the APC model, and proposed the relation to cigarette smoking. Likewise, Ito *et al.*[4] applied the model to incidence rates and mortality of some cancers in Osaka, Japan, and discussed the factor characteristics of each cancer. Lee *et al.*[5] analyzed mortality data of hepatocellular carcinoma (HCC) in Taiwan using the APC model.

From the etiological point of view, however, persistent infections with hepatitis B virus (HBV) or hepatitis C virus (HCV) are the primary cause of HCC in Japan.[6,7] HCC is principally caused by persistent infections with HBV and HCV that were responsible for 16% and 80% of the cases in 1995,[6] 13% and 81% in 2000,[8] and 15% and 68% in 2005 of the cases, respectively.

Because HCC accounts for the great majority (94%) of liver cancer in Japan,[9] they were deemed equivalent and will be collectively referred to as HCC in this study.

Since HCV was cloned in 1989,[10] anti-HCV screening was introduced to blood donors for the first time in the world in Japan.[11] The opportunity to undergo HCV testing has increased swiftly in hospitals and clinics, as well as in health check-ups. We analyzed the utility of the APC model, as well as the limitation, in simulating yearly deaths due to HCC in Japan. We went on to assess how countermeasures against hepatitis and HCC implemented since 1990, such as hepatitis virus screening and antiviral treatments, influenced the HCC mortality predicted by the APC model.

METHODS

Data sources

SEX- AND AGE-SPECIFIC mortality data of HCC were obtained from Vital Statistics of Japan[1] for 15 time points in 5-year increments from 1940 through 2010 (e.g. 1940, 1945, 1950). During the study period, the International Classification of Diseases (ICD) changed six times, and therefore we needed to employ the time-dependent codes listed in Table 1. Vital Statistics of Japan in 1944 and 1945 are not published, so we used Vital Statistics of Japan in 1943 to represent number of deaths and population in 1945. No ethical problem occurred in this study, because only census data were used as the data source.

Table 1 Target cause of death due to liver cancer

Year	ICD	Code
1940, 1945	ICD4	46 (二)
1950, 1955	ICD6	155, 156
1960, 1965	ICD7	155, 156
1970, 1975	ICD8	155, 197.8
1980, 1985, 1990	ICD9	155
1995, 2000, 2005, 2010	ICD10	C22

ICD, International Classification of Diseases.

Data analysis

All mortality data were tabulated into 13 5-year age groups (from 20–24 to 80–84 years) in each of 15 5-year time periods (from 1940 to 2010).

First, we estimated the sex-specific effects of age factor, time period factor and birth cohort factor on HCC mortality using the APC model:

$$y_{ij} \sim \text{Poisson}(\mu_{ij}),\ \log(\mu_{ij}) = \log(P_{ij}) + \mu + A_i + P_j + C_k,$$

where μ, A_i, P_j and C_k denote intercept, factor of i-th age group ($i = 1, 2, \ldots, 13$), factor of j-th time period ($j = 1, 2, \ldots, 15$) and factor of k-th birth cohort ($k = 1, 2, \ldots, 27$), respectively. μ_{ij}, y_{ij} and P_{ij} denote expected number of deaths, real number of deaths and population in i-th age group, and j-th time period, respectively. The APC model has methodical drawbacks, such as the "identification problem" (see Appendix I for details). We assumed that two effects of the birth cohort factor, C_9 (1896–1900) and C_{10} (1901–1905), would be the same with respect to the influence of this problem by Barrett's technique.[12] We set the baseline of each factor as 20–24 years old (age factor), year 1940 for time period (period factor) and 1896–1900 and 1901–1905 for birth year cohorts (birth cohort factor), respectively, in the calculation of 95% confidence interval (95% CI).

We estimated effects and their 95% CI of age factor, period factor and birth cohort factor by the maximum likelihood method, and estimated the mortality by the APC model using estimated effects for evaluating the validity of the model. The expanded determination coefficient R^2_{COR}[13] was used for comparison between observed and estimated mortality rates (see Appendix II for details).

Second, we estimated the effects of age, period and birth cohort factors by using data confined to 1940–1990 in the same manner, and estimated number of deaths due to HCC in 1995, 2000, 2005 and 2010 on the basis of these effects. We assumed that effects of the period factor after 1990 and those of the birth cohort factor after 1970 would have remained unchanged.

Statistical analyses were performed using JMP ver. 9 (SAS Institute, Cary, NC, USA).

RESULTS

Performance of APC model in simulating mortality due to HCC

THE 3-D PLOTS of sex- and age-specific mortality rates from 1940 through 2010 are depicted in Figure 1, for comparison of the observed mortality against that estimated by APC model in males (a vs b) and females (c vs d). Observed mortality rates are closely reproduced by predicted mortality rates in both sexes with very high expanded determination coefficients ($R^2_{COR} > 0.99$).

Risk of HCC deaths in relation to age, time period and birth cohort

The effects of age factor, time period factor and birth cohort factor on the APC model are displayed graphically in Figure 2. Age effect was based on the 20–24 year old group with 95% CI values. There was a trend for higher risk for HCC mortality with increasing ages. The effect of the period factor did not change enormously. With respect to 95% CI values based on the year 1940, there was no difference in the age-specific risk for HCC mortality. In late years, however, the risk of HCC deaths decreased gradually in males.

The birth cohort effect is exhibited based on 95% CI of the 1896–1905 birth year group. In males, it was high in birth cohorts born during 1916–1940, and culminated in the 1931–1935 birth year cohort. In females, the risk of HCC mortality was the highest in 1881–1935 birth year cohorts.

Discrepancy between HCC deaths predicted by APC from those observed since 1990

Numbers of HCC deaths were estimated by the APC model based on 1940–1990 data, and they are compared against observed numbers in Figure 3. In males, predicted numbers of deaths became higher than observed numbers since 2000. [Correction added on 11 October 2013, after first online publication: 'In males, predicted numbers of deaths became lower than observed numbers since 2000' has been corrected to '. . . higher than observed'.] Predicted HCC deaths in 2010 are 26 883.4, which correspond to 138.3% of the 19 444 observed. [Correction added on 11 October 2013, after first online publication: 'Predicted HCC deaths in 2010 are 26 883.4, which correspond to 72.3% of the 19 444 observed' has been corrected to '. . . correspond to 138.3% of the 19 444 observed'.] In females, by remarkable contrast, predicted numbers of

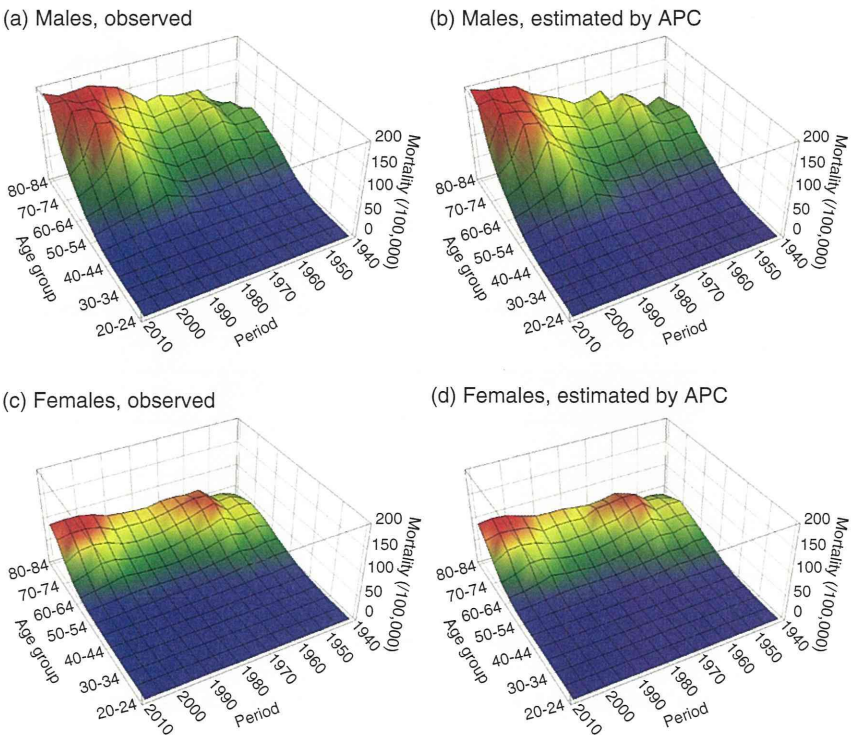

Figure 1 Trend in observed and estimated age-specific mortalities of hepatocellular carcinoma (HCC) in males and females. Observed and estimated (by the age–period–cohort [APC] model) mortalities (per 100 000 people) due to HCC during 1940 through 2010 are shown in the 3-D plot. (a) Observed mortality in males, (b) mortality estimated by the APC model in males, (c) observed mortality in females, (d) mortality estimated by the APC model in females.

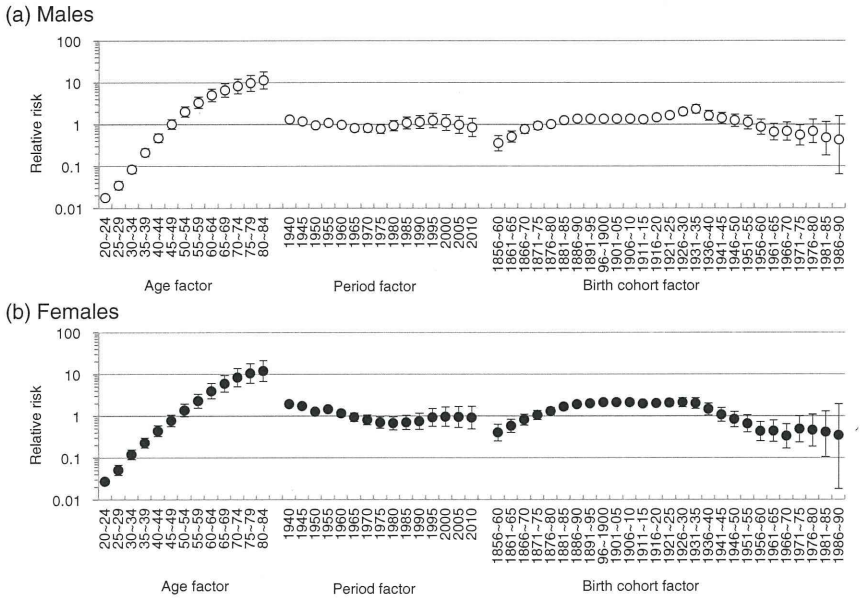

Figure 2 Effects of age, period and birth cohort factors on hepatocellular carcinoma (HCC) mortality in males and females predicted by the age–period–cohort (APC) model. The relative risk of age factor, period factor and birth cohort factor were estimated by the APC model in (a) males and (b) females. The baselines of age, period and cohort effects were 20–24 years old, the year 1940, and 1896–1900 as well as 1901–1905 birth year cohorts, respectively.

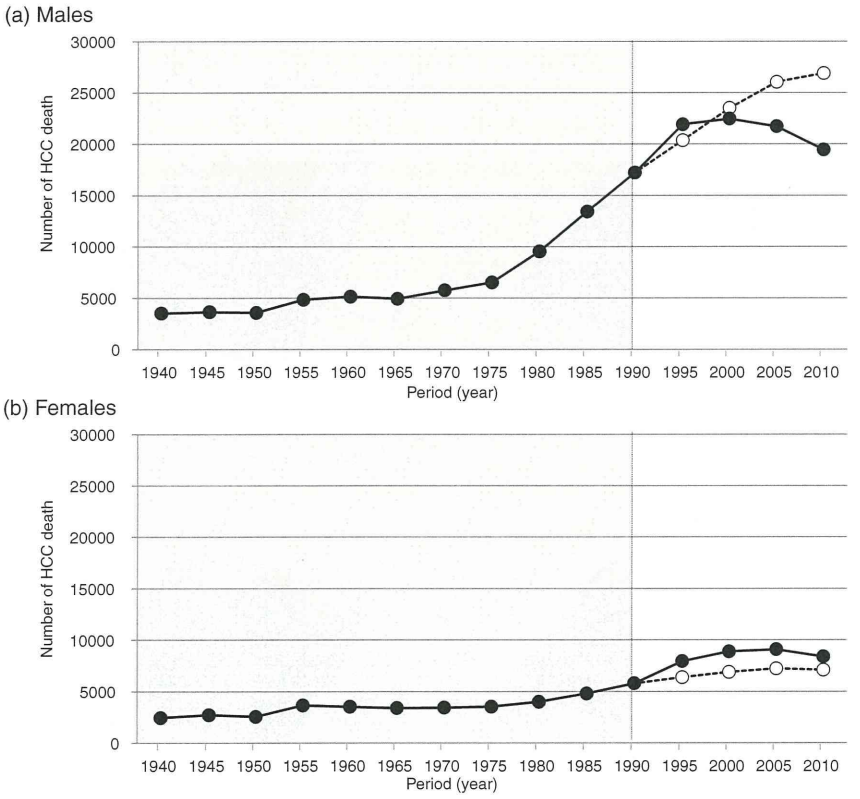

Figure 3 Comparison between observed and predicted numbers of deaths. Number of deaths during 1991 through 2010 were estimated based on mortality during 1940–1990 by the age–period–cohort (APC) model in (a) males and (b) females. ○, predicted; ●, observed.

death were a little lower than those observed. [Correction added on 11 October 2013, after first online publication: 'In females, by remarkable contrast, predicted numbers of death were a little higher than those observed' has been corrected to '. . . lower than observed'.] Thus, predicted HCC deaths in 2010 are 7093.1, corresponding to 84.7% of the 8374 observed. [Correction added on 11 October 2013, after first online publication: 'Thus, predicted HCC deaths in 2010 are 7093.1, corresponding to 118.1% of the 8374 observed' has been corrected to '. . . corresponding to 84.7% of the 8374 observed'.]

Predicted and observed numbers of sex- and age-specific HCC deaths in 2010, as well as differences between them, are given in Table 2. In males, observed HCC deaths were lower than those predicted through all age groups; observed HCC deaths accounted for 55.6–90.9% of those predicted. Likewise, in females aged 64 years or less, observed HCC deaths were lower than those predicted, and accounted for 21.1–99.4%. In females aged 65 years or more, on the contrary, observed HCC deaths were higher than those predicted, and corresponded to 115.1–132.7%.

Table 2 Comparison between predicted and observed number of deaths due to hepatocellular carcinoma in 2010

Sex and age	No. of deaths		
	Predicted	Observed	Ratio†
Male			
20–24	3.6	2	55.6%
25–29	7.5	5	66.7%
30–34	22.0	20	90.9%
35–39	64.5	40	62.0%
40–44	128.3	100	77.9%
45–49	261.4	229	87.6%
50–54	705.6	549	77.8%
55–59	1 984.4	1 258	63.4%
60–64	4 127.8	2 462	59.6%
65–69	4 266.0	2 993	70.2%
70–74	4 762.5	3 665	77.0%
75–79	6 677.7	4 752	71.2%
80–84	3 872.0	3 369	87.0%
Total	26 883.4	19 444	72.3%
Female			
20–24	2.9	1	34.5%
25–29	6.0	4	66.7%
30–34	17.8	6	33.7%
35–39	40.4	15	37.1%
40–44	71.1	15	21.1%
45–49	81.1	41	50.6%
50–54	153.8	80	52.0%
55–59	297.7	220	73.9%
60–64	599.3	596	99.4%
65–69	843.9	971	115.1%
70–74	1 312.3	1 606	122.4%
75–79	1 873.5	2 439	130.2%
80–84	1 793.4	2 380	132.7%
Total	7 093.1	8 374	118.1%

†Ratio = observed/predicted.

DISCUSSION

WE ANALYZED HCC mortality data by the APC model. Based on HCC deaths registered during 1940 through 2010 in Japan,[1] approximately 30 000 people died of HCC annually. According to hepatitis virus carrier rates among the first-time blood donors,[14] the peak frequency of hepatitis B surface antigen (HBsAg) was demonstrated by the 1941–1945 birth cohort, and the peak frequency of antibody to HCV by the 1931–1935 birth cohort. Hence, 1931–1935 birth years have the highest birth cohort effect in males with the APC model.

The national project for preventing mother-to-baby transmission of HBV was implemented in 1986 in Japan. As a result, the HBsAg positive rate among birth cohorts born after 1986 is extremely low at 0.04%.[15] In this study, birth cohorts born after 1986 were not subject to analysis and, therefore, we cannot evaluate the effect of the national immunoprophylaxis project by the APC model. However, we can reasonably expect that the birth cohort effect by the project will manifest itself in future analysis.

We applied the APC model to HCC mortality rate, and it reproduced the observed rate faithfully. However, in males, the observed mortality in 2010 is lower than the predicted mortality in 2010, which were calculated using data until 1990. This discrepancy would be a reflection of the introduction of new antiviral treatments and progress in surgical techniques since the 1990s, as well as the promotion of hepatitis virus screening and construction of clinical network between hospitals and clinics in each prefecture. On the contrary, in females, the observed number of HCC deaths in 2010 was a little higher than the predicted. The observed mortality of HCC would have increased because the female life expectancy was prolonged, and decompensated cirrhosis did not become the cause of death with progress of the treatment. In addition, it would reflect a lower response to interferon therapies

in women than men aged more than 50 years.[16] Furthermore, women may have fewer chances for receiving antiviral therapies than men. Also, we have demonstrated that the cumulative incidence of HCC increased with age of over 60 years in women, which is 10 years later than in men by the Markov model.[17] Another possibility is that effects of some factors, such as obesity, might have impacted especially women aged 65 years or more; they cannot be predicted by data before 1990 in Japan.

Comparison of HCC deaths predicted by the APC model with those observed demonstrates, for the first time, the impact of medical treatments for hepatitis and HCC in Japan and medical as well as control policies implemented by the Japanese government, including screening for HBV and HCV infections.[6,7] At the same time, the APC model is found to be limited in the application to predict HCC mortality in Japan since 2000.

The APC model examines mortality by three factors, and there are identification problems, such as "birth cohort = period – age". Thus, some methods have been invented to improve the application of the APC model to mortality data; effects of these methods are not in agreement, however. We employed the special structure in the birth cohort factor (Barrett's technique).[12] We accomplished a unique solution for each effect, but it may or may not be valid under another assumption.

Several limitations exist in this study. First, six time changes in the ICD codes might have influenced some effects, especially the period effect in the APC model. Second, we could not adjust confounding factors in applying the APC model, such as carrier rates of HBV and HCV infections; complete data on them are not available all through the studied period 1940–2010. Third, during this period, the difference of diagnostic ability might have influenced the analytic results obtained by the APC model. Finally, we must evaluate and discuss the results, keeping in mind the assumption of the birth cohort effect.

In conclusion, while the APC model is useful for reproducing observed HCC deaths, it would not be able to predict the mortality or incidence of the disease that can be influenced by medical intervention and prophylactic policies. In these regards, the present study does not only verify a high performance of the APC model in estimating HCC mortality, but also demonstrates the limitation of it in the application to disease that can be prevented by treatment or screening that keeps improving with time.

ACKNOWLEDGMENTS

THIS WORK WAS supported in part by grants for the Research on Hepatitis of the Ministry of Health, Labor and Welfare in Japan.

REFERENCES

1 Ministry of Health Labour and Welfare. *Vital Statistics of Japan*. Tokyo, Japan: Health, Labour and Welfare Association, 1940–2010.
2 Holford TR. The estimation of age, period and cohort effects for vital rates. *Boimetrics* 1983; **39**: 311–24.
3 Pham TM, Ozasa K, Kubo T *et al.* Age-period-cohort analysis of chronic obstructive pulmonary disease mortality in Japan, 1950–2004. *J Epidemiol* 2012; **22**: 302–7.
4 Ito Y, Ioka A, Nakayama T, Tsukuma H, Nakamura T. Comparison of trends in cancer incidence and mortality in Osaka, Japan, using an age-period-cohort model. *Asian Pac J Cancer Prev* 2011; **12**: 879–88.
5 Lee LT, Huang HY, Huang KC, Chen CY, Lee WC. Age-period-cohort analysis of hepatocellular carcinoma mortality in Taiwan, 1976–2005. *Ann Epidemiol* 2009; **19**: 323–8.
6 Yoshizawa H. Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. *Oncology* 2002; **62** (Suppl 1): 8–17.
7 Yoshizawa H, Tanaka J. A national project for the management of viral hepatitis toward prevention of hepatocellular carcinoma in Japan. In: Kowalski JB, Morrissey RF, eds. *International Kilmar Conference proceedings*. Laval: Polyscience Publications, 2004; 247–64.
8 Yoshizawa H, Tanaka J, Miyakawa Y. National prevention of hepatocellular carcinoma in Japan based on epidemiology of hepatitis C virus infection in the general population. *Intervirology* 2006; **49**: 7–17.
9 Kudo M, Arii S, Ikai I *et al.* 18th Report from Liver Cancer working group in Japan (2004~2005). *Kanzo* 2010; **51**: 460–84.
10 Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a Cdna clone derived from a blood-borne non-A, non-B viral-hepatitis genome. *Science* 1989; **244**: 359–62.
11 Watanabe J, Matsumoto C, Fujimura K *et al.* Predictive value of screening tests for persistent hepatitis C virus infection evidenced by viraemia. Japanese experience. *Vox Sang* 1993; **65**: 199–203.
12 Barrett JC. Age, time and cohort factors in mortality from cancer of the cervix. *J Hyg Camb* 1973; **71**: 253–9.
13 Cameron AC, Windmeijer FG. R-squared measures for count data regression models with applications to healthcare utilization. *J Bus Econ Stat* 1996; **14**: 209–20.
14 Tanaka J, Kumagai J, Katayama K *et al.* Sex- and age-specific carriers of hepatitis B and C viruses in Japan estimated by

the prevalence in the 3,485,648 first-time blood donors during 1995–2000. *Intervirology* 2004; **47**: 32–40.
15 Koyama T, Mito H, Tanakashi K, Tanaka J, Isa KM, Yoshizawa H. Perinatal hepatitis B virus infection in Japan. In: Mushawar IK, ed. *Congentital and Other Related Infectious Diseases of the Newborn*. Oxford: Elsevier Science & Technology Books, 2006; 141–51.
16 Sezaki H, Suzuki F, Kawamura Y *et al.* Poor response to pegylated interferon and ribavirin in older women infected with hepatitis C virus of genotype 1b in high viral loads. *Dig Dis Sci* 2009; **54**: 1317–24.
17 Tanaka J, Kumada H, Ikeda K *et al.* Natural histories of hepatitis C virus infection in men and women simulated by the Markov model. *J Med Virol* 2003; **70**: 378–86.
18 Nakamura T. A Bayesian cohort model for standard cohort table analysis. *Proc Inst Stat Math* 1982; **29**: 77–96.
19 Tango T. Estimation of age, period and cohort effects: decomposition into linear trend and curvature components. *Jpn J Appl Stat* 1985; **14**: 45–59. (In Japanese.)
20 Ohtaki M, Kim D-K, Munaka M. A nonparametric method for estimating interaction effect of age abd period on mortality. *Environ Health Perspect* 1990; **87**: 115–21.
21 Kamo K, Tonda T, Satoh K. Cancer mortality risk visualization on age-period plane. *Proc Inst Stat Math* 2011; **59**: 217–37.

APPENDIX I

Identification problem

THE AGE–PERIOD–COHORT (APC) model is constructed by three parts: (i) age factor; (ii) period factor; and (iii) birth cohort factor. However, three factors are not independent (birth cohort = period – age), so it has an "identification problem" in the methodology. For instance, let μ, A_i, P_j and C_k be one solution of the APC model, then

$$\mu^* = \mu,\ A_i^* = A_i - t(2i - I + 1)/2,\ P_j^* = P_j - t(2j - J + 1)/2,\ C_k^* = C_k - t(2k - K + 1)/2$$

is also the solution of the APC model for any number t. Thus, we cannot get a proper solution without some conditions.

There are several methods which overcome the identification problem. For example, Nakamura[18] proposed a Bayesian APC model, which assumes that the successive parameters should change gradually. Meanwhile, effects in each factor can have mathematically separate linear trend and curvature components. Based on this, Tango[19] suggested estimating only the calculable part that they designated "curvature components". On the other hand, Ohtaki *et al.*[20] or Kamo *et al.*[21] suggested an interaction model, which contains the age factor, period factor and interaction of the age and period factor, instead of the birth cohort factor.

APPENDIX II

Criteria of goodness of fit

USUALLY, DETERMINATION COEFFICIENT R^2 is used for simple and multivariate regression analysis because of assumption of variance. We used modified determination coefficient as below:[13]

$$R^2_{COR} = \frac{\left(\sum (r_{ij} - \bar{r})(\hat{r}_{ij} - \bar{\hat{r}})\right)^2}{\sum (r_{ij} - \bar{r})^2 \sum (\hat{r}_{ij} - \bar{\hat{r}})^2}$$

as criteria of goodness of fit, where r_{ij} means mortality, symbol "hat" means estimator and symbol "bar" means average. R^2_{COR} has a similar character with R^2 such as $0 \le R^2_{COR} \le 1$.

Hepatology Research

Hepatology Research 2014 doi: 10.1111/hepr.12288

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

Tomoki Sato,[1] Son Huy Do,[1] Takako Asao,[1] Tomoyuki Akita,[1] Keiko Katayama,[1] Kozo Tatara,[2] Yuzo Miyakawa[3] and Junko Tanaka[1]

[1]*Department of Epidemiology, Infectious Disease Control and Prevention, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima,* [2]*Japan Public Health Association, and* [3]*Miyakawa Memorial Research Foundation, Tokyo, Japan*

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]

Correspondence: Professor Junko Tanaka, Department of Epidemiology, Infectious Disease Control and Prevention, Institute of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan.
Email: jun-tanaka@hiroshima-u.ac.jp
Financial disclosure: None to declare.
Conflict of interest: None.
Received 11 October 2013; revision 15 November 2013; accepted 2 December 2013.

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).

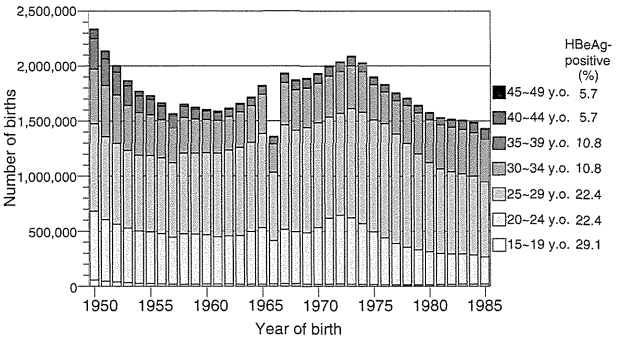

Figure 1 Number of births from mothers in 5-year age groups shifting during 1950–1985. Each component in bar graphs indicates number of live births stratified by the age of mother (15–19, 20–24, . . . , 45–49 years old). Age-specific hepatitis B e-antigen positive rates among hepatitis B virus carrier 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 ($P < 0.05$).

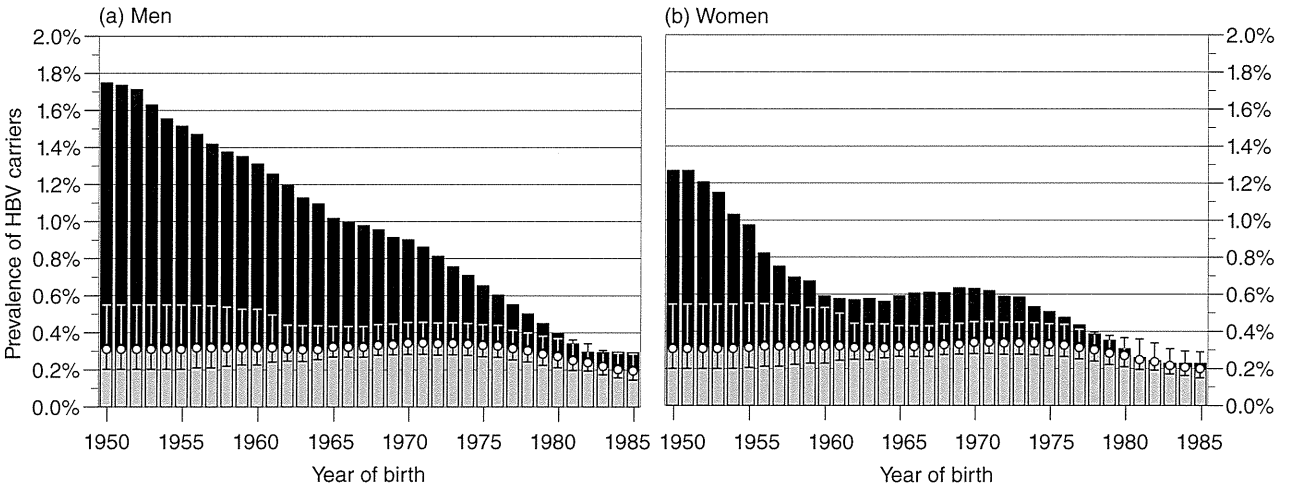

Figure 2 Hepatitis B virus (HBV) carrier rates and proportions of vertical and horizontal transmissions in yearly birth groups during 1950–1985. HBV carrier rates of vertical and horizontal transmissions are shown. Bars indicate the 95% confidence interval of vertical transmission rate. (a) Men, (b)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

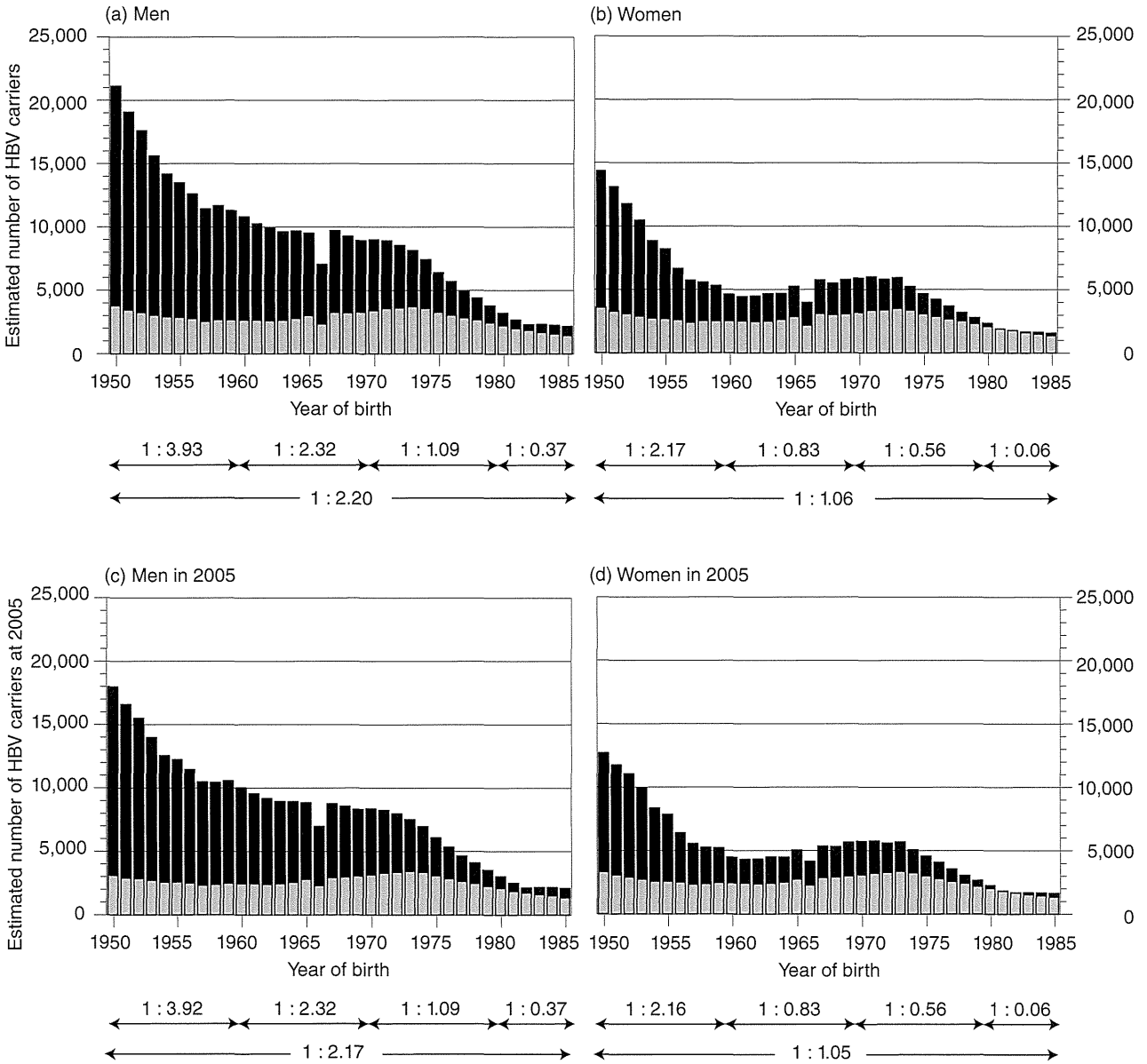

Figure 3 Estimated numbers of hepatitis B virus (HBV) carriers with vertical or horizontal transmission who were born during the 36 years between 1950 and 1985 and alive in 2005 in yearly birth groups. The ratio of the number of HBV carriers between vertical and horizontal transmissions are shown below 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.

ACKNOWLEDGMENT

THIS WORK WAS supported by a Grant-in-Aid from Ministry of Health, Labour and Welfare in Japan (Research on Hepatitis).

REFERENCES

1 World Health Organization. Viral hepatitis: report by the Secretariat. Sixty-Second World Health Assembly 2009. Available at: http://apps.who.int/gb/ebwha/pdf_files/A62/A62_22-en.pdf. Accessed October 6, 2013.
2 CDC. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Morb Mortal Wkly Rep* 2008; **57**: 1–20. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm. Accessed October 6, 2013.
3 Beasley RP, Trepo C, Stevens CE, Szmuness W. The e antigen and vertical transmission of hepatitis B surface antigen. *Am J Epidemiol* 1977; **105**: 94–8.
4 Shiraki K. Perinatal transmission of hepatitis B virus and its prevention. *J Gastroenterol Hepatol* 2000; **15** (Suppl): E11–5.
5 Okada K, Kamiyama I, Inomata M, Imai M, Miyakawa Y, Mayumi M. E antigen and anti-e in the serum of asymptomatic carrier mothers as indicators of positive and negative transmission of hepatitis B virus to their infants. *N Engl J Med* 1976; **294**: 746–9.
6 Shiraki K, Yoshihara N, Sakurai M, Eto T, Kawana T. Acute hepatitis B in infants born to carrier mother with the antibody to hepatitis B e antigen. *J Pediatr* 1980; **97**: 768–70.
7 National institute of infectious diseases. Factsheet on hepatitis B virus vaccination (in Japanese). 2010. Available at: http://www.mhlw.go.jp/stf/shingi/2r9852000000bx23-att/2r9852000000bxqf.pdf. Accessed October 6, 2013.

8 Eto T, Shiraki K. National project on the prevention of mother-to-infant infection by hepatitis B virus in Japan. *Acta Paediatr Jpn* 1989; **31:** 681–4.
9 Ministry of Health Labour and Welfare. *Vital Statistics of Japan*. Tokyo: Health, Labour and Welfare Statistics Association, 1950–85.
10 Statistics Bureau, Ministry of Internal Affairs and Communications. *2005 Population Census of Japan*. Tokyo: Statistics Bureau Ministry of Internal Affairs and Communications, 2007.
11 Tanaka J, Kumagai J, Katayama K *et al.* Sex- and age-specific carriers of hepatitis B and C viruses in Japan estimated by the prevalence in the 3,485,648 first-time blood donors during 1995–2000. *Intervirology* 2004; **47:** 32–40.
12 Sasaki T, Hattori T, Mayumi M. A large-scale survey on the prevalence of HBeAg and anti-HBe among asymptomatic carriers of HBV. Correlation with sex, age, HBsAg titre and s-GPT value. *Vox Sang* 1979; **37:** 216–21.
13 Chang MH. Chronic hepatitis virus infection in children. *J Gastroenterol Hepatol* 1998; **13:** 541–8.
14 Hsu HY, Chang MH, Chen DS, Lee CY, Sung JL. Baseline seroepidemiology of hepatitis B virus infection in children in Taipei, 1984: a study just before mass hepatitis B vaccination program in Taiwan. *J Med Virol* 1986; **18:** 301–7.
15 Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. *N Engl J Med* 1975; **292:** 771–4.
16 Rani M, Yang B, Nesbit R. Hepatitis B control by 2012 in the WHO Western Pacific Region: rationale and implications. *Bull World Health Organ* 2009; **87:** 707–13.
17 Nair PV, Weissman JY, Tong MJ, Thursby MW, Paul RH, Henneman CE. Efficacy of hepatitis B immune globulin in prevention of perinatal transmission of the hepatitis B virus. *Gastroenterology* 1984; **87:** 293–8.
18 World Health Organization. Hepatitis B. 2013. Available at: http://www.who.int/mediacentre/factsheets/fs204/en/. Accessed October 6, 2013.
19 Shiraki K, Nagata I, Iizuka T, Kaji S. Mother-to-infant infection by hepatitis B virus and its prevention in Japan. *Int Hepatol Commun* 1996; **5:** 74–8.
20 Tanaka J, Koyama T, Mizui M *et al.* Total numbers of undiagnosed carriers of hepatitis C and B viruses in Japan estimated by age- and area-specific prevalence on the national scale. *Intervirology* 2011; **54:** 185–95.
21 Kobayashi M, Hosaka T, Suzuki F *et al.* Seroclearance rate of hepatitis B surface antigen in 2,112 patients with chronic hepatitis in Japan during long-term follow-up. *J Gastroenterol* 2013; [Epub ahead of print].
22 Kato Y, Nakao K, Hamasaki K *et al.* Spontaneous loss of hepatitis B surface antigen in chronic carriers, based on a long-term follow-up study in Goto Islands, Japan. *J Gastroenterol* 2000; **35:** 201–5.
23 Chu CM, Liaw YF. HBsAg seroclearance in asymptomatic carriers of high endemic areas: appreciably high rates during a long-term follow-up. *Hepatology* 2007; **45:** 1187–92.
24 Koyama T, Mito H, Takahashi K, Tanaka J, Mushahwar IK, Yoshizawa H. Perinatal hepatitis B virus infection in Japan. In: Mushahwar IK, ed. *Congenital and Other Related Infectious Diseases of the Newborn*. Oxford: Elsevier Science & Technology Books, 2006; 141–51.
25 Tamada Y, Yatsuhashi H, Masaki N *et al.* Hepatitis B virus strains of subgenotype A2 with an identical sequence spreading rapidly from the capital region to all over Japan in patients with acute hepatitis B. *Gut* 2012; **61:** 765–73.
26 Sugauchi F, Orito E, Ohno T *et al.* Spatial and chronological differences in hepatitis B virus genotypes from patients with acute hepatitis B in Japan. *Hepatol Res* 2006; **36:** 107–14.
27 Ozasa A, Tanaka Y, Orito E *et al.* Influence of genotypes and precore mutations on fulminant or chronic outcome of acute hepatitis B virus infection. *Hepatology* 2006; **44:** 326–34.
28 Kobayashi M, Ikeda K, Arase Y *et al.* Change of hepatitis B virus genotypes in acute and chronic infections in Japan. *J Med Virol* 2008; **80:** 1880–4.
29 Uchida Y, Kouyama JI, Naiki K *et al.* A novel HBV strain developing due to recombination between genotypes H and B strains isolated from a Japanese patient. *Hepatol Res* 2013; [Epub ahead of print].

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 $p_1p_2 \exp\left(\pm 1.96\sqrt{(1-p_1)/n_1p_1 + (1-p_2)/n_2p_2}\right)$.

Special Report

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Report from a Viral Hepatitis Policy Forum on implementing the WHO framework for global action on viral hepatitis in North Asia

Ding-Shinn Chen[1], Stephen Locarnini[2,*], Suzanne Wait[3], Si-Hyun Bae[4], Pei-Jer Chen[5], James Y.Y. Fung[6], Hong Soo Kim[7], Sheng-Nan Lu[8], Joseph Sung[9], Junko Tanaka[10], Takaji Wakita[11], John Ward[12], Jack Wallace[13], and the CEVHAP North Asia Workshop on Viral Hepatitis[†]

[1]*National Taiwan University College of Medicine, Taipei, Taiwan;* [2]*Molecular Research, Victorian Infectious Diseases Reference Laboratory, North Melbourne, Australia;* [3]*SHW Health Limited, London, United Kingdom;* [4]*Department of Internal Medicine, Seoul St. Mary Hospital, Catholic University Medical College, Seoul, South Korea;* [5]*Hepatitis Research Centre, National Taiwan University and Hospital, Taipei, Taiwan;* [6]*Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong;* [7]*Division of Gastroenterology, Department of Internal Medicine, SoonChunHyang University Hospital, Cheonan, South Korea;* [8]*Division of Hepatogastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan;* [9]*The Chinese University of Hong Kong, Shatin, Hong Kong;* [10]*Department of Epidemiology, Infectious Disease Control and Prevention, Hiroshima University, Institute of Biomedical and Health Sciences, Hiroshima, Japan;* [11]*Department of Virology II, National Institute of Infectious Diseases, Tokyo, Japan;* [12]*Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, United States;* [13]*Australian Research Center in Sex, Health and Society, LaTrobe University, Melbourne, Australia*

Background & Aims: The World Health Organisation (WHO) Prevention & Control of Viral Hepatitis Infection: Framework for Global Action offers a global vision for the prevention and control of viral hepatitis. In October 2012, the Coalition to Eradicate Viral Hepatitis in Asia Pacific (CEVHAP) organised the North Asia Workshop on Viral Hepatitis in Taipei to discuss how to implement the WHO Framework in the North Asia region. This paper presents outcomes from this workshop.
Methods: Twenty-eight representatives from local liver associations, patient organisations, and centres of excellence in Hong Kong, Japan, Korea, and Taiwan participated in the workshop.
Findings: Priority areas for action were described along the four axes of the WHO Framework: (1) awareness, advocacy and resources; (2) evidence and data; (3) prevention of transmission; and (4) screening and treatment. Priorities included: axis 1: greater public and professional awareness, particularly among primary care physicians and local advocacy networks. Axis 2: better economic data and identifying barriers to screening and treatment uptake. Axis 3: monitoring of vaccination outcomes and targeted harm reduction strategies. Axis 4: strengthening links between hospitals and primary care providers, and secure funding of screening and treatment, including for hepatocellular carcinoma.
Conclusions: The WHO Framework provides an opportunity to develop comprehensive and cohesive policies in North Asia and the broader region. A partnership between clinical specialists, primary care physicians, policy makers, and people with or at risk of viral hepatitis is essential in shaping future policies.

Keywords: Hepatitis B; Hepatitis C; Asia; Policy.
Received 4 April 2013; accepted 29 June 2013
* Corresponding author. Address: WHO Regional Reference Laboratory for Hepatitis B, 10 Wreckyn Street, North Melbourne, VIC 3051, Australia. Tel.: +61 3 9342 2637; fax: +61 3 9342 2666.
E-mail address: Stephen.Locarnini@mh.org.au (S. Locarnini).
† See Addendum.

Introduction

In 2012, the World Health Organisation (WHO) launched the *Prevention & Control of Viral Hepatitis Infection: Framework for Global Action.* This strategy offers a global vision for the prevention and control of viral hepatitis [1]. The Framework was welcomed by hepatitis experts and advocacy groups who have been struggling for the attention of policymakers about this 'silent epidemic' for many years [2,3].

Asia is home to 75% of all chronic hepatitis B cases [4] and China alone has more cases of hepatitis C infection than all of Europe or the Americas [5]. The majority of people infected with either hepatitis B virus or hepatitis C virus do not know that they are infected, and are not aware of the precautions they need to take to avoid infecting others or to enable them to reduce the impact of the infection [6]. Uptake of screening, when available, is low, and treatment rates are 4–10% in Asia compared to rates of 20% in the United States [7].

Against this background, the Coalition to Eradicate Viral Hepatitis in Asia Pacific (CEVHAP) was established in 2010 to contribute towards an Asia Pacific region free from the significant health, social and economic burden of viral hepatitis (www.cevhap.com). CEVHAP is uniquely positioned to support and facilitate the implementation of the WHO framework in different countries across the region through its network of members who are experts in their respective fields in the Asia Pacific region and globally.

In October 2012, CEVHAP organised the North Asia Workshop on Viral Hepatitis in Taipei, with participants from Hong Kong, Japan, Korea, and Taiwan. These four jurisdictions were chosen because, to varying degrees, they have some initiatives in place

ELSEVIER

Journal of Hepatology **2013** vol. 59 | 1073–1080

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

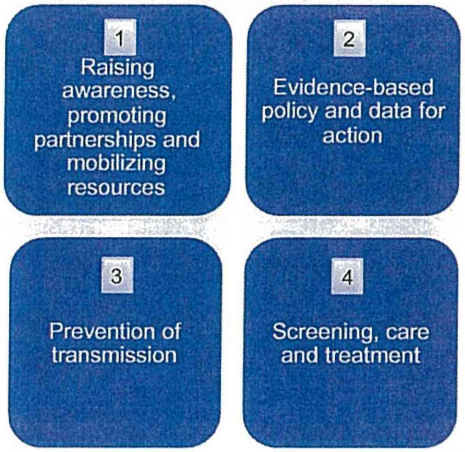

Fig. 1. The four strategic axes for policy development recommended in the WHO Prevention & Control of Viral Hepatitis Infection: Framework for Global Action.

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.

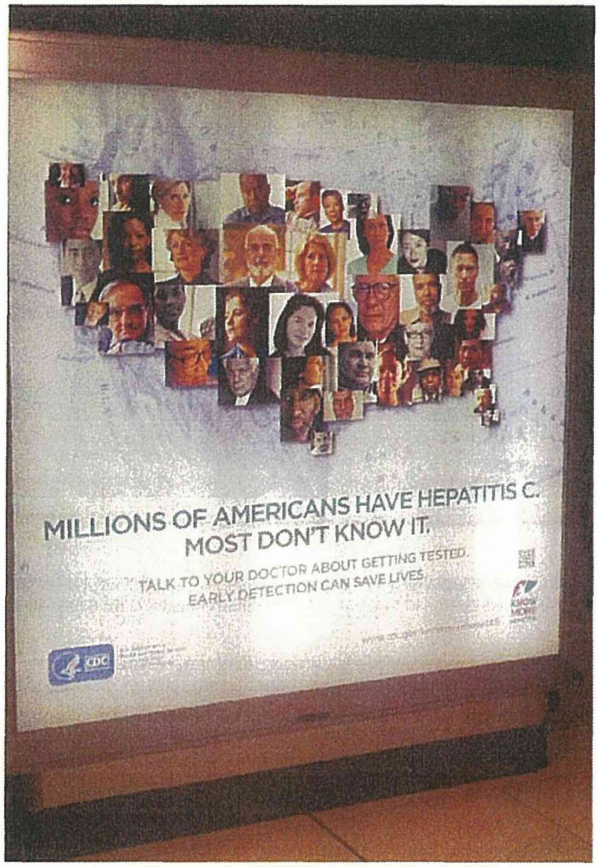

Fig. 2. Example of a diorama on viral hepatitis at a US airport.

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].

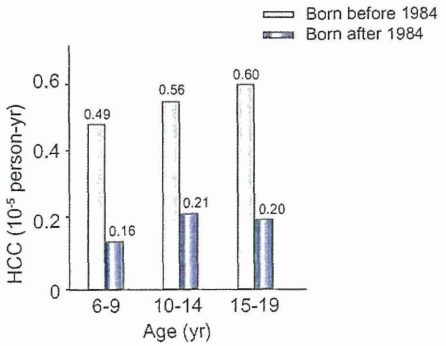

Fig. 3. Incidence of HCC by age in cohorts born before and after infant vaccination program against hepatitis B virus in Taiwan (started in 1984) [27].

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.

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].

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.

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.