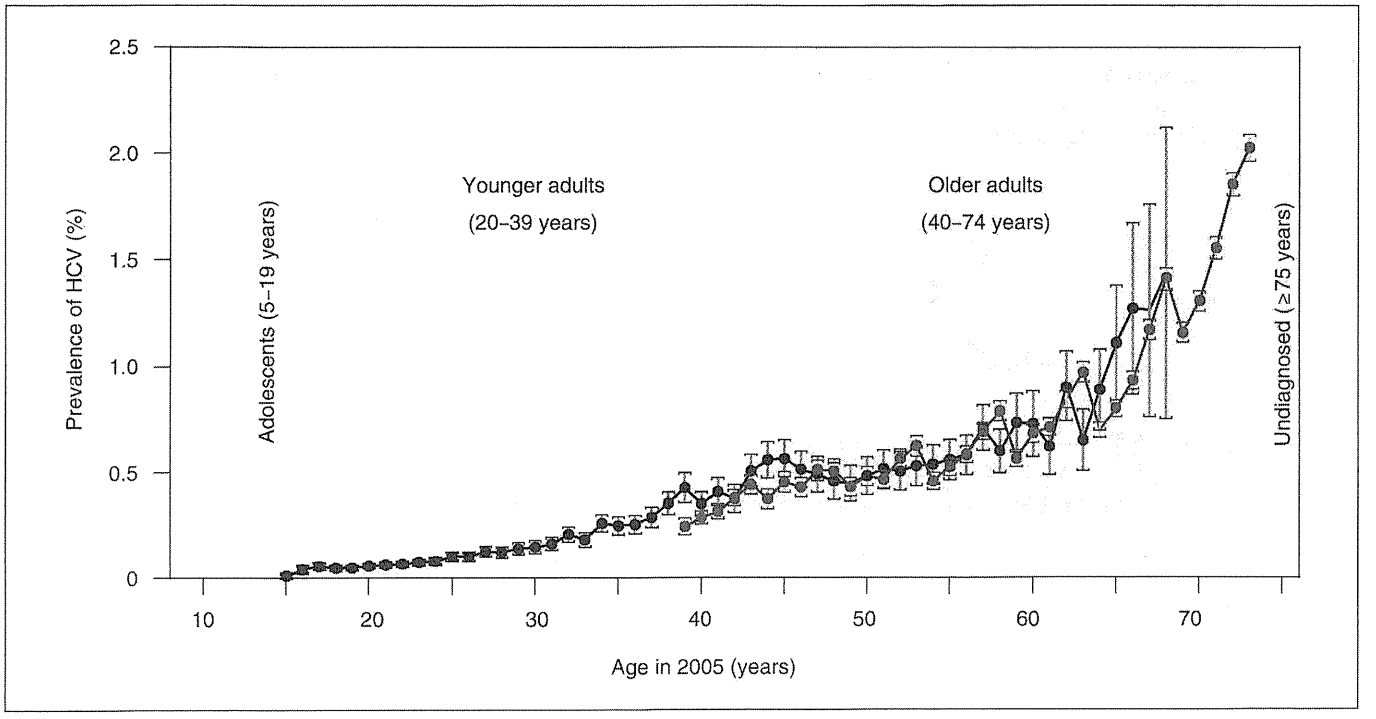

Fig. 1. Age-specific prevalence of HCV in Japan. The prevalence of HCV was determined in the first-time blood donors aged from 15 to 68 years (blue dots) and examinees of periodical health check-ups aged from 39 to 73 years (red dots). Their ages were adjusted to those in the year 2005. Bars indicate ranges of 95% CI.

to possess HCV RNA in serum [5]. Results of two distinct populations were well in accord. For the first-time blood donors, however, the variation (95% CI) widened increasingly with age. It would have reflected decreases in the first-time blood donors with age, since the majority of these (83.5%) were aged ≤39 years. As the prevalence of HCV in blood donors ≥40 years was unreliable in them, that in examinees of periodical check-ups was adopted for estimating the national prevalence of HCV.

Area-Specific Prevalence of HCV in Eight Jurisdiction Areas

In view of distinct geographic distribution of HCV, the prevalence of HCV in the general population would not be applicable to every area in Japan. Figure 2 compares results in the first-time blood donors and recipients of health check-ups among 8 jurisdiction areas spanning from north (Hokkaido) to south (Kyushu). They unfolded a wide variety in the age-specific prevalence of HCV. Although the prevalence of HCV increased with age in all areas, the slope of increase differed widely among them. Hence, it was necessary to employ a distinct age-specific prevalence in each of the 8 areas for estimating HCV carriers precisely.

Table 1. Age-specific prevalence of HCV in three different populations

Age in 2005	n	HCV-positive, n	Prevalence, % (95% CI)
School children			
5–9	17,390	2	0.012 (0.000–0.027)
10–14	29,817	3	0.010 (0.000–0.021)
15–19	32,049	7	0.022 (0.006–0.038)
Blood donors			
20–24	1,205,966	1,122	0.065 (0.061–0.070)[a]
25–29	536,560	874	0.114 (0.105–0.123)[a]
30–34	408,814	1,089	0.186 (0.173–0.200)[a]
35–39	278,024	1,190	0.300 (0.279–0.320)[a]
HCV screening			
40–44	611,146	2,127	0.348 (0.333–0.363)
45–49	495,032	2,292	0.463 (0.444–0.482)
50–54	675,350	3,485	0.516 (0.499–0.533)
55–59	947,438	5,974	0.631 (0.615–0.646)
60–64	1,081,854	8,423	0.779 (0.762–0.795)
65–69	1,264,496	13,722	1.085 (1.067–1.103)
70–74	1,054,472	17,649	1.674 (1.649–1.698)

[a] The prevalence in blood donors was based on an assumption of HCV infection persisting in 70% of those with anti-HCV [5].

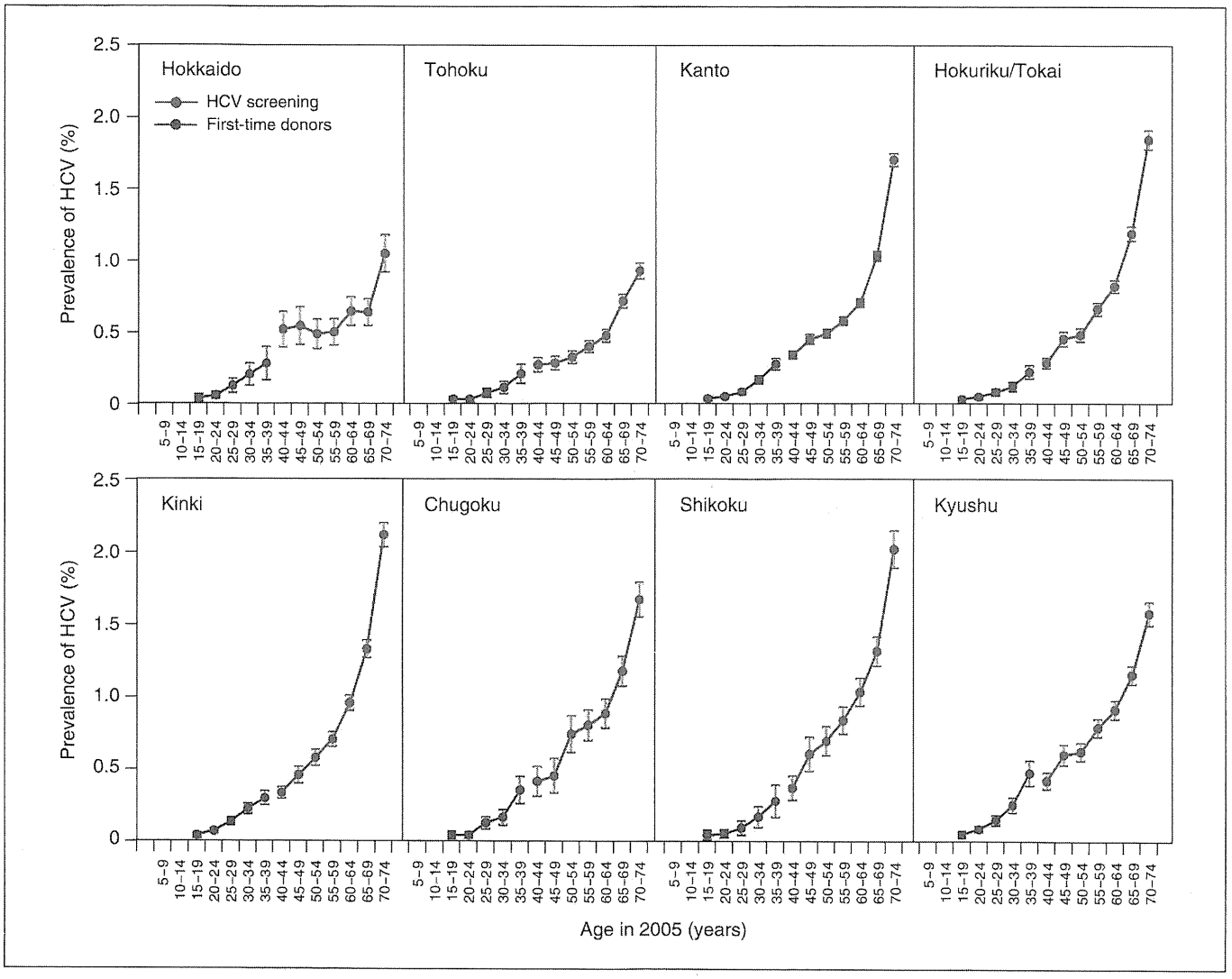

Fig. 2. Age-specific prevalence of HCV in 8 jurisdiction areas in Japan. The prevalence of HCV is calculated in each of twelve age groups notched by 5 years. The prevalence in five groups ≤39 years was represented by the first-time blood donors, and that in seven groups ≥40 years by recipients of HCV screening. Bars indicate ranges of 95% CI.

Prevalence of HCV in Adolescents

Since blood donors were restricted to 16–64 years of age, and health examinees were targeted on 40–70 years, they did not cover individuals aged ≤15 or ≥75 years in the year 2005. To fill in an opening on the younger side, the age-specific prevalence of HCV was determined in school children and adolescents in the Iwate prefecture (table 1). The prevalence in infants aged 0–4 years was assumed similar to that in the children aged 5–9 years; an extremely low prevalence of HCV (0.012%) would support such an assumption.

Simulating Prevalence of HCV in the Elderly

The prevalence of HCV appeared to be an exponential function of the age, according to its profiles in the first-time blood donors and examinees of health check-ups (fig. 1). Based on this assumption, a formula was constructed to simulate the prevalence of HCV in age groups ≥75 years for each of the 8 jurisdiction areas in Japan (see Materials and Methods).

Figure 3 compares actual (dots) and simulated data (red line) of five age groups from 50 to 74 years (corresponding to age codes 10–14) among the 8 areas. There was a high coefficient of determination between them,

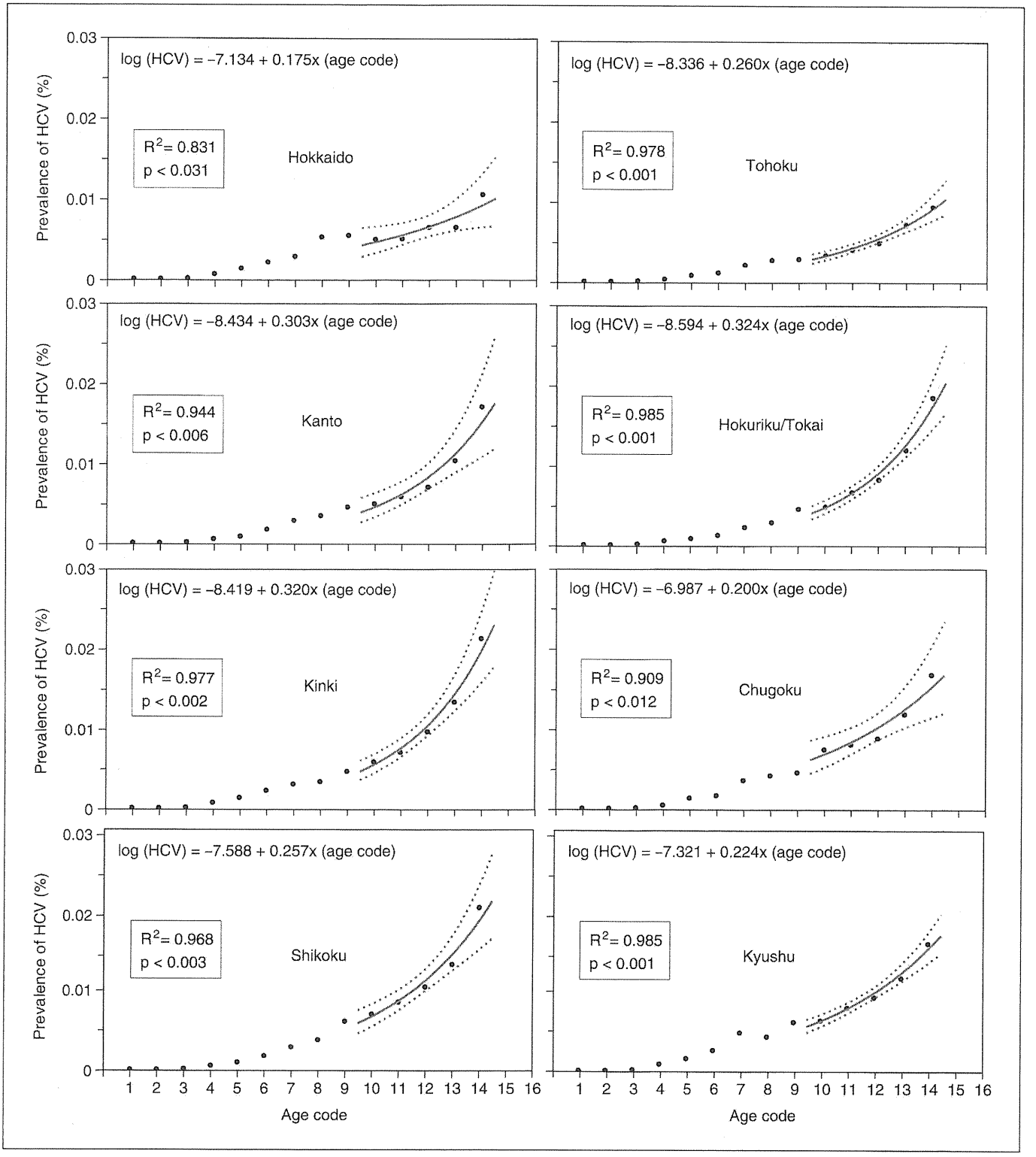

Fig. 3. Simulation of age-specific prevalence of HCV in the elderly. Prevalence of HCV in the first-time blood donors as well as examinees of periodical health check-ups (dots) and that simulated by formulation (red line with ranges of 95% CI in dotted line) are shown for 8 jurisdiction areas in Japan. Formula is shown at the top of each area. Age codes are: 1, 5–9 years; 2, 10–14 years; 3, 15–19 years; 4, 20–24 years; 5, 25–29 years; 6, 30–34 years; 7, 35–39 years; 8, 40–44 years; 9, 45–49 years; 10, 50–54 years; 11, 55–59 years; 12, 60–64 years; 13, 65–69 years; 14, 70–74 years, and 15, 75–79 years.

Table 2. Regional and total HCV carriers in Japan

Areas	Population	HCV carriers (95% CI)	Carrier rate
Hokkaido	5,620,813	26,097 (19,356–34,413)	0.46%
Tohoku	12,047,975	50,688 (42,754–59,953)	0.40%
Kanto	41,247,892	235,328 (195,408–293,611)	0.57%
Hokuriku/Tokai	19,294,443	132,434 (114,216–154,446)	0.69%
Kinki	22,657,542	173,808 (147,548–207,173)	0.52%
Chugoku	7,650,977	53,296 (42,299–67,698)	0.70%
Shikoku	4,083,698	35,159 (28,746–43,004)	0.86%
Kyushu	14,682,313	101,092 (89,379–113,993)	0.80%
Total	127,285,653	807,903 (679,886–974,292)	0.63%

Table 3. Age-specific prevalence of HBV in three different populations

Age in 2005	n	HBV-positive, n	Prevalence, % (95% CI)
School children			
5–9	17,363	3	0.017 (0.000–0.037)
10–14	29,817	14	0.047 (0.022–0.072)
15–19	32,049	12	0.037 (0.016–0.059)
Blood donors			
20–24	1,205,966	1,826	0.151 (0.144–0.158)
25–29	536,560	1,650	0.308 (0.293–0.322)
30–34	408,814	1,759	0.430 (0.410–0.450)
35–39	278,024	1,327	0.477 (0.452–0.503)
HBV screening			
40–44	613,960	5,491	0.894 (0.871–0.918)
45–49	497,589	5,373	1.080 (1.051–1.109)
50–54	679,893	8,700	1.280 (1.253–1.306)
55–59	950,508	12,891	1.356 (1.333–1.379)
60–64	1,085,119	13,282	1.224 (1.203–1.245)
65–69	1,268,304	12,406	0.978 (0.961–0.995)
70–74	1,057,469	9,545	0.903 (0.885–0.921)

with R^2 values ranging from 0.831 to 0.985 ($p < 0.031$ and $p < 0.001$, respectively), attesting to the validity of this simulation. Of note, the factor *b* in formula (by which age codes were multiplied) varied broadly among the 8 areas. Thus, it was the highest in Hokuriku/Tokai at 0.324 and lowest in Hokkaido at 0.175, with close to twofold differences between them.

Estimation of Undiagnosed HCV Carriers in Eight Areas and the Entire Nation

Based on age- and area-specific prevalence of HCV, numbers of undiagnosed HCV carriers were calculated for 8 jurisdiction areas, and they were compiled in the entire nation (table 2). The prevalence of HCV in each of three age groups (75–79, 80–84 and ≥85 years) was simulated by the formula, while that of HBV was represented by the prevalence in the group of 70–74 years. As of the year 2005, 127,285,653 were registered in the national census of Japan, and 807,903 of these are estimated to have undiagnosed HCV infection at an overall carrier rate of 0.63%. There was an increasing gradient in the prevalence of HCV along the north-to-south axis of Japan.

Age-Specific Prevalence of HBV

Figure 4 depicts age-specific prevalence of HBV in 2005. It was deduced from HBsAg in the first-time blood donors (15–69 years) and examinees of periodical health check-ups (39–73 years). Since the prevalence of HBV in the elderly did not increase with age so sharply as that of HCV (fig. 1), it was presumed not to increase further and stay around 1% in the individuals ≥75 years. The age-specific prevalence of HBV tabulated in three different

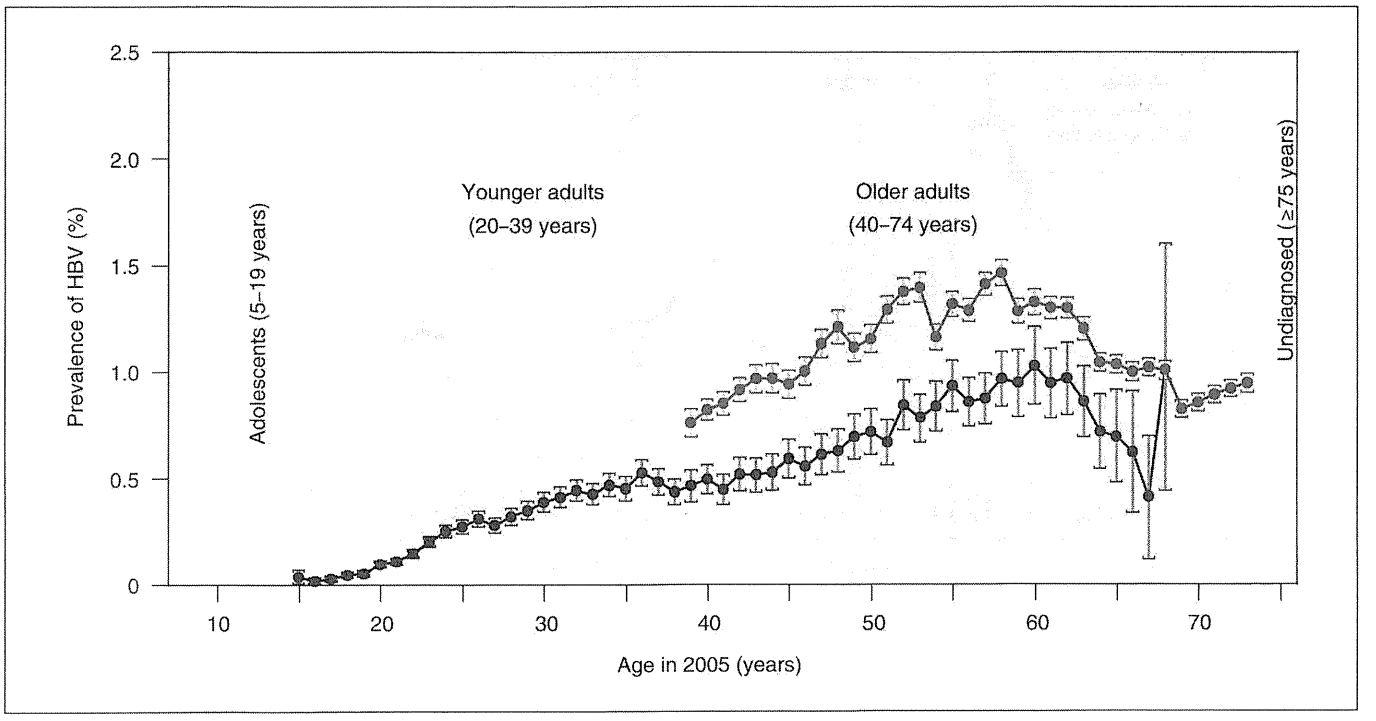

Fig. 4. Age-specific prevalence of HBV in Japan during 2002–2006. The prevalence of HBV was determined in the first-time blood donors aged from 15 to 68 years (blue dots) in the year 2005 and examinees of periodical health check-ups aged from 39 to 73 years (red dots) in the year 2005. Bars indicate ranges of 95% CI.

populations is listed in table 3. There was a constant decline with decreasing age in the frequency of HBV in individuals ≤39 years, and it was particularly low in children ≤9 years (0.017%).

In examinees of periodical health check-ups, the age-specific prevalence of HBV did not diverge and stayed within a narrow 95% CI (fig. 4). By contrast, that in the first-time blood donors dispersed widely. Such a variation in the age-specific prevalence of HBV would have been ascribed to the first-time blood donors who clustered in age groups ≤40 years.

Area-Specific Prevalence of HBV in Eight Jurisdiction Areas

The age-specific prevalence of HBsAg varied widely among 8 jurisdiction areas (fig. 5). HBsAg was most frequent in the age group of 55–59 years in every area, and reached 3.1% in the northern-most Hokkaido. The peak frequency decreased in central Japan (1.1% in Kanto and Hokuriku/Tokai), and increased towards the southern end (1.9% in Kyushu). Thus, the prevalence of HBsAg was determined individually along the axis of Japan in estimating the total number of HBV carriers in Japan.

Estimation of Undiagnosed HBV Carriers in Eight Areas and the Entire Nation

Numbers of undiagnosed HBV carriers were complied by multiplying age-specific prevalence of HBsAg by corresponding subpopulations in 8 jurisdiction areas (table 4). In total, 903,145 of the 127,285,653 (0.71%) individuals are estimated to have undiagnosed HBV infection in Japan in 2005.

Shift of Undiagnosed HCV and HBV Carriers during 5 Years (2000–2005) in Japan

Table 5 compares numbers of HCV and HBV carriers aged 15–69 years between 2000 and 2005 for 8 jurisdiction areas in Japan. Data for the year 2000 were extracted from a previous survey [5]. Data for the year 2005 were obtained in the first-time blood donors during 2001–2006 in this study by the same method as in the previous survey [5]. Undiagnosed HCV and HBV carriers decreased during 5 years by 55 and 47.5%, respectively. The overall carrier rate of HCV declined sharply from 0.95 to 0.44%, and that of HBV from 1.04 to 0.55% in Japan.

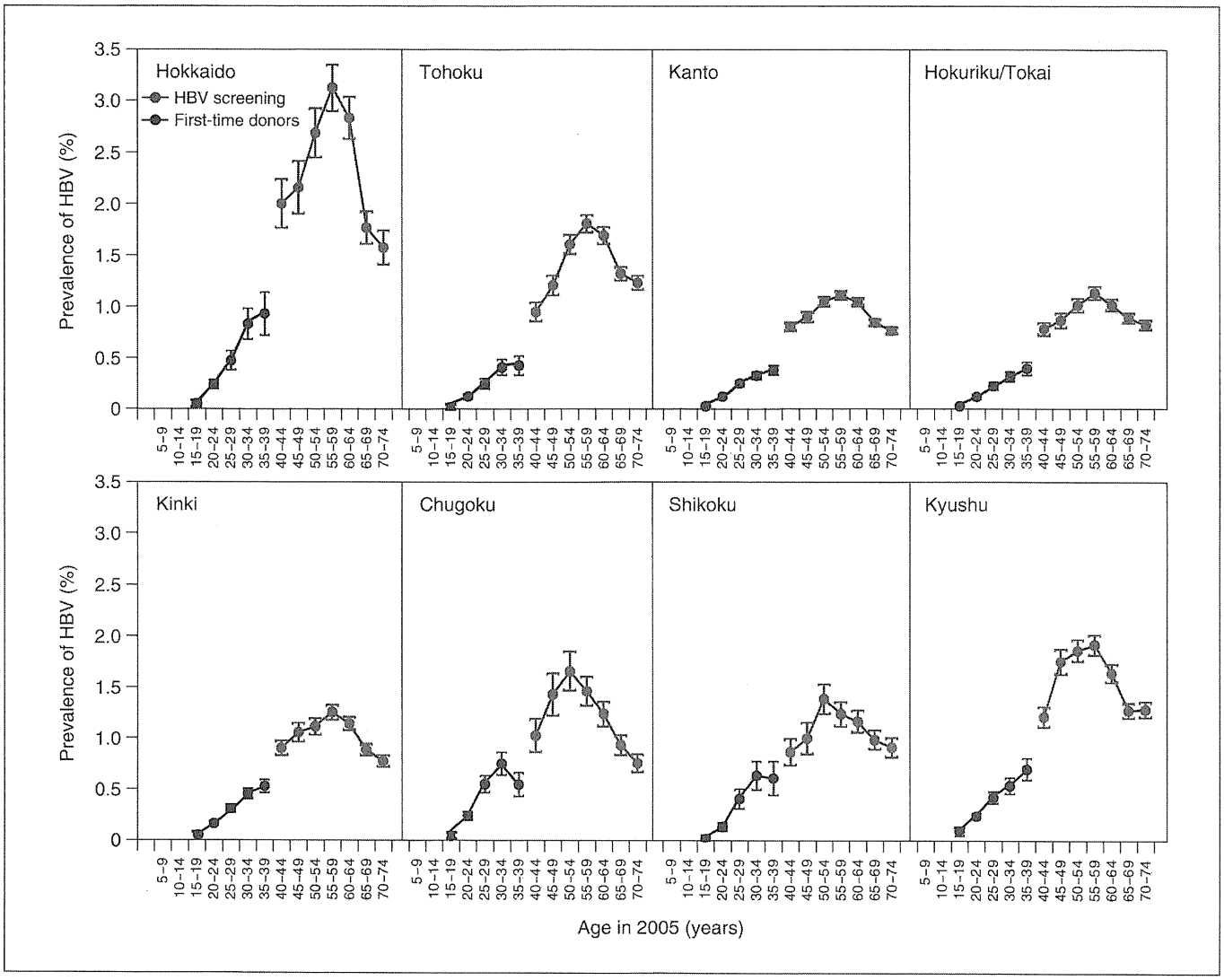

Fig. 5. Age-specific prevalence of HBV in 8 jurisdiction areas in Japan. The prevalence of HBV is calculated in each of twelve age groups notched by 5 years. The prevalence in five groups ≤39 years was represented by the first-time blood donors and that in seven groups ≥40 years by recipients of HCV screening. Bars indicate ranges of 95% CI.

Table 4. Regional and total HBV carriers in Japan

Areas	Population	HBV carriers (95% CI)	Carrier rate
Hokkaido	5,620,813	80,573 (72,314–88,765)	1.43%
Tohoku	12,047,975	104,736 (97,742–111,816)	0.87%
Kanto	41,247,892	231,799 (220,129–244,105)	0.56%
Hokuriku/Tokai	19,294,443	109,709 (101,722–117,581)	0.56%
Kinki	22,657,542	144,965 (134,387–155,464)	0.64%
Chugoku	7,650,977	59,948 (52,705–67,121)	0.78%
Shikoku	4,083,698	29,776 (26,080–33,437)	0.73%
Kyushu	14,682,313	141,639 (132,111–151,282)	0.96%
Total	127,285,653	903,145 (837,189–969,572)	0.71%

Table 5. Decrease of undiagnosed HCV and HBV carriers in the 15- to 69-year-old population in Japan

	Survey in 2000[a]		Survey in 2005		Difference	
	number estimated	carrier rate in area[b]	number estimated	carrier rate in area[b]	number estimated	balance
Shift of HCV carriers during 5 years from 2000 to 2005						
Hokkaido	41,139	0.99%	17,658	0.44%	−23,481	−57.1%
Tohoku	61,658	0.71%	30,525	0.37%	−31,133	−50.5%
Kanto	277,644	0.90%	126,283	0.41%	−151,361	−54.5%
Hokuriku/Tokai	88,724	0.64%	48,360	0.35%	−40,364	−45.5%
Kinki	178,871	1.06%	70,526	0.43%	−108,345	−60.6%
Chugoku	72,431	1.32%	24,595	0.47%	−47,836	−66.0%
Shikoku	43,497	1.49%	16,504	0.59%	−26,993	−62.1%
Kyushu	120,989	1.16%	64,115	0.63%	−56,874	−47.0%
Total	884,954	0.95%	398,567	0.44%	−486,387	−55.0%
Shift of HBV carriers during 5 years from 2000 to 2005						
Hokkaido	106,896	2.56%	54,557	1.35%	−52,339	−49.0%
Tohoku	104,923	1.21%	48,490	0.58%	−56,433	−53.8%
Kanto	255,207	0.83%	132,414	0.43%	−122,793	−48.1%
Hokuriku/Tokai	78,481	0.56%	51,477	0.37%	−27,004	−34.4%
Kinki	165,915	0.98%	85,083	0.52%	−80,832	−48.7%
Chugoku	90,041	1.64%	37,706	0.71%	−52,335	−58.1%
Shikoku	38,411	1.32%	19,162	0.69%	−19,249	−50.1%
Kyushu	127,879	1.23%	77,941	0.77%	−49,938	−39.1%
Total	967,753	1.04%	506,830	0.55%	−460,923	−47.6%

[a] Data for the year 2000 were extracted from a previous survey of hepatitis virus infections in Japan [5].
[b] The carrier rate specific for respective jurisdiction area was applied.

Discussion

There are many constraints in estimating total HCV and HBV infections in a given nation. Since it is not feasible to test every member for serological markers of hepatitis virus infection, populations representative of the entire nation have served for the estimation. Volunteer blood donors are recruited, but they have a restricted age range (16–64 years in Japan). Students attending schools and universities can close the opening in younger generations, but infants younger than the school age are not enrolled. Moreover, there are no means of estimating carrier rates of hepatitis virus infections in the individuals aged beyond the eligibility of blood donation. In addition, blood donors are selected individuals who are leading healthy lives above the average. In the survey of inhabitants in sentinel counties of the USA [6], who represent the average Americans, patients with liver disease and persons with restricted activities, such as those incarcerated or institutionalized, are not included.

Patients with clinical liver disease, as well as individuals found with HCV or HBV infection by health check-ups, can receive the medical care. However, many blood donors found with viral infections have developed severe liver disease already, and therefore, cannot receive efficient medical interventions [7, 8]. Hence, it is necessary to detect undiagnosed HCV and HBV infections hidden in the society. For this purpose, periodical health check-ups for screening hepatitis virus markers were started in April 2002 on the individuals, who turned 40, 45, 50, 55, 60 and 70 years, by a 5-year national project in Japan. The target age range (40–70 years) was selected due to a high incidence of hepatocellular carcinoma [9]. Since by far the majority of the first-time blood donors were younger than 40 years, the prevalence of HCV or HBV beyond that age dispersed widely (fig. 1, 4). In this study, therefore, the coverage by the first-time blood donors was confined to 20–39 years of age, and it was taken place by examinees of health check-ups aged 40–74 years; they left age groups ≤15 and ≥75 years uncovered, however.

The national prevalence of hepatitis virus infections in individuals ≤19 years was presumed to be similar to that in the Iwate prefecture situated in northern Japan. Since the prevalence of HCV or HBV infection in them was extremely low and stayed between 0.01 and 0.02%, such an assumption would not have affected the overall results to any significant extent. The prevalence of HCV in age groups ≥75 was simulated by a premise that it would be an exponential function of the age. Consequently, the formula based on profiles in five age groups from 50 to 74 years (at a 5-year notch) was extrapolated to three age groups ≥75 years. The simulation matched closely with the prevalence determined in corresponding age groups, with R^2 values ranging from 0.83 to 0.99 ($p < 0.05$ and $p < 0.01$, respectively) throughout 8 jurisdiction areas in Japan (fig. 3).

Japan has an axis spanning 2,000 kilometers from the north-east towards the south-west over the four major islands (Hokkaido, Honshu, Shikoku and Kyushu). Within a rather small land, the prevalence of HCV or HBV is not uniform all over Japan. The prevalence of HCV had an increasing gradient from north to south, and was the highest in Kyushu (table 2), while that of HBV was the highest in Hokkaido, decreased in between and then increased towards Kyushu (table 4). Reflecting such local differences, age-specific prevalence of HCV or HBV differed widely among 8 jurisdiction areas (fig. 2, 5).

Based on the results obtained on the area- and age-specific prevalence of HCV or HBV, carriers of these hepatitis viruses in 8 jurisdiction areas were tabulated separately over age groups from 20 to 74 years. Those in age groups ≤19 years were represented by the Iwate prefecture. The prevalence of HCV in age groups ≥75 years was simulated by the formula, and that of HBV was represented by individuals aged 70–74 years. Japan was populated by 127,767,994 people in 2005. Of these, 807,903 (95% CI 679,886–974,292) were estimated to have undiagnosed HCV infection at an overall prevalence of 0.63%, and 903,145 (837,189–969,572) to possess undiagnosed HBV infection at that of 0.71%. These estimates are much less than publically inferred numbers of HCV and HBV carriers in Japan at 1.5–2.0 million each. Leaving aside HCV and HBV carriers who have developed liver disease and stayed outside the scope of the present study, our estimates based on reasonable scientific grounds are much smaller; they add up barely half of generally referred figures around 1.5–2.0 million in Japan.

Based on the sex- and age-specific prevalence of hepatitis virus markers in the 3,478,422 first-time blood donors during 2001–2006, with the same criteria used in the previous study [5], we have estimated the number of undiagnosed HCV carriers aged 15–69 years in the year 2005 to be 398,567 (95% CI 295,410–501,453) and that of undiagnosed HBV carriers to be 506,830 (95% CI 398,115–616,113). In the previous study [5], undiagnosed HCV and HBV carriers aged 15–69 years in the year 2000 were assessed to be 884,954 (95% CI 725,082–1,044,826) and those with HBV to be 967,753 (95% CI 806,760–1,128,745). They decreased by 55.0 and 47.6%, respectively, during 5 years (table 5). In support of this view, the incidence of HCV or HBV infection during 10 years (1994–2000) in Japan is very low and estimated at 1.86 (95% CI 1.06–3.01) or 2.78 (1.87–4.145) per 100,000 person-years [10]. Decreases in undiagnosed HCV and HBV carriers in Japan would have been attributed to increased chances of receiving tests for hepatitis virus infections at health checkups and medical institutions, as well as increased awareness due to educational programs or other healthcare campaigns or screening programs in high-risk individuals. Additionally, there would have been a cohort effect in individuals aged 15–69 years who have shifted by 5 years during the observation period.

The results of the Third National Health and Nutrition Survey (HANES III, 1988–1994) [11] and those of more recent HANES (2001–2002) [6] in the USA are essentially similar with respect to age-specific profiles of HCV infection, and shifted by 10 years. The incidence of de novo HCV and HBV infections may have decreased substantially both in the USA and Japan, driven partly by the introduction of the nucleic acid amplification test and a more stringent questionnaire on donors to exclude blood donations in the window period of infection [12–17]. The national burden of HCV infection has been reported in Great Britain [18], where the prevalence of anti-HCV in hospitalized patients was 3.4% and that in the first-time blood donors was 0.03% in the year 2008.

In spite of many improvements in the control of hepatitis virus infections, there are many HCV and HBV carriers buried in the society who need immediate identification for receiving timely and efficient medical interventions. Treatment of viral hepatitis keeps improving, especially for liver disease induced by HCV. The sustained virological response in the patients infected with HCV of genotype 1, who have received triple therapy with pegylated interferon, ribavirin and protease inhibitors, has increased to 70% or higher, from 50% with the state-of-care therapy with pegylated interferon and ribavirin [19, 20]. With the advent of new antiviral drugs that will enter the scene in the foreseeable future, the virological response is expected to increase further. There would be

nothing like early detection of HCV and HBV infections for appropriate and timely medical care to prevent the progression of liver disease. Such a rational strategy will benefit not only patients themselves, but also merit the society and government, which are going to be burdened with ever-increasing morbidity and mortality along with skyrocketing costs.

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C型肝炎ウイルス感染とその予防対策

輸血，血液製剤によるHCV感染の現状とその予防対策

Present status of transfusion-associated hepatitis C virus infection and efficiency after implementation of nucleic acid amplification testing

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Key words：核酸増幅検査，輸血，ウインドウ期，HCV感染

はじめに

1989年，C型肝炎ウイルス(HCV)はウイルス粒子の発見[1]に先駆けてウイルス遺伝子の断片として発見された[2]．更に，HCV抗体の測定として遺伝子組換え技術により酵母で発現させたC100-3タンパクを抗原とした系が使用可能となった[3]．これにより，輸血後肝炎の調査は堰を切ったように進み，その主因がHCVであることが明らかとなった[4]．その後，輸血後肝炎の征圧を目指して，献血血液に対してHCV抗体スクリーニング検査(第一世代)が導入され，1992年には第二世代の試薬に変更された．同スクリーニング検査の導入により，輸血によるC型肝炎は激減し，主な残存リスクはウインドウ期(WP)の献血血液によるC型肝炎となった．現在，WPの献血血液を排除するために，B型肝炎ウイルス(HBV)，HCVおよびヒト免疫不全ウイルス(HIV)に対する核酸増幅検査(NAT)を導入し，血清学的検査を補っている．これにより，輸血の安全性は格段に向上した．一方，HCVの感染経路については，静注用薬物乱用者，針刺し事故，透析，性感染，出産時，医原性など，今なお議論されているが[1]，過去には非加熱血液製剤や輸血での感染も問題となっていた．

本稿では主に輸血によるHCV感染の現状とその予防策を中心に解説した．

1. 輸血によるHCV感染の予防対策の歩みと輸血後肝炎の変遷

日本赤十字社が行ってきた輸血の安全性確保対策と輸血後肝炎の変遷を示す(**表1**，**図1**)．1960年代前半までの売血時代には輸血を受けた患者の50％以上が肝炎を発症していたが，1960年代後半に献血制度への切り替えにより，輸血後肝炎は16％に減少した．1972年にHBs抗原検査を開始し，1986年の400mL採血，成分採血の導入により高単位製剤の供給が可能になり患者への献血者曝露数が減り，更に輸血後肝炎は8.7％になった．1989年にはHBV感染既往献血者の排除のためにHBc抗体検査(導入時期はHI法で2^6以上不適→現在は，輸血感染症の解析結果からCLEIA法でs/co値が12以上(HIで2^5相当)を不適としている)を導入した．今でもその出庫基準は変わっておらず，HBV感染既往献血者の血液(HBc抗体がCLEIAでs/co値が<12)による感染が問題となっている．HCV(当時は非A非B)に対する安全性確保対策は，献血制度および高単位製剤の供給を第一歩

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表1 献血血液に対する感染症スクリーニング導入の変遷

導入年	月	HCV関連検査項目	その他検査項目
1952(昭和27)年	4		梅毒血清学的検査
1964(昭和39)年	8		献血の推進について閣議決定
1970(昭和45)年	10		肝機能検査(GPT, GOT)
1972(昭和47)年	1		HBs抗原検査(DRID法)
	4		HBs抗原検査変更(ES法)
1975(昭和50)年	10		肝機能検査変更(GOT)
1978(昭和53)年	4		HBs抗原検査変更(RPHA法)
1981(昭和56)年	1		肝機能検査変更(GPT)
1986(昭和61)年	11		HIV抗体検査(EIA法)
			HTLV-1抗体検査(PA法)
1987(昭和62)年	10		HIV抗体検査変更(PA法)
1989(平成1)年	12	HCV抗体検査(EIA法)	HBc抗体検査(HI法)
1992(平成4)年	2	HCV抗体検査変更(PHA法：第二世代試薬)	
1993(平成5)年	9	HCV抗体検査変更(PHA法またはPA法：第二世代試薬)	
1994(平成6)年	3		HIV-2抗体検査(PA法)
1996(平成8)年	9		検体保管開始
	10		HIV1/2抗体検査変更(PA法：コンビネーション試薬)
1997(平成9)年	9		ヒトパルボウイルスB19抗原検査(RHA法)
1998(平成10)年	2		梅毒血清学的検査変更(TPPA法)
1999(平成11)年	10	HBV, HCV, HIV核酸増幅検査(NAT)導入 検体プールサイズ500本	
2000(平成12)年	2	HBV, HCV, HIV核酸増幅検査(NAT)検体プールサイズを500から50本	
2004(平成16)年	8	HBV, HCV, HIV核酸増幅検査(NAT)検体プールサイズを50本から20本	
2008(平成20)年	8	・HBV, HCV, HIV-1/2核酸増幅検査(NAT)試薬・機器変更 検体プールサイズ20本 ・HCV抗体検査変更(CLEIA法)	HBs抗原, HBs抗体, HBc抗体, HIV-1/2抗体, HTLV-1抗体, 梅毒トレポネーマ抗体, ヒトパルボウイルスB19抗原検査(CLEIA法)

に，1970年10月，献血血液のスクリーニング検査に肝機能検査を非A非B肝炎の代替え検査として導入したのが輸血によるHCV感染に対する征圧の第一歩であった．その後，1989年12月に，輸血後肝炎の主因を成すウイルスとして特定されたHCVを検出するための抗体検査(c100-3: 第一世代)が導入され，1992年2月には，コアタンパクを追加し感度と特異性を向上させた第二世代の試薬に変更した．更に，HCV抗体検査のWPを短縮するために，1999年10月より500人分の献血者検体をプールし，それを検体としたNATが開始された(血清学的検査に合格した血液のみに対して実施)．2000年2月にNATの検出感度を高めるためにプー

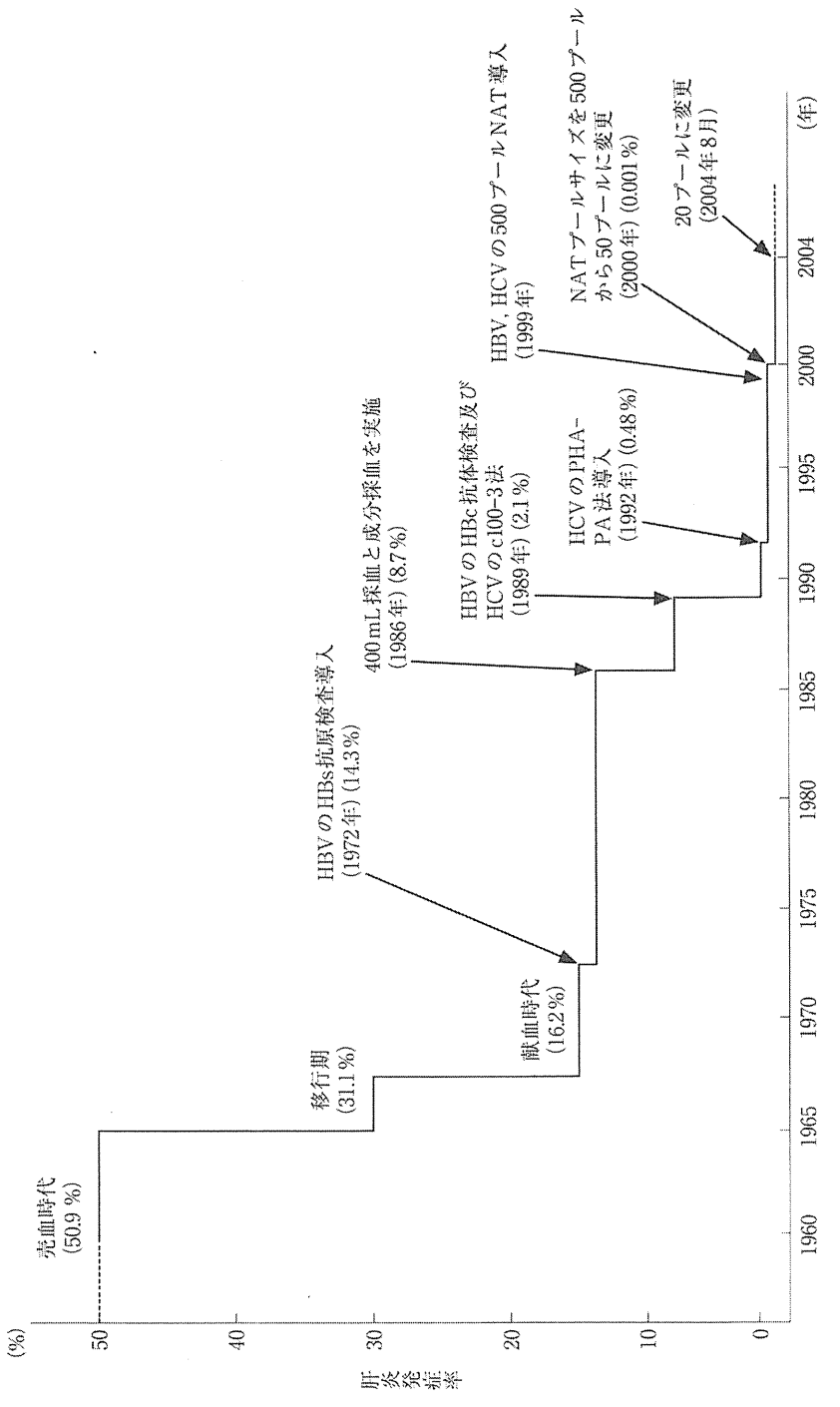

図1 輸血後肝炎の変遷

'日本赤十字社輸血後肝炎の防止に関する特定研究班'研究報告書(1993.4－1996.3)一部改変を基に厚生労働省作成

ルサイズを50人分に縮小し，2004年8月にプールサイズを20とした．2008年には第二世代の試薬・機器へ変更となり，検査に使用する検体量を200 μLから850 μLへと4.25倍増量し検出感度の向上を図った．また，第二世代の試薬ではHIV-1だけでなくHIV-2も捕捉が可能となり，輸血用血液の安全性が強化され現在に至っている．HCVに対するNATの検出感度は33.5 copies/mL(12.4 IU/mL)である．また，輸血後感染症報告などの科学的解析を可能にするために，1996年9月から全国血液センターは献血血液の検体を保管するシステムを整備した．

2. HCV抗体スクリーニング検査の導入効果

HCV抗体スクリーニング検査(第一世代)の導入効果について，導入前後の輸血後肝炎の発生頻度を2群(1-10単位輸血群と11-20単位輸血群)で解析した結果，それぞれ，導入前4.9％と16.3％の発生頻度であったのに対して，導入後は1.9％と3.3％に減少した[5]．しかし，HCV抗体スクリーニング検査(第一世代)導入後も，輸血後肝炎の発生が認められ，かつ症例報告としても抗c100-3抗体陰性の輸血によるC型肝炎が報告された[6]．このことから，c100-3タンパクを抗原とした第一世代のHCV抗体スクリーニング検査は感度と特異性が低く，HCV感染例を十分に検出できないことが示唆された．その後，コアタンパクを加えた第二世代の試薬に変更された．変更後の輸血後肝炎の発生頻度を6,458例の輸血患者を対象に追跡調査を行ったところ，輸血後肝炎は0.48％まで減少し，C型肝炎の確診例は1例も確認されなかった[7]．HCVには数種の遺伝子型が存在することが知られているが，コアタンパクをコードする遺伝子領域の塩基配列は遺伝子型間でよく保存されている．つまり，コアタンパクを加えた第二世代の抗体測定系はHCV遺伝子型に関係なくHCV感染例を効率よく検出でき，スクリーニング検査としては極めて有用であることが確認された．しかし，1994年，HCV-RNA陽性，HCV抗体陰性のWPが疑われる献血血液によるC型肝炎が1992年2月(第二世代の試薬に変更)以降の輸血で初めて報告された[8]．一方，1993年から日本赤十字社は輸血感染症の実態調査として医療機関から報告される輸血後感染症報告の解析を開始した．当初は献血血液の検体が保管されていなかったことから，報告症例に対しては，当該献血者の理解と協力を求め，原因究明用の検体を再採血し，その血液で精査する調査(追跡調査)であった．症例にもよるが1本の輸血症例から100本を超える輸血症例まで多彩で，全報告例の追跡調査は困難であり，報告症例のうち，約25％が解析可能例にすぎなかった．また，当該輸血用血液を直接検査できないことからWPの献血血液を特定できないという難点があった．このような要因から1994-95年の調査では，輸血によるC型肝炎を見いだすことはできなかった．医療機関から報告された症例の中で，輸血によるC型肝炎が初めて特定されたのは1996年であった．これは，都内の血液センターで先行的に開始(1994年4月より)した検体保管システムが功を奏したことによる．感染の原因となった輸血用血液はHCV抗体陰性，HCV-RNA陽性で遺伝子型が2a型(患者も2a型)で，当該献血者を追跡調査した結果，HCV抗体が陽転していた．WPの献血血液によるC型肝炎として国内で科学的に証明された初の症例である[9]．1996年9月，献血血液の検体保管が全国の血液センターで開始され，1997年，1998年，1999年に輸血によるC型肝炎が，それぞれ1例，7例，5例と複数確認された(**表2，3**)．NAT導入後の輸血によるHCV感染は，2000年から2004年まで確認されず，2005年，2006年に50プールNATのWPに採血された血液で各々1例が確認され，2007年に20プールに感度を上げてからの1例を確認したのが最後で，2008年以降，2010年10月までにNATシステムの改良に伴い輸血によるHCV感染は確認されていない．つまり，現在の輸血によるHCV感染の残存リスクは1<10,000,000で輸血リスクとして許容できるものである．仮にNATを導入していなければ，約10年間に120例以上の患者が不幸にも輸血に

表2 輸血後HCV感染として医療機関から報告された数と輸血との関連性

年	報告数	関連性が高い	関連性が低い	不明例
1994	23	0	6	17
1995	25	0	17	8
1996	33	1	17	15
1997	29	1	24	4
1998	51	7	42	2
1999	60	5	54	1
2000	56	0	56	0
2001	51	0	51	0
2002	33	0	32	1
2003	58	0	57	1
2004	70	0	70	0
2005	64	1	62	1
2006	45	1	44	0
2007	33	1	32	0
2008	29	0	29	0
2009	18	0	18	0

よりHCVが感染した可能性があったことになる．逆をいえば，NAT導入前にも同様に1年間に10例以上の感染例を見逃していたことになる．

3. 感染原因となった血液の特徴

原因血液はすべて，当該献血時はHCV抗体陰性で医療機関に供給されたものであった．しかし，医療機関から輸血後感染症として報告を受け，事後に保管検体を精査したところ17例(献血者は16例)すべてにHCV-RNAが検出された．再検査でもHCV抗体は陰性であった．追跡できた献血者はすべて，HCV抗体が陽転しており(データ省略)，WPの献血血液であることが確認された．ウイルスの遺伝子型は解析できた15例のうち1b型が8例，2a型が6例，2b型が2例であった．年齢は，平均31歳(19-49歳)と若年齢層で，男女比は6：9であった(**表4**)．献血者への感染経路は特定されていない．アメリカでも25歳以下の若年齢者層の感染リスク行為が問題となっているが[10]，我が国でも軽視できない状況にある．一方，NATが開始されてから2010年7月までにHCV抗体陰性，HCV-RNA陽性の献血血液が122例確認されている．検出頻度は，27-70万回の献血に1回となる．当然ながらこれらの血液は輸血には使用されていないが，その血液中のHCVの特徴を次にまとめた．

4. NATから検出されたWPに献血された血液の特徴

NATのみ陽性の113検体を測定した結果，遺伝子型別では1a：1例，1b：30例，2a：53例，2b：29例と2a型が半数近くを占め，1b型と2b型がほぼ同数を占めていた．HCVによる慢性肝疾患患者では1b型が約70％，2a型が約20％で2b型が約10％を占めると報告されており，NATで検出された遺伝型割合とは大きく乖離する．慢性肝疾患患者では少なくとも10年以上前(多くは第二次世界大戦後の混乱期と考えられている)の感染であり，現在の献血者のスクリーニングNATで検出された113例はすべてHCV抗体陰性の感染初期例で，感染経路の違いによる差であると考えられる．HCV-RNA検出献血者の性別は男性71例(62.8％)，女性42例(37.2％)と男性の方が多かったが，平成18年度の全献血者の男女比とほぼ一致しており，性別による差は認められなかった．年代別では10歳代13人(11.5％)，20歳代48人(42.5％)，30歳代29人(25.7％)，40歳代13人(11.5％)，50歳代5人(4.4％)，60歳代5人(4.4％)と，20歳代，30歳代で陽性者が多く認められた．しかし，これを平成18年度の献血者年代別構成比と比較すると，10歳代，20歳代で陽性比率が構成比を上回っており，30歳代では構成比とほぼ一致した．40歳代，50歳代では逆に構成比を下回っており，10歳代，20歳代の若年齢層で新たなHCV感染が多く発生しているのではないかと考えられた．遺伝子型と年代との間には明確な傾向は認められなかったが，遺伝子型2bの比率が男性で有意に高いことがわかった．これらの例を採血地域別に遺伝子型を

表3 血液センターに報告された輸血感染症

	HBV	HCV	HIV	PVB19	HEV	バベシア	マラリア	細菌
1991							1	
1992								
1993	1							
1994	1							
1995	1							
1996	1	1						
1997	12	1	1					
1998	22	7						
1999	21	5	2(1)			1		
2000	5			1				2
2001	7							
2002	8			3	1			
2003	12		1	1				
2004	20				2			
2005	11	1		3	1			1&
2006	6	1		1	1			3
2007	13	1*						
2008	4				2			2
2009	7				1			2

*: 20プールWP
(1): 献血者は1名
&: 医療機関と日赤とでの解析結果乖離例

比較すると，遺伝子型1bは中部以西の西日本で多く認められ，関東・東北ではやや低く北海道では検出されていない．2aは中部で一番高かく北海道ではやや低かったが，その他の地域では差が認められなかった．逆に2bは東北・中部で検出されておらず，九州でやや低めであったがその他の地域ではあまり差が認められなかった．

5. NAT導入後の輸血によるC型肝炎の発生状況と残存リスク

感染初期のHCVのramp-up期間での倍加速度は約5.8-21時間とHBVの4日に比して著しく早く[11,12]．特に，HCVに対するNATはHCV抗体検査のWPを大幅に短縮させ，その導入効果は絶大なものであった．このような理由から，NAT導入以来，輸血によるC型肝炎はわずか3例しか確認されておらず，20プールサイズのWPが原因となったのは1例のみであるが，現行のNATシステムでは，感染例は特定されていない．しかし，海外ではNATウインドウの理論的リスクが報告されている(数百万回の献血に1回)[13]し，個別NAT陰性の輸血用血液によるC型肝炎が報告されている[14]．また，HCVの感染価はチンパンジー接種実験から50％感染率が10 copies/mL[15]と少なく，我が国においても決してゼロリスクとはいえない[16]．しかし，このリスクは前述したようにリスクという概念からは許容できるものと著者は認識している．毎年，輸血によるHCV感染の疑い症例として

表4 原因血液と患者の背景

症例	報告年	患者成績				献血者成績			
		年齢(性)	原疾患	ALT(IU/L) MAX.	genotype	個別NAT	genotype	HCV抗体	年齢(性)
1	1996	46(男)	S状結腸癌	581	2a	+	2a	−	23(女)
2	1997	70(女)	急性リンパ性白血病	254	1b	+	1b	−	26(男)
3	1998	63(男)	骨髄異型成症候群	123	1b	+	1b	−	19(女)
4	1998	60(男)	出血性胃潰瘍	81	2a	+	2a	−	34(男)
5	1998	56(男)	胃癌	221	2a	+	2a	−	34(男)
6	1998	32(男)	広範囲熱傷	245	N.T	+	1b	−	23(女)
7	1998	65(男)	十二指腸出血	211	2a	+	2a	−	48(男)
8	1998	78(女)	急性骨髄性白血病	107	1b	+	1b	−	29(女)
9	1998	63(男)	右大腿骨頸部骨折	308	1b	+	1b	−	49(女)
10	1999	48(男)	多発性骨髄腫	11	2b	+	2b	−	32(女)
11	1999	75(男)	肝細胞癌	298	2b	+	2b	−	38(男)
12	1999	38(女)	再生不良性貧血	46	1b	+	1b	−	20(女)
13	1999	48(男)	胃潰瘍	903	1b	+	1b	−	27(男)
14	1999	69(男)	多発性骨髄腫	69	N.T	+	N.T	−	37(男)
15	2005	81(女)	骨髄異型成症候群	407	1b	+	1b	−	44(女)
16	2006	35(女)	常位胎盤早期剥離	12	2a	+	2a	−	21(女)
17	2007	54(女)	再生不良性貧血	26	2a	+	2a	−	22(男)

症例4，5の献血者は同一
上記以外に初流血除去・保存前白血球除去も導入済み

医療機関から報告されてくるが，特定される例は極めて少なく，輸血とは別経路のHCV感染を疫学的に調査することが必要ではないかと思われる．

6. イギリスでの現状(SHOTより)

輸血による肝炎は2004年にHEVの1例，2005年にHBVの1例が同定されているが，それ以降は，細菌感染が主な原因となっている．

(from http://www.shotuk.org/shot-reports/reports-and-summaries-2001-2002/)

7. 血液製剤によるHCV感染

血液製剤でHCV感染が問題となったのは，非加熱製剤である．最近では，過去にフィブリノゲン製剤，血液凝固因子製剤を投与された患者で問題となった．免疫グロブリン製剤でもバクスター社のGammagardに関連したHCV感染が報告され，HCVを不活化するS/D処理が製造工程に導入された経緯もある[17]．その後，血漿分画製剤についてはウイルスの除去・不活化工程を2種以上導入することが義務付けられ，少なくとも，HBV・HCV・HIVの製造工程中のウイルスクリアランス指数が10^9以上を担保しなくてはいけないことになっている．また，国内原料血漿については，NAT導入によりウイルス混入量が極限まで少なくなっている．更に，2010年度中にはHIV，HBV，HCVを検出するNATの感度がHBV-DNA(2,000 IU/mL)，HCV-RNA(2,000 IU/mL)，HIV-RNA(4,000 IU/mL)と規定される予定であるが(血液製剤のウイルスに対する安全性確保を目的としたNATに必要とされる検出限界値について．平成22年10月6日付厚生労働省医薬食品局血液対策課よ