Table 1. Epidemiology of hepatitis B and hepatitis C in Hong Kong, Japan, Korea, and Taiwan.

	Hepatitis B			Hepatitis C			Hepatocellular carcinoma (HCC)			
Country [Ref.]	Prevalence of chronic hepatitis B infection, general population (%)	Estimated number of carriers ($x10^6$)	Age group with highest number of carriers	Prevalence in general population (%)	Dominant genotype	Time trends	Incidence in men; women (rate per 100,000 persons)	% due to hepatitis B infection*	% due to hepatitis C*	Median age of onset
Hong Kong [41]	8.8	0.7	>20 yr (prevalence increases with age)	0.30%	1b, 6a	Very low prevalence, most common in IDUs	29.9; 8.3	75-80	3-6 [44]	63 for men, 71 for women
Japan [12;20;42]	0.71	0.9	50-64 yr	0.63%	70% 1b, 20% 2a, 10% 2b	Risk factors changing over time and by region	2.42; 1	15	67.7	66.4 for men, 69.9 for women
Korea [43]	2.8	2.25-2.27	30-50 yr	1.29% (in >40 population)	1b, 2a	Mostly >40 age group people. Lack of data on youth, little data on role of injecting drug use	45; 33.6	20	72	Incidence increases after age 40, peak at 55
Taiwan [30;44]	10-12	2.5-3	35 (or 40)-55 (or 60) yr	4.4% (>20 yr)**	1b, 2a	Most disease in older groups. Significant geographic variations (from 0-90% depending on village) (45)	53; 21	53 [30]	28 (8% due to B + C) [30]	58 average, mean age 10 yr lower for HBV *vs.* HCV-caused HCC***

HCC, hepatocellular carcinoma; IDU, injecting drug users.
*The remainder of cases of HCC is caused by alcohol and other factors such as aflatoxin.
**This data is from populations participating in screening programmes only.
***One would expect the relative proportion of HCV-related HCC and the age of onset of HCC to increase in future.

in the area of viral hepatitis and have broadly similar health infrastructures. These localities are also in a privileged position compared to other countries in the Asia Pacific region, in that they have the resources to build on existing successes and lead the drive for further policy change across the region. Summary epidemiological data on hepatitis B and hepatitis C in these four jurisdictions is presented in Table 1.

The aim of the workshop was to ensure that participants understood the WHO framework; to support participants in building or strengthening advocacy networks, and to identify local priorities for implementing the framework within their respective jurisdictions.

This paper summarises the outcomes of this workshop and identifies steps to be taken to translate the WHO Framework into sustainable national policies on viral hepatitis in North Asia.

Materials and methods

The 28 workshop participants were identified within the existing CEVHAP network of local liver associations, patient organisations, and centres of excellence in Hong Kong, Japan, Korea, and Taiwan. The agenda for the one and a half day workshop was developed in close consultation with a small group of CEVHAP experts. To assist participants in their preparation, a briefing paper describing the scope of viral hepatitis, focusing on hepatitis C and hepatitis C virus, within the four jurisdictions was distributed prior to the meeting (CEVHAP, data on file).

The workshop used the four axes of the WHO Prevention & Control of Viral Hepatitis Infection: Framework for Global Action to guide discussions (Fig. 1) and consisted of expert presentations, group discussions, and country-level workshops.

Results

This paper uses the four axes of the WHO framework to describe the workshop results. The priority areas for action in the four participating jurisdictions are presented in Table 2 and are discussed in more detail in the section below.

Axis 1: Raising awareness, promoting partnerships, and securing resources

In North Asia, the general public, people at risk of infection, the medical community and policymakers generally have a poor understanding of viral hepatitis, its natural history and

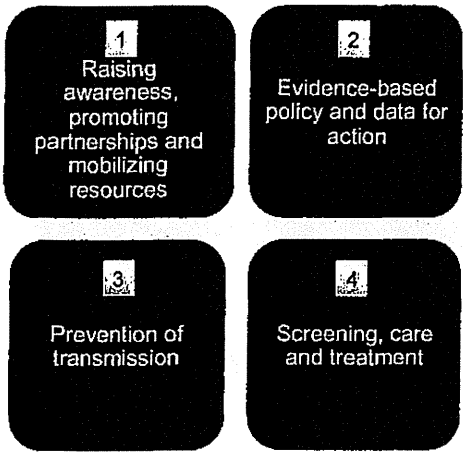

Fig. 1. The four strategic axes for policy development recommended in the WHO Prevention & Control of Viral Hepatitis Infection: Framework for Global Action.

manifestations. Awareness among primary care physicians is particularly low and targeted educational efforts are needed to encourage these providers to test their patients for viral hepatitis and refer them towards appropriate care pathways. Investment in developing better relationships between primary care and hepatitis specialist services may help engage primary care physicians.

Local advocacy networks that bridge civil society, liver specialists, primary care physicians and other community care providers are still lacking in Taiwan, Hong Kong, and Korea particularly. This lack of a strong advocacy base makes it more difficult to engage the media in the first place or to overcome media fatigue about viral hepatitis. The media plays a vital role in raising awareness of viral hepatitis, particularly among the general public and those at risk of infection. The awareness campaigns run in the United States and Korea provide interesting examples of media engagement on viral hepatitis (Case studies 1 and 2).

A key to the success of awareness campaigns on viral hepatitis is to find the issues that resonate best with media, the public, and policymakers. The fact that viral hepatitis is one of the main causes of liver cancer is indeed compelling and one with potential to grab the attention of these key stakeholders. For example, a recent study by the International Agency for Research on Cancer showed that one in six cancers was caused by infection and concluded that prevention of viral hepatitis and other infections could have a substantial effect on reducing the future burden of cancer [8]. These data may be very powerful in convincing policymakers of the need to mobilise resources towards the prevention and management of viral hepatitis.

Table 2. Priorities for action in Hong Kong, Japan, Korea, and Taiwan according to the four strategic axes of the WHO Global Framework.

Priorities for action
1. Raising awareness, promoting partnerships and mobilizing resources
Greater public awareness
Greater awareness of primary care physicians
Building patient advocacy
Strengthening hospital-primary care networks
2. Evidence-based policy and data for action
Economic data on the burden of viral hepatitis
Better data on barriers to screening and treatment
Centralised surveillance
Accurate estimates of the number of chronic hepatitis cases
3. Prevention of transmission
Better monitoring of vaccine effectiveness
Universal vaccination of children and improved access to vaccination by people at greater risk
Targeted harm reduction strategies
Better data on vaccine failure
4. Screening, care and treatment
Improved availability and funding of screening [public funds and/or employer-based]
Linking screening to effective monitoring and treatment
Funding screening for hepatocellular carcinoma
Improved access to treatment of chronic hepatitis and hepatocellular carcinoma

Case Study 1: How to engage the public on hepatitis: the 'KNOw More Hepatitis' in the United States

In 2011, the United States Centers for Disease Control and Prevention (CDC) launched an education campaign, 'KNOw More Hepatitis' [9]. Insights from focus groups consisting of people with high prevalence rates of infection (for example, 'baby-boomers' for hepatitis C) helped guide the development of targeted messages for each risk population [10]. The campaign made creative use of social and other media:

- It used powerful, evidence-based messages to engage the media. One example was "Hepatitis now kills more Americans than HIV", which was the key conclusion of a recently published article in the *Annals of Internal Medicine* [11].
- An online hepatitis risk assessment tool was featured on the CDC website, which allowed individuals to conduct a quick, confidential assessment of their risk for hepatitis A, hepatitis B or hepatitis C in the privacy of their own homes.
- The campaign has an active Facebook page, 11,000 followers on Twitter, and public service advertisements on YouTube. 400 tweets translated into over 3.3 million media impressions, demonstrating the power of social media to engage target audiences on viral hepatitis.
- Six national airports donated space worth up to $4 million for Dioramas which featured rotating posters on viral hepatitis (Fig. 2).

Case Study 2: Conveying the 'right level of fear'? The Korean experience

In March 2011, the Korean Association for the Study of the Liver (KASL) launched an awareness campaign on viral hepatitis. A 30-minute television advertisement showed patients with end-stage liver disease. The message was: "if you don't manage your disease, this is what is going to happen." The goal was to shock the public into action.

The impact of the advertisement was significant: the day after it featured, KASL was ranked top of Google searches. But the increased attention also had unintended adverse consequences: people infected with viral hepatitis reported the loss of relationships or employment as a result of the advertisement. KASL immediately launched a lower-intensity campaign that focused on the importance of seeking proper care for chronic hepatitis infection.

The lesson learned by KASL was that it is important to convey the 'right' level of fear about viral hepatitis in order to raise awareness of the urgency of the situation in terms of the risks of advanced liver disease. However, too much fear may create panic and inertia, if the perceived message is that nothing that can be done to improve the outcomes of people with the viral hepatitis or that policy makers, physicians, and the public are powerless to effect change.

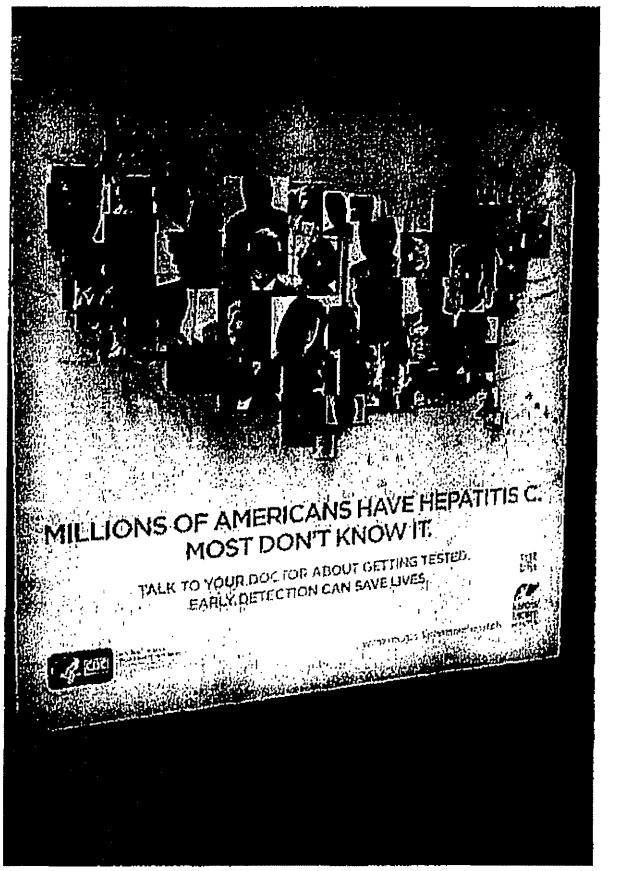

Fig. 2. Example of a diorama on viral hepatitis at a US airport.

Axis 2: Evidence-based policy and data for action

One key condition for successful advocacy and a sustained public health response is reliable data. With viral hepatitis, the fact that so many people remain undiagnosed makes it difficult to convey to policy makers the full scale of the problem [12]. Better surveillance is needed to capture chronic as well as acute cases of viral hepatitis. More reliable prevalence estimates in high risk populations, such as people who are poor, those who inject drugs, prisoners, and sex workers, are needed as these groups are usually poorly represented in existing surveillance studies.

Reliable economic data are critical to demonstrate to national governments the need for them to invest in viral hepatitis prevention and control. Sometimes showing policy makers the cost of 'doing nothing' can exemplify the most compelling case for investment [13].

One area where more research is greatly needed is to find the barriers to uptake of screening and treatment among individuals at risk. These data are critical to shift the behaviours of individuals towards more active disease management.

Finally, insights from patients, such as those gathered in a survey of the Japan Hepatitis Council (Case study 3) may help channel efforts towards areas that will make the greatest difference to individuals living with viral hepatitis.

Case Study 3: The combined power of advocacy and data: The Japan Hepatitis Council

Japan has a powerful patient advocacy base consisting of over 80 local, regional and national associations acting under the umbrella of the Japan Hepatitis Council. Pressure from these groups over the government's failure to implement blood and mass vaccination safety measures was instrumental in the creation of the Basic Act of Hepatitis Measures in 2010. As part of this Act, each prefecture is required to have a hepatitis patient representative on its local council.

A recent survey of members of the Japan Hepatitis Council helped identify some of the main challenges for policy development in Japan [14]:

- **High mortality from hepatocellular carcinoma (HCC):** Japan has one of the highest rates of HCC in the world and counts 30,000 deaths due to HCC every year.
- **Low uptake of screening:** A national screening programme against hepatitis B and C has existed since 2002, targeting individuals aged 40-70 years. However, uptake rates remain low (7-27%) and screening is poorly integrated into general practice [15, 16].
- **Poor linkage to treatment:** 48% of those who test positive for hepatitis B (and 65% of those testing positive for HCV) fail to seek medical care [12] and only half of those with hepatitis C who do seek care complete their course of treatment [14].
- **High costs of care:** Government funding for antiviral treatment of hepatitis B and hepatitis C has gradually increased since 2008, however patients are still left with a significant co-payment and many patients report crippling personal economic costs.
- **Stigma and discrimination:** Thirty percent of respondents report having experienced discrimination due to viral hepatitis, especially in medical institutions. Several respondents felt that their hepatitis status hindered their marriage prospects and employment options. Many admitted that they hid their condition from others as a result.

Axis 3: Prevention of transmission

Vaccination against hepatitis B has had a marked impact on reducing the incidence of hepatitis B infection (Case study 4). However, gaps in the region remain. Japan only offers vaccination to infants born to hepatitis B-infected mothers, whereas in Taiwan this is one group in whom vaccination efforts have been less successful. In all countries, careful evaluation of the impact of vaccination and of the benefits of extending vaccination to high risk groups is needed.

Injecting drug use is now the predominant route of transmission for hepatitis C in north Asia [17] and this is a critical target group for prevention strategies. Co-infection of hepatitis B and hepatitis C and/or HIV is a key concern in people who inject drugs, as it is associated with more rapid progression to liver disease and death [18,19]. Targeted education and prevention measures, including vaccination, are needed to control transmission in other individuals at high risk of infection, including people who have tattoos and acupuncture, women of childbearing age, men who have sex with men, and prisoners. And continued education about the risks of transmission through sexual contact and the need for safe sex practices is needed for the general population.

Re-use of needles and syringes in medical practice is common practice in Asia and nosocomial spread of hepatitis C has been observed in outpatient clinics [20] as well as dialysis units [21–23]. Information about safe injection practices and the prevention of transmission should be essential components of professional education efforts.

Case Study 4: Taiwan: a vaccination success story

Taiwan launched one of the first universal vaccination programmes against hepatitis B in 1984 and the programme is heralded around the world as a true success story [24, 25]. Today, systematic vaccination is offered to all newborns, health workers and schoolchildren who missed the neonatal vaccination (catch-up vaccination). The impact of the programme on seroprevalence levels has been considerable (Fig. 3) and horizontal transmission amongst children decreased [26]. The HCC incidence among children has been significantly reduced, making the hepatitis B vaccine the first effective vaccine for the prevention of cancer [27]. The programme has also provided important insights into the natural history of hepatitis B, for example about the duration of conferred immunogenicity and the potential need for booster vaccinations [28].

Complacency must be avoided, however, as thousands of deaths due to viral hepatitis still occur every year in Taiwan. Prevalence rates have not decreased in adults [29] and the impact of vaccination is much lower in rural areas than in urban centres [28, 30]. Also, the success of vaccination cannot be taken for granted: diligent, continuous monitoring of the quality of available vaccines and of the outcomes of vaccination programmes is needed for the public health impact of the vaccination programme against hepatitis B virus to continue in Taiwan [31, 32].

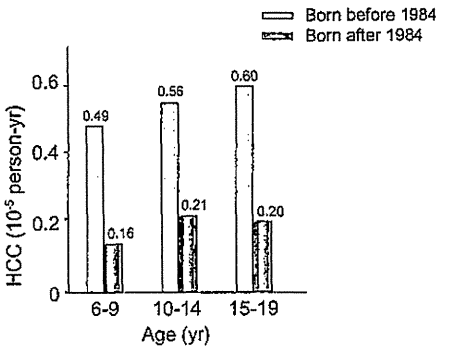

Fig. 3. Incidence of HCC by age in cohorts born before and after infant vaccination program against hepatitis B virus in Taiwan (started in 1984) [27].

Special Report

Axis 4: Screening, care, and treatment

Greater availability, awareness and uptake of screening for both hepatitis B and hepatitis C were highlighted as the most pressing needs by participants from all countries in the CEVHAP workshop. Countries differ in what screening programmes have been implemented and to what extent screening is covered by public funds. Barriers to screening are likely to be specific to each local context, not to mention each individual (Table 3). It is critical that the confidentiality of screening results is ensured; in many countries, the results of screening may be sent to a person's employer, causing discrimination and often loss of employment for the person concerned.

Another significant issue is the need to ensure greater linkage from screening to treatment, given a large proportion of individuals who test positive at screening are known not to seek treatment. Comprehensive care models are urgently needed to make sure that individuals who are infected receive appropriate information, counselling, and care throughout all phases of their condition [33]. In many countries, better collaboration between primary care physicians and liver specialists is needed to ensure that individuals who test positive are referred to appropriate care.

A commonly cited barrier to treatment was lack of public funding. Overall, government funding for antiviral therapies for both hepatitis B and hepatitis C has improved considerably over the past decade in all four jurisdictions (see Case study 5). However, out-of-pocket costs are often still high for many patients, be it for diagnosis, monitoring tests [21,34], or antiviral therapies. Funding of antiviral therapies in some countries is often limited to a given number of years, which may impact on compliance with long-term treatment regimens.

It is also important to recognise that lack of funding may sometimes be used as an excuse for not offering available treatments to patients. In truth, physicians are often unaware of existing treatment options, or they remain unconvinced of their benefit despite their inclusion in clinical guidelines and thus adopt a 'watch and wait' approach to treatment.

Case Study 5: The Importance of secure government funding for the treatment of viral hepatitis in Hong Kong

The Hong Kong government has funded antiviral therapy for hepatitis B and C since 2009, supported by annually renewable funding of approximately HKD 100 million. In 2010, an additional annually renewable HKD 76 million fund was set up for hepatitis B, with an estimated 3000 to 4000 extra patients receiving treatment. Funding for treatment is provided to hospitals as a prospective sum. Most of the funding has gone towards hepatitis B as the number of patients with hepatitis B infection is overwhelmingly greater than those with hepatitis C infection.

This secured funding has meant that patients with hepatitis B infection are offered guaranteed funding for their treatment without any limit as to its duration, which in Hong Kong practice, means nucleos(t)ide analogue treatment for life. Physicians claim this funding has transformed their relationship with their patients. Previously, patients would resist the prescription of long-term therapy for hepatitis B due to the financial burden it posed on them. Compliance was a significant problem. Since the changes in funding, the willingness to embark on life-long treatment has increased and compliance rates have improved significantly in patients with chronic hepatitis B infection in Hong Kong.

Experts believe that it was the demonstration of the cost-effectiveness of existing treatments that helped secure the funding, as well as the existence of two regular forums on hepatitis, the Scientific Working Group on Viral Hepatitis Prevention, and the Center for Health Protection, which offer an opportunity for governments to consult with leading liver specialists and for experts to present data to policy makers to help guide policy decisions.

Table 3. Barriers to screening linked to individuals, providers and the healthcare system.

Source of barrier	Barriers
Individuals	Unaware that one is at risk of viral hepatitis Unaware that the disease can have serious long-term effects Unaware that effective treatments exist Cultural beliefs Stigma associated with viral hepatitis Costs associated with testing [lack of funding]
Health care providers	Social stigma Poor understanding of the availability and effectiveness of treatment Lack of disease management approach - 'wait and see' attitude to viral hepatitis Cost barriers to access treatment Lack of awareness about the need for monitoring [hepatitis B]
Healthcare system	Lack of continuity/no linkage from screening to care Cost of therapy/lack of government reimbursement

Adapted from [38].

Discussion

Medical science and public policy have reached a critical, and exciting, juncture for viral hepatitis: 179 countries worldwide have implemented vaccination programmes against hepatitis B. Up to 95% of cases of hepatitis B infection are now treatable and up to 60% of those of hepatitis C infection are curable [27,35,36]. Cirrhosis can be reversed [37] and treatment of liver cancer, once thought to be impossible, is now possible. Yet three-quarters of those infected with hepatitis B virus and 65% of those infected with hepatitis C virus do not know they are infected [3]. Screening uptake is low, as is uptake and adherence to treatment, with the result that outcomes for individuals infected with viral hepatitis remain suboptimal.

The CEVHAP North Asia Workshop on Viral Hepatitis highlighted the key challenges facing Hong Kong, Japan, Korea, and Taiwan in their fight against viral hepatitis. These challenges are similar to those in other regions [2,3]. The WHO Framework provides a blueprint for action, but the onus is on governments to reduce the burden posed by hepatitis locally, within the constraints and possibilities of their local epidemiology, resources, health care infrastructure, and advocacy base.

The research community has an important role to play in guiding policy development on viral hepatitis. Liver specialists, in partnership with voluntary sector organisations, may help ensure that key facts about viral hepatitis – for example, that hepatitis B is treatable and hepatitis C is curable – are communicated to the media, the public and policymakers in a way that is accessible and compelling. Social research and observational studies may help create a better understanding of the health seeking behaviours of people at risk of viral hepatitis and identify existing barriers to screening, diagnosis, and proper treatment.

The WHO Framework provides a unique opportunity to countries around the world to take stock of how they have addressed the challenges posed by viral hepatitis in the past and create comprehensive, cohesive policies that may have a lasting impact. This will require a collaborative effort from primary care physicians, specialists, governments, individuals at risk and people living with viral hepatitis. Working in partnership with other more high-profile disease areas, for example non-communicable diseases, may present opportunities to raise the profile of viral hepatitis. Indeed, lessons may be learned from other disease areas – such as breast cancer, cardiovascular disease and HIV/AIDS – which have raised awareness, secured funding and developed comprehensive policies that have changed the lives of people living with the condition. The WHO Framework provides the steer to do the same for the millions of people worldwide infected with viral hepatitis.

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Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Addendum

Participants of the Coalition to Eradicate Viral Hepatitis in Asia Pacific [CEVHAP] North Asia Workshop on Viral Hepatitis included: from Taiwan: Ding-Shinn Chen, Pei-Jer Chen, Sheng-Nan Lu, Pei-Ming Yang; from Hong Kong: Joseph Sung, Ching-Lung Lai, James Y.Y. Fung; from Korea: Si Hyun Bae, June Sung Lee, Hong Soo Kim, Sang-Hoon Ahn, Goo Hyeon Yoon; from Japan: Junko Tanaka, Takaji Wakita, Hideki Aizaki, Atsuko Yonezawa, Yukio Lino, Yoichi Abe; from the United States: John Ward, Lily Lou; from the UK: Charles Gore; from Malaysia: Rosmawati Mohamed; from Australia: Stephen Locarnini and Jack Wallace. The workshop was facilitated by Suzanne Wait (UK) and Jennifer Johnston (Australia).

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Hepatology Research

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Original Article

Estimating numbers of persons with persistent hepatitis B virus infection transmitted vertically and horizontally in the birth cohort during 1950–1985 in Japan

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Aim: We estimated numbers of persons, born between 1950 and 1985 in Japan, who were persistently infected with hepatitis B virus (HBV) through vertical and horizontal infections.

Methods: HBV carrier rates with vertical and horizontal infections were computed using sex- and age-specific prevalence rates of hepatitis B surface antigen (HBsAg) and hepatitis B e-antigen (HBeAg) by mathematical model. Probabilities of vertical HBV transmission in babies born to carrier mothers with and without HBeAg were presumed to be 90% and 10%, respectively.

Results: HBV carrier rates with vertical infection stayed contrast at approximately 0.3% in birth cohorts through 36 years (1950–1985), both in men and women. By a remarkable constant, HBV carrier rates with horizontal infection decreased steadily from 1.43% to 0.10% in men and from 0.95% to 0.03% in women. The estimated total number of HBV carriers born between 1950 and 1985 was 522 500 (355 488–693 606). Of them, the numbers of HBV carriers with vertical and horizontal infections were 197 574 (149 505–288 709) and 324 926 (205 983–404 896); they accounted for 37.81% and 62.19%, respectively, with a ratio of 1:1.64. The ratio between vertical and horizontal infections was 1:2.20 in men and 1:1.06 in women.

Conclusion: Vertical HBV infection had stayed constant until immunoprophylaxis of mother-to-baby transmission was implemented in 1986 in Japan. In contrast, horizontal HBV infection decreased over years. The decrease would be due to many factors, including improved socioeconomic environments, advanced medical maneuvers and equipment, and careful vaccination procedures.

Key words: hepatitis B e-antigen, hepatitis B virus carrier, horizontal infection, newborns, vertical infection

INTRODUCTION

THERE ARE AN estimated 350 million people infected persistently with hepatitis B virus (HBV) in the world.[1] Of them, the majority (75%) are living in Asia, and approximately 25% die of serious long-term complications of HBV infections, such as decompensated cirrhosis and hepatocellular carcinoma (HCC).[2]

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Persistent HBV infection is mainly established by vertical transmission from carrier mothers or horizontal transmission during their infancy. It is clinically and epidemiologically relevant to examine numbers of HBV carriers with vertical and horizontal transmissions, and the ratio between them, because different strategies are required to prevent each of them.

Hepatitis B e-antigen (HBeAg) in the serum of carrier mothers is a useful marker for a high possibility of vertical transmission. Persistent HBV infection is established in 90% of babies born to carrier mothers with HBeAg,[3–6] while only in 10% of babies born to those without HBeAg.[7] Thus, it is possible to estimate the number of vertical HBV infection in babies born to a given cohort of mothers in whom prevalence rates of hepatitis B surface antigen (HBsAg) and HBeAg are known.

Vertical HBV transmission can be prevented by passive and active immunoprophylaxis of babies born to carrier mothers with hepatitis B immunoglobulin and vaccine. Since 1986, the national immunoprophylaxis program was implemented in babies born to HBeAg positive carrier mothers in Japan. It is efficient in preventing mother-to-baby transmission, except in babies who have been infected with HBV *in utero*.[8]

In this study, numbers of vertical and horizontal HBV infection were estimated for men and women who were born during the 36 years between 1950 and 1985, before immunoprophylaxis was started in Japan.

METHODS

Study cohorts

FROM THE VITAL Statistics of Japan,[9] the following data were obtained for the Japanese born during 1950–1985: (i) the number of births by sex; (ii) the number of deliveries by-mothers in 5-year age groups; (iii) sex ratio of newborns; and (iv) the mortality rate. From the census in Japan, the number of subpopulation stratified by sex and age at 2005 was obtained.[10]

HBV markers in study cohorts

Hepatitis B surface antigen positive rates stratified by sex and birth year were obtained for the first-time blood donors during 1995–2000 in Japan,[11] and from the fact sheet on HBV by the National Institute of Infectious Diseases.[7] HBeAg positive rates among HBsAg positive women grouped by 10 years were reported by Sasaki *et al.*[12] The study design conformed to the 1975 Declaration of Helsinki.

Assumptions

We assumed that age-specific HBV carrier rates in mothers who were born before 1930 to be the same as those in the birth group from 1931 to 1935, which is the oldest birth group among studied subjects.[11] The possibility of HBV transmission to her baby was assumed to be 90% for a carrier mother with HBeAg, and 10% for a carrier mother without HBeAg.[7]

Estimation

Estimation of the numbers of HBV carriers with vertical infection in birth groups notched by 1 year from 1950 to 1985

1 The number of babies born to HBV carrier mothers in 1-year notched birth year j (j = 1950, 51, 52, . . . , 85:36 points) was estimated by the equation: $\Sigma_i (N_{ji} * S_{ji})$: numbers of births to mothers in the age group "i", N_{ji} (i = 1 for 15–19 years old [y.o.], i = 2 for 20–24 y.o., . . . , i = 7 for 45–49 y.o.) (Fig. 1) and HBV carrier rate in the corresponding age group of mothers, S_{ji} (i = 1 for birth in [j − 19] − [j − 15], i = 2 for birth in [j − 24] − [j − 20], . . . , i = 7 for birth in [j − 49] − [j − 45]).

2 The numbers of babies whose mothers were positive and negative for HBeAg were estimated using a group-specific HBeAg positive rate E_i (Fig. 1), and HBeAg negative rate, $1 - E_i$, by the respective equations: $\Sigma_i N_{ji} * S_{ji} * E_i$ and $\Sigma_i N_{ji} * S_{ji} * (1 - E_i)$.

3 The number of HBV carrier babies with vertical infection (CV_j) was estimated by the formula: $CV_j = 0.1 * \Sigma_i N_{ji} * S_{ji} * (1 - E_i) + 0.9 * \Sigma_i N_{ji} * S_{ji} * E_i$.

4 Using the sex ratio (G_j), the numbers of HBV carriers with vertical infection (CV^M_j) for men and (CV^F_j) for women were calculated in birth groups notched by 1 year, by the respective equations: $CV^M_j = G_j / (1 + G_j) * CV_j$ and $CV^F_j = 1 / (1 + G_j) * CV_j$.

5 Finally, rates of HBV carriers with vertical infection in men (BS^MV_j) and women (BS^FV_j), respectively, to total number of birth in men (N^M_j) and women (N^F_j) were estimated in birth groups notched by 1 year by respective equations: $(BS^MV_j) = CV^M_j / N^M_j$ and $(BS^FV_j) = CV^F_j / N^F_j$ with 95% confidence interval (CI).

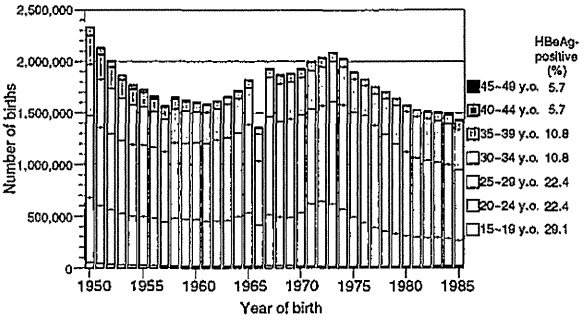

Figure 1 Number of births from mothers in 5-year age groups shifting during 1950–1985. Each component in bar graphs indicates number of live births stratified by the age of mother (15–19, 20–24, . . . , 45–49 years old). Age-specific hepatitis B e-antigen positive rates among hepatitis B virus carrier women are shown on the right.

Estimation of the number of HBV carriers with horizontal infection in birth groups notched by 1 year from 1950 to 1985

At first, number of HBV carriers was calculated by multiplying the number of births (N^M_j and N^F_j) by the HBV carrier rate in men and women in 1-year notched birth year j (33 points; 1950–1982), which were calculated by the 5-year moving average method, and that in birth year j (3 points; 1983–1985) was assumed as the same as that in the birth year cohort of 1982. The number of HBV carriers with horizontal infection (CH^M_j and CH^F_j) was calculated by subtracting the estimated number of HBV carriers with vertical infection (CV^M_j and CV^F_j) from the estimated total number of HBV carriers.

Estimation of the number of HBV carriers taking into account the mortality rate at 2005

Multiplying the numbers of HBV carriers in 1-year notched birth groups by the corresponding sex- and age-specific survival rates at 2005, the numbers of HBV carriers presumed to be alive at 2005 were obtained. They were summed to estimate the total numbers of HBV carriers.

Statistical analysis

We constructed 95% CI for the rate of HBV carriers with vertical infection using 95% CI for production of two positive rates (see Appendix for details). The χ^2-test was used for comparison of HBV carrier rates with vertical and horizontal infections. A *P*-value less than 0.05 was considered to indicate statistical significance.

RESULTS

HBV carrier rates and proportions of vertical and horizontal transmissions during 1950–1985

FIGURE 2 ILLUSTRATES HBV carrier rates in men and women born between 1950 and 1985 in Japan. HBV carrier rates decreased gradually both in men and women during these years, from 1.75% to 0.30% and from 1.27% to 0.23%, respectively.

Contribution of vertical or horizontal infection to carrier rates was estimated by a mathematical model described in Methods. The rate of HBV carriers with vertical infection stayed constant at approximately 0.3% in birth cohorts between 1950 and 1980, and decreased to 0.20% in the birth cohort of 1985. By a remarkable contrast, the rate of HBV carriers with horizontal infection decreased gradually between 1950 and 1985 both in men and women, from 1.43% to 0.10% and from 0.95% to 0.03%, respectively. The extent of decrease, in the rate of HBV carriers with horizontal infection, was higher for men than women (1.33% vs 0.92%, $P < 0.001$). The difference in HBV carrier rate with horizontal infection between men and women was statistically significant in groups born before 1972 ($P < 0.05$).

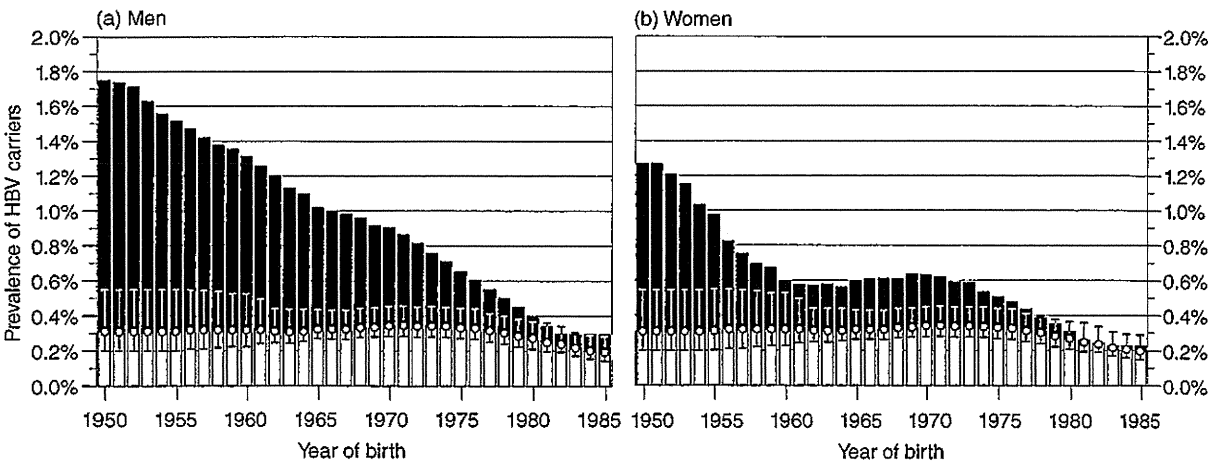

Figure 2 Hepatitis B virus (HBV) carrier rates and proportions of vertical and horizontal transmissions in yearly birth groups during 1950–1985. HBV carrier rates of vertical and horizontal transmissions are shown. Bars indicate the 95% confidence interval of vertical transmission rate. (a) Men, (b) women. ■, horizontal transmission; □, vertical transmission.

Estimation of the numbers of HBV carriers with vertical and horizontal infections in birth groups notched by 1 year between 1950 and 1985

Estimated numbers of HBV carriers with vertical and horizontal transmissions in 1-year notched birth cohorts during the 36 years between 1950 and 1985 are illustrated in Figure 3, both for men and women. The results are summarized in Table 1.

The estimated total number of HBV carriers born between 1950 and 1985 was 522 500. Of them, the estimated number of HBV carriers with vertical infection was 197 574, and those with horizontal infection was

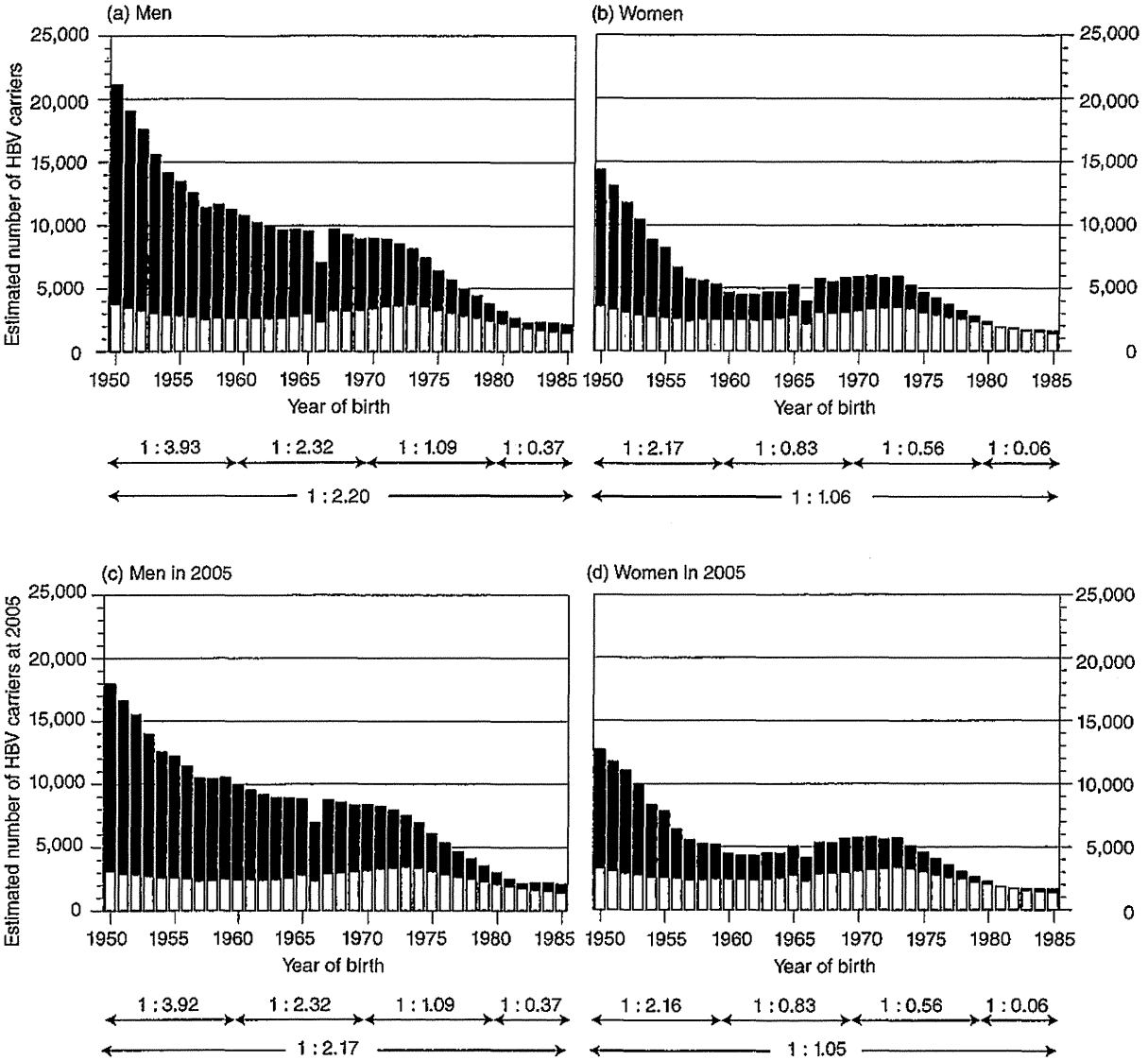

Figure 3 Estimated numbers of hepatitis B virus (HBV) carriers with vertical or horizontal transmission who were born during the 36 years between 1950 and 1985 and alive in 2005 in yearly birth groups. The ratio of the number of HBV carriers between vertical and horizontal transmissions are shown below for indicated time periods. (a) Men, (b) women, (c) men in 2005, (d) women in 2005. ■, horizontal transmission; □, vertical transmission.

Table 1 Estimated numbers of hepatitis B virus carriers with vertical or horizontal transmission who were born during the 36 years between 1950 and 1985 and alive in 2005

	Estimated number of HBV carriers (95% confidence interval)		
	Total	With vertical transmission	With horizontal transmission
Whole			
Total	522 500 (355 488–693 606)	197 574 (149 505–288 709)	324 926 (205 983–404 896)
Men	324 945 (235 765–414 592)	101 673 (76 948–148 542)	223 273 (158 817–266 047)
Women	197 555 (119 723–279 014)	95 901 (72 557–140 167)	101 654 (47 166–138 847)
In 2005			
Total	486 038 (329 981–646 011)	185 871 (140 826–271 096)	300 168 (189 155–374 914)
Men	297 031 (215 484–379 016)	93 773 (71 094–136 631)	203 258 (144 390–242 385)
Women	189 007 (114 497–266 995)	92 098 (69 732–134 465)	96 909 (44 765–132 529)

324 926; they accounted for 37.81% and 62.19% of total carriers, respectively, with a ratio of 1:1.64. Of 324 945 HBV carrier men, 101 673 had vertical infection and 223 273 had horizontal infection, accounting for 31.29% and 68.71%, respectively, with a ratio of 1:2.20.

Likewise, of 197 555 HBV carrier women, 95 901 had vertical infection and 101 654 had horizontal infection; they accounted for 48.54% and 51.46%, respectively, with a ratio of 1:1.06.

Moreover, the ratio between the number of HBV carriers with vertical infection and those with horizontal infection increased remarkably in men from 1:3.93 in the birth cohort during 1950–1959 to 1:2.32 during 1960–1969 and to 1:1.09 during 1970–1979, and reached the highest at 1:0.37 during 1980–1985. Similarly, in women, the ratio between the number of HBV carriers with vertical infection and those with horizontal infection increased steadily with 1:2.17, 1:0.83, 1:0.56 and 1:0.06 in birth cohorts during 1950–1959, 1960–1969, 1970–1979 and 1980–1985, respectively. However, during 1950–1985, while the number of HBV carriers with vertical infection decreased slightly, the number of HBV carriers with horizontal infection declined remarkably, both for men and women.

In women, the number of horizontal transmissions increased slightly during 1963–1973. This was, however, not the case for men in whom horizontal transmission decreased steadily through the study period (1950–1985).

Estimation of the number of HBV carriers taking into account the mortality rate at 2005

The number of live HBV carriers of a given birth year was calculated, taking into account the corresponding mortality rate at 2005 for the birth groups of 1950–1985 (Fig. 3). The estimated number of HBV carriers born between 1950 and 1985 and alive in 2005 is 486 038, corresponding to 93.02% of the 522 500 carriers who were born during the 36 years. Of them, the estimated number of HBV carriers with vertical infection is 185 871 (38.24%) and those with horizontal infection is 300 168 (61.76%), with a ratio of 1:1.61 (Table 1). Of 297 031 HBV carrier men, 93 773 (31.57%) had vertical transmission, and 203 258 (68.43%) had horizontal infection, with a ratio of 1:2.17. Likewise, of 189 007 HBV carrier women, 92 098 (48.73%) had vertical infection, and 96 909 (51.27%) had horizontal infection, with a ratio of 1:1.05.

In addition, the ratio between the number of HBV carriers alive in 2005 with vertical infection and those with horizontal infection in men also increased considerably from 1:3.92 in the birth cohort during 1950–1959 to 1:2.32 in 1960–1969, then to 1:1.09 in 1970–1979 and peaked at 1:0.37 in 1980–1985. Likewise for women, in birth cohorts during 1950–1959, 1960–1969, 1970–1979 and 1980–1985, the ratio between the number of HBV carriers alive in 2005 with vertical infection and those with horizontal infection was 1:2.16, 1:0.83, 1:0.56 and 1:0.06, respectively, showing an increasing trend between 1950 and 1985. As a whole, through the 36-year period, the number of HBV carriers alive in 2005 with horizontal infection decreased to an extent higher than those with vertical infection.

Thus, 93.02% of HBV carriers born during 1950–1985 would be alive in 2005. In the total of 486 038 carriers living in 2005, there were 297 031 (61.11%) men and 189 007 (38.89%) women with a ratio of 1.57:1 (Table 1). Overall, horizontal transmission was approximately sesquialteral as frequent as vertical transmission among HBV carriers. Proportion of horizontal

transmission was higher in men than women who carried HBV (68.43% vs 51.27% [1.33:1], $P < 0.001$).

DISCUSSION

PERSISTENT HBV INFECTION in a given community had been maintained by two principal routes. One of them is the vertical infection from mothers who carry HBV to their babies, and the other is the horizontal infection, typically during an early childhood.[13–15] The contribution of vertical or horizontal transmission to establish HBV carrier state is subject to host and viral factors, and varies among different countries. In Asian countries where HBV is endemic, with the prevalence of HBsAg of 8% or higher,[16] the vertical infection had been the main route of transmission for establishing HBV carrier state.

In 1980, plasma-derived hepatitis B (HB) vaccine was produced and introduced to babies born to mothers infected with HBV. As the HB vaccine was very efficient in preventing vertical infection,[17] the World Health Organization recommended universal vaccination of all babies, regardless of the mother's infection with HBV. By the end of 2011, the HB vaccine was introduced to 179 (93%) of the 193 member states; 93 (52%) recommended the first dose within 24 h of birth to prevent vertical transmission of HBV.[18] Hence, the contribution of vertical transmission to establish persistent HBV infection, in comparison with that of horizontal transmission, has to be examined in persons born before the implementation of HB vaccine to prophylaxis of vertical transmission.

Japan is a country of low endemicity for HBV, with the prevalence of HBsAg of less than 2% at the same level as those in Australia and New Zealand, although they belong to Asia.[16] Because the vertical infection was regarded as the principal route for establishing persistent HBV carrier state, a national program for passive and active immunoprophylaxis of babies born to carrier mothers was launched in 1986.[8] Initially, only the babies born to carrier mothers with HBeAg were indicated to immunoprophylaxis, in view of a high efficacy (~90%) of transmitting persistent HBV infection to their babies.[3–7,19] Since 1995, the indication was expanded to include babies born to carrier mothers without HBeAg.

In this study, we estimated the contribution of vertical and horizontal transmissions to the HBV carrier state in Japan. To avoid the effect of immunoprophylaxis, persons born during the 36 years between 1950 and 1985, before the start of immunoprophylaxis in 1986, were examined. A mathematical model was devised to estimate the number of HBV carriers with vertical infection. It involved HBsAg positive rates stratified by sex and birth year examined in the first-time blood donors during 1995–2000 in Japan,[11] and retrieved from the fact sheet on HBV by the National Institute of Infectious Diseases.[7] HBeAg positive rates among HBsAg positive women in 10-year age groups were reported by Sasaki *et al.*[12] The efficacy of vertical infection was assumed to be 90% for carrier mothers with HBeAg and 10% for those without HBeAg.[7] Then, the number of HBV carriers with horizontal infection was obtained by subtracting the number of HBV carriers with vertical infection from the total number of HBV carriers.

There were remarkable differences between the contribution of vertical and horizontal infections to the HBV carrier rate in birth cohorts during 1950–1985 (Fig. 2). The rate of HBV carriers with vertical infection stayed constant at 0.3% through the 36 years. By contrast, the rate of carriers with horizontal infection kept decreasing through these years, from 1.43% to 0.10% in men, and from 0.95% to 0.03% in women.

Numbers of HBV carriers with vertical and horizontal infections were obtained for persons born during 1950–1985 (Table 1). However, they would not represent numbers of HBV carriers in recent years, because some of them would have been deceased. Hence, numbers of HBV carriers with vertical and horizontal infections were obtained for persons who would be alive in 2005, the year when sex- and age-specific prevalence rates of HBsAg were determined in the first-time blood donors.[20]

The estimated number of HBV carriers who were born between 1950 and 1985 and alive in 2005 is 486 038, corresponding to 93.02% of the 522 500 carriers who were born during the 36 years. Of them, the estimated number of HBV carriers with vertical infection is 185 871 and those with horizontal infection is 300 168, accounting for 38.24% and 61.76%, respectively, with a ratio of 1:1.61. Proportion of horizontal infection was greater for men than women who carried HBV (68.43% vs 51.27%, $P < 0.001$). The higher proportion of horizontal infection in men than women would be due to increased chances of body contacts during physical activities in boys than girls, resulting in the break of skin and contamination with HBsAg positive blood. In addition, immune responses to protect from persistent HBV infection might have been lower in boys than girls.

It is of a particular note that the HBV carrier rate had already decreased during 1950–1985 in Japan, before the immunoprophylaxis program was started in 1986. The decrease was due to reduction of horizontal HBV infection (Fig. 2). The diminution of horizontal HBV

infection would be due to many factors, including improved socioeconomic environments, improved awareness of risks for infection, such as sharing a toothbrush and shaver, and advanced medical maneuvers and equipment, as well as careful vaccination procedures. Disposable needles and syringes, introduced in the early 1960s and universally distributed in the late 1970s in Japan, would have given the highest impact on decreasing horizontal transmission to establish the HBV carrier state.

It may be worth mentioning that, in women, the number of horizontal transmission increased slightly during 1963–1973 (Fig. 3). This was, however, not the case for men in whom horizontal transmission decreased steadily through the study period (1950–1985). It is not certain why horizontal infection of HBV increased preferentially in women during 1963–1973. However, vertical infection increased in women also during this period. Therefore, when the ratio of vertical to horizontal transmission was compared during four timespans of approximately 10 years in the entire study period (Fig. 3), the ratio kept increasing throughout 1950–1985 in women (from 1:2.16 to 1:0.06), as in men (1:3.92 to 1:0.37).

It has to be pointed out that this study has limitations. The HBV carrier rate of pregnant mothers may have been underestimated, because HBsAg positive rates in the first-time blood donors surveyed during 1995–2000 were used to estimate it.[11] Hence, the number of HBV carriers with vertical infection might have been underestimated. Moreover, the loss of HBsAg in the natural course, which is reported in recent years,[21] might have influenced the estimation in this study toward underestimation of HBV carriers.[22,23] However, such a large-scale survey in the 1990s with the standardized HBsAg screening level throughout the entirety of Japan had not existed except in the first-time blood donors, the database used for this mathematical model. In addition in the 1990s, the questionnaires to donors before their donation had not been strict enough to exclude the high-risk group of HBV and HCV infections than in the 2000s. Therefore, it may be worthwhile to estimate the proportion of the number of HBV carriers with vertical and horizontal infections in the first-time blood donors nowadays.

These constraints notwithstanding, contribution of horizontal infection to establish HBV carrier state, in comparison with that of vertical infection, decreased remarkably over years in Japan, even before the immunoprophylaxis of babies born to HBV carrier mothers was implemented in 1986. Furthermore, the prevalence of HBsAg in children decreased sharply from 0.75% (78/10 437) in the children born during 1978–1980 to 0.04% (12/32 049) in those during 1986–1990.[24] It is to be hoped that yearly trends of horizontal and vertical transmissions to establish HBV carrier states during the post-World War II era, described herein, may help in decision-making in Japan, whether to keep resorting solely to selective vaccination, or step toward mass vaccination of babies and/or teenagers. Increasing horizontal transmission for the persistent HBV carrier state transmitted by sexual contacts, typically with a foreign subgenotype A2,[25–29] must be taken into considerations in making such decisions. For this purpose, it is imperative to estimate the number of horizontal infection with genotype A, which is expected to have accumulated rapidly, by extensive epidemiological surveys in Japan.

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APPENDIX

WE CONSTRUCTED 95% confidence intervals (CI) for the rate of hepatitis B virus (HBV) carriers with vertical infection using 95% CI for production of two positive rates. In the Appendix, we show the conduction of 95% CI for production of two positive rates. Let n_1 and n_2 be numbers of two independent groups, x_1 and x_2 be numbers of positive in each group, and $p_1 = x_1 / n_1$, $p_2 = x_2 / n_2$ be positive rates in each group. Then, the 95% CI of $\log p_1$ and $\log p_2$ are asymptotically normal distributed with asymptotic variance $(1-p_1)/n_1p_1$ and $(1-p_2)/n_2p_2$. Thus, 95% CI for product of two positive rates is given by $p_1p_2 \exp\left(\pm 1.96\sqrt{(1-p_1)/n_1p_1 + (1-p_2)/n_2p_2}\right)$.

ウイルス肝炎と肝癌の撲滅を目指した実地診療のすすめかた

C型肝炎はどのように日本で蔓延し肝癌をもたらしたのか—肝癌抑制の実地診療のすすめかた—

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はじめに

ウイルス性肝炎の病因ウイルスの一つであるC型肝炎ウイルス(HCV)は1989年になってHCV遺伝子の一部がクローニングされた，肝炎ウイルスの中では新しいウイルスである．その後，世界中で急速にその測定系の開発と普及が推進された．

World Health Organization(WHO)は，HCV関連抗体検査が輸血用血液のスクリーニングとして広く導入されはじめる1992年以前には，世界中の輸血後肝炎の主な原因はHCVであり，特にアメリカにおける輸血後肝炎の90%はHCVによるものであったことを報告[1]している．1990年代に入ると，肝炎ウイルスの検査や調査などが広く行われ，徐々に社会におけるC型肝炎ウイルスの感染状況が明らかとなってきた．

C型肝炎ウイルスは，HCVに感染しているヒトの血液に感受性のある個体が曝露することにより感染が起こる．HCVに感染すると，約30%は一過性の感染で治癒するが，約70%が持続感染状態(キャリア化)になるといわれている．したがって，特定の集団の中で，感染リスクの高い行為が繰り返されるとその集団におけるHCVキャリアの累積が起こり，HCVキャリア率がきわめて高くなる可能性があると考えられる．

世界全体ではHCVキャリア率は平均約2%，毎年300～400万人が新規にHCVに感染し，HCVに持続感染している人は約1.5億人と試算[2]され，年間35万人以上がHCV関連の疾患で死亡していると推定されている．

本稿では，わが国におけるC型肝炎ウイルスによる感染状況を示すとともに，輸血後肝炎発生率，HCV新規感染率，HCVキャリア数の状況，対策について述べてみたい．

肝癌死亡とその成因—日本と世界の状況—

わが国における死因は，1981年以降ほぼ30年にわたり悪性新生物が第1位を占めている．最新(2011年)の人口動態統計資料によると総死亡数1,253,066人のうち，1位：悪性新生物357,305人(28.5%)，2位：心疾患194,926人(15.6%)，3位：肺炎124,749人(10.0%)，4位脳血管疾患123,867人(9.9%)となり，脳血管疾患と肺炎の順位が入れ替わった．

悪性新生物による死亡を部位別にみると，「肝」(肝および肝内胆管)の悪性新生物による死亡は，前年に比べやや減少し3.2万人(男性20,972人，女性10,903人)であったが，依然として部位別にみた同死亡数の上位から4番目(肺7.0万人，胃5.0万人，大腸4.5万人)に位置している．

わが国の肝癌による死亡の年次推移を図1に示す．1950年代はじめから1970年代半ばまでは人口10万人あたり10人前後(死亡実数は1万人以下)であった死亡数は，その後増加し，2002年に人口10万対27.5のピークを示した後，

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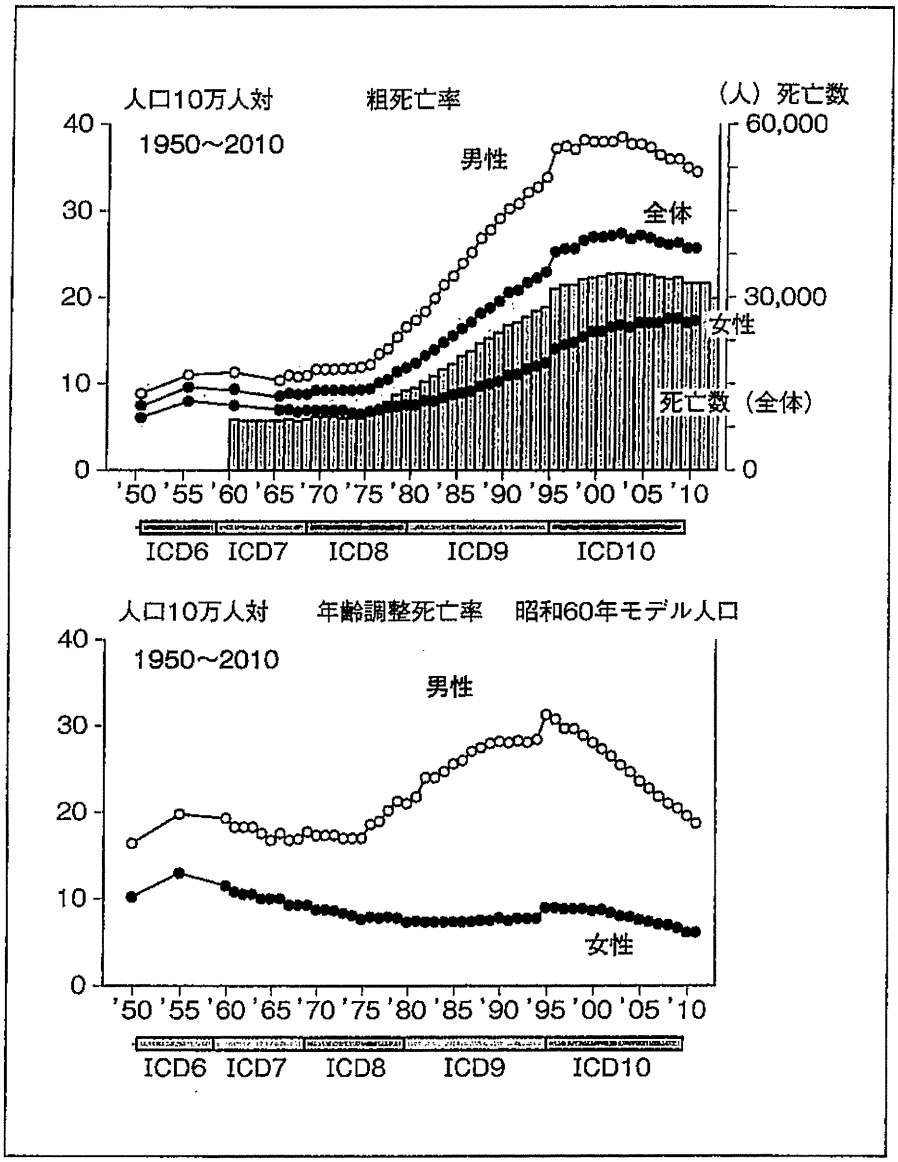
■ 1992年以前には，世界中の輸血後肝炎の主な原因はHCVであり，特にアメリカにおける輸血後肝炎の90%はHCVによるものであった．

■ 世界全体ではHCVキャリア率は平均約2%，毎年300～400万人が新規にHCVに感染し，HCVに持続感染している人は約1.5億人．

■ わが国の肝癌による死亡数：男性の肝癌死亡は女性の約2倍の高値を示すが，2002年以後，男性では減少傾向が，女性では依然として微増状態．

■ 肝癌死亡の年齢調整死亡率は，男女とも減少傾向．

図1　わが国における肝癌による死亡の推移



若干の減少あるいは横ばい状態を保っている．男性の肝癌死亡は女性の約2倍の高値を示すが，2002年以後，男性では減少傾向が，女性では依然として微増状態にある．一方，1985年モデル人口を基準集団とした年齢調整死亡率の年次推移をみると，1995年にICD10への移行に伴う段差増があるものの，男女とも減少傾向が認められる．他の癌と同様に治療の進歩に伴う延命効果や肝癌リスク集団の減少などが考えられる．

なお，国立がん研究センターの資料(がん対策情報センター癌情報サービス)によると，

■ B型肝炎ウイルス(HBV)の持続感染に起因する肝癌の死亡割合は1980年代から現在に至るまで10万人対3～4人と増減なくほぼ一定の値を示している.

■ 現在でも肝癌死亡の約7割がHCVの持続感染に起因している.

■ 1998年以降,非B非C型に由来する肝癌による死亡の割合が肝癌の10～15%を占める.

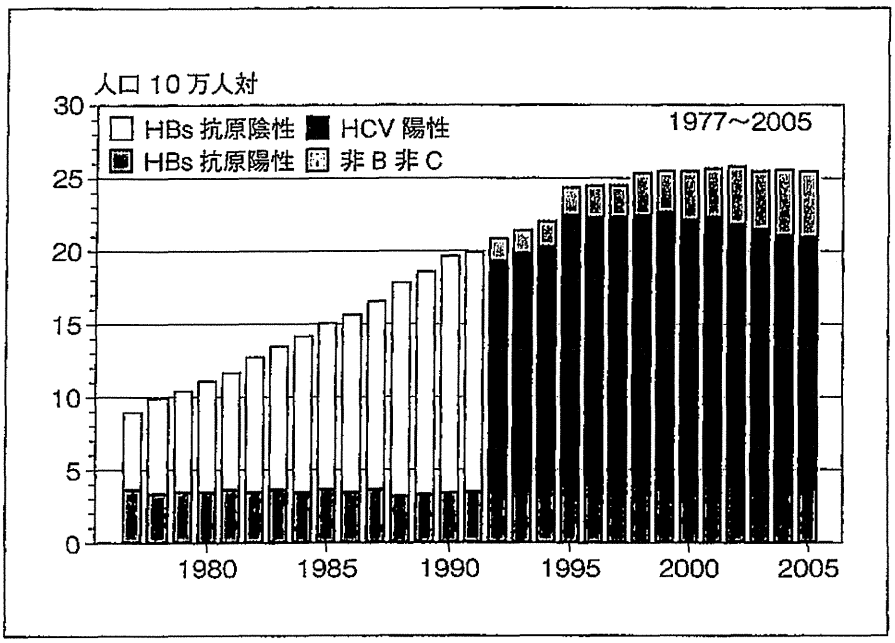


図2 成因別にみた肝細胞癌死亡の推移—推計値—
(厚生労働省大臣官房統計情報部:人口動態統計全国原発性肝癌追跡調査報告より推計)

2005年の肝癌罹患者数は男性では28,729人,女性では13,465人,計約4.2万人と,肝癌実死亡数よりもやや多い値を示している.男性は女性の2倍多い肝癌罹患(発生)がみられ,この傾向は世界においても同様である[3].

次に,病因ウイルス別にみた肝癌死亡の推移について,2年に一度の大規模調査を行ってきた日本肝癌研究会の調査成績(1982～2009)と人口動態統計資料を用いて推定したものを示す(図2).

B型肝炎ウイルス(HBV)の持続感染に起因する肝癌の死亡割合は1980年代から現在に至るまで10万人対3～4人と増減なくほぼ一定の値を示している.一方,1970年代から2000年代にかけて肝癌による死亡が増加した原因は非A非B型によるものと考えられるが,HCV感染の診断が可能となった1992年以降,そのほとんどがHCVの持続感染によるものであることがみてとれる.すなわち,現在でも肝癌死亡の約7割がHCVの持続感染に起因していることがわかる.また,1998年以降,非B非C型に由来する肝癌による死亡の割合が肝癌の10～15%を占め徐々に増加傾向にあり,その原因についてはnon-alcoholic steatohepatitis(NASH)との関連も示唆されている[4,5].

肝癌死亡の地理的分布

肝癌(肝および肝内胆管の悪性新生物)による死亡の地理的分布状況および経年推移の把握を目的として,厚生労働省疫学研究班では,指定統計調査票の使用の承認を得て,肝癌標準化死亡比Standard Mortality Ratio(SMR, Bayes推

■ 2001～2005年では，西日本地域を中心に標準化死亡比の高い地域が認められており，特に中国・四国・九州地域の肝癌死亡が高い傾向がある．

■ わが国では地域と時期により異なった肝癌死亡の変遷が観察される．

■ 1975年代以後，肝癌死亡の増加がみられたのはHCVの持続感染に起因する肝癌が増加したことが原因であると推測できる．

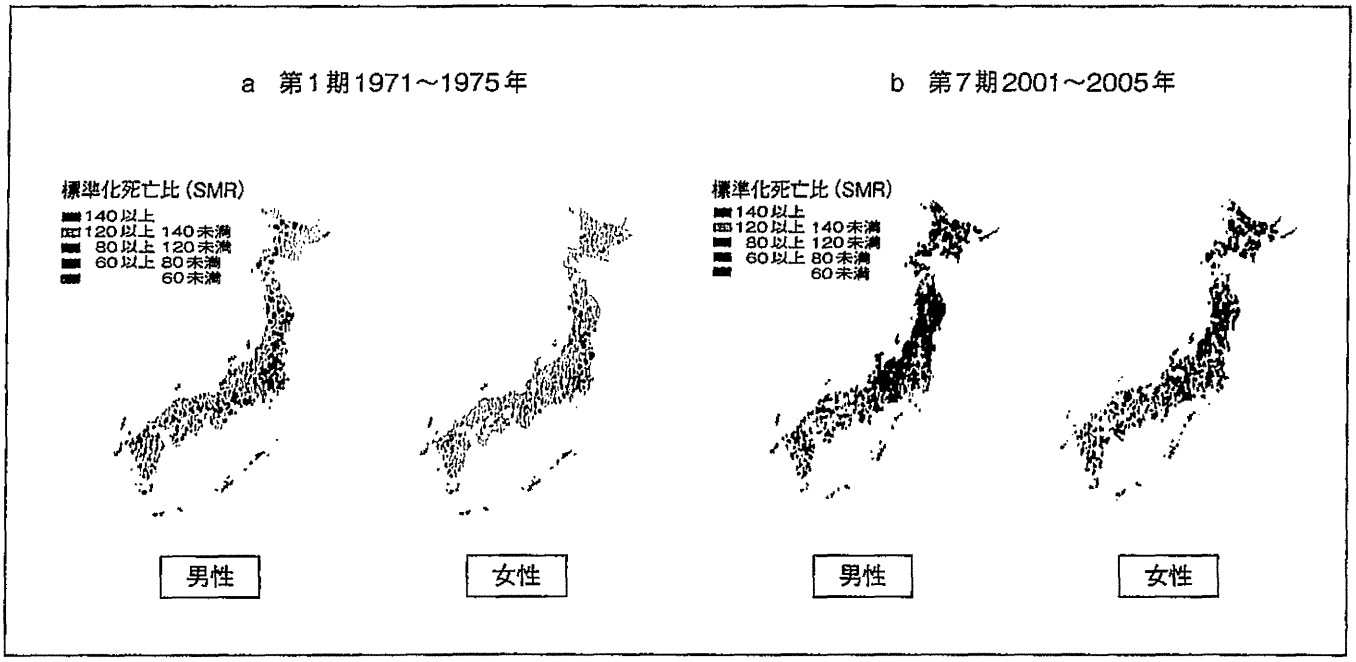


図3 市町村別にみた肝癌年齢調整死亡比（Bayesian method）の経年推移

定量による）を1971年から2005年までの7期別に算出している．図3に，第1期1971～1975年，第7期2001～2005年について男女別に示す．

肝癌標準化死亡比は全国平均を100として市町村別にその高低を示しているが，1971～1975年（第1期）では肝癌死亡の顕著な地域差は認められない．この時期は，図1および図2を参考にすると，肝癌死亡は人口10万人あたり10程度と低く，その成因はHBVの持続感染に起因するものが約4割と多くを占めていることがわかる．一方，2001～2005年（第7期）では，西日本地域を中心に標準化死亡比の高い地域が認められており，特に中国・四国・九州地域の肝癌死亡が高い傾向がある．この時期の肝癌死亡は人口10万人あたり27程度と高く，HBVの持続感染に起因するものが約1.5割すなわちHCVの持続感染に起因するものが約7割と多いことがわかる．

このようにわが国では地域と時期により異なった肝癌死亡の変遷が観察され，1975年代以後，肝癌死亡の増加がみられたのはHCVの持続感染に起因する肝癌が増加したことが原因であると推測することができる．

一般集団におけるC型肝炎ウイルス感染状況

一般集団におけるC型肝炎ウイルスの感染状況を把握するため，2000年以後に得られた二

■ 40歳以下の年齢集団のHCVキャリア率は初回供血者集団を元に，40歳以上の年齢集団のHCVキャリア率は節目検診受診者集団の資料を元に算出.

■ HCVキャリア率は，8地域ともに高年齢層において高い値を示す.

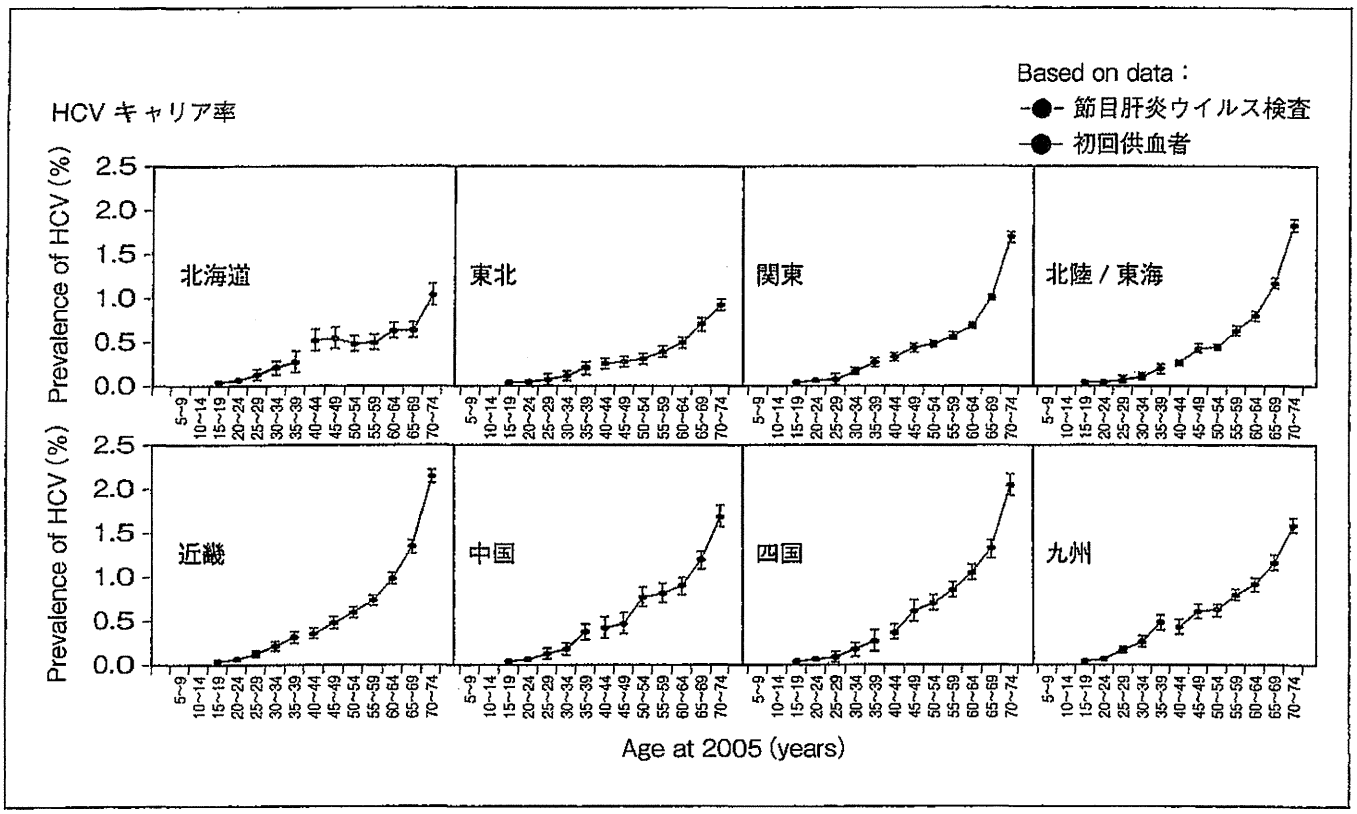


図4　8地域別年齢階級別にみたHCVキャリア率
(文献6)より引用)

つの大規模集団の特性を考慮して算出・推計した8地域別5歳刻みの年齢階級別にみた肝炎ウイルスキャリア率(HCVキャリア率)を示す[6](図4).

二つの大規模集団とは，日本赤十字血液センターにおける2001年から2006年の6年間の初回供血者3,748,422人，もう一つは，2002年から5ヵ年計画で実施された肝炎ウイルス検診の節目検診受診者のうち，HCV検診受診者6,304,276人である.

日本赤十字血液センターの献血時のスクリーニング検査は，輸血用血液の安全性確保のために行われるものであり，全国一律の基準，同一の試薬を用いて精度を維持し判定されている.また，節目・節目外検診は，老人保健法の住民検診に組み込まれた形で，公的補助により肝炎ウイルス検査(C型肝炎ウイルス検査，B型肝炎ウイルス検査)が行われたものであり，全国統一の検査手順に従って判定されたものである．図4に示した40歳以下の年齢集団のHCVキャリア率は初回供血者集団の資料を元に，また，40歳以上の年齢集団のHCVキャリア率は，