

Seroepidemiology of HBV Infection in South Korea, 1995 through 1999

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Background : We analyzed serologic data that were obtained from the Korea Association of Health from 1995 to 1999 to estimate the reliable prevalence of HBV in South Korea.

Methods : 603,375, 639,465, 621,476, 612,705 and 650,398 serum samples were annually tested for HBsAg. Of HBsAg positive persons whose serum samples were available, HBeAg positivity was checked.

Results : HBsAg positivities among subjects between 6 and 19 years old were 8.2%, 3.9%, 2.1%, 2.6% and 1.3%. HBsAg positivities among subjects above 20 years old were 8.9%, 6.4%, 5.9%, 5.4% and 5.4%. The positive rates of HBeAg were 39.8 to 62.9% among subjects between 6 and 19 years old, and 18.3 to 37.9% among persons above 20 years old, in each year. In both subgroups, HBsAg positivity in the latter year was significantly lower than that in the former year ($p < 0.001$). It also showed that HBsAg positivities among subjects between 6 and 19 years old have been significantly lower than those among subjects above 20 years old, but those of HBeAg the exact reverse of HBsAg since 1996 ($p < 0.001$).

Conclusions : It was observed that prevalence of HBV infection in the late 1990s, especially in the group between 6 and 19 years old, was conspicuously lower than that in the past. The nationwide vaccination programme might be one of the most important contributors to this tendency in Korea.

Key Words : epidemiology; hepatitis B virus; Korea; vaccination

INTRODUCTION

Over 300 million of people all over the world are estimated to be being infected with hepatitis B virus (HBV), and part of the infected persons are suffering from acute or chronic hepatitis B, liver cirrhosis and primary

hepatocellular carcinoma¹⁾. The positive rate of hepatitis B surface antigen (HBsAg) has been reported to be only 0-3 percent in the United States^{2,3)}, but that in North East Asia, including China, Taiwan and Japan, before a vaccination programme was introduced, had been known to reach 8-10 percent^{4,5)}.

The natural course of HBV infection is known to be very different between Asians and Westerners. Western patients, who usually become infected as adults by percutaneous routes such as sexual contacts, transfusion and intravenous drug abuse, have an acute hepatitis-like state and rarely become chronically infected.

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However, Asian patients, who usually become infected perinatally and have high HBeAg (hepatitis B e antigen) seropositivity, not only almost invariably remain chronically infected with a relatively lower level of liver enzymes but also have high risk for liver cirrhosis and primary hepatocellular carcinoma^{6,7)}. Until now, there have been no definite treatment options and strategies for eradicating HBV. Furthermore, drugs, including interferon and the nucleoside analogue lamivudine, are not indicated to HBV healthy carriers. Therefore, in Asia, headed by South Korea, Taiwan, China and Japan, the vaccination programme for newborns during the perinatal periods born from mothers who have HBV infection is one of the most effective strategies that can reduce the number of patients with HBV infection and its sequelae^{8,9)}.

In South Korea, an immunization programme for HBV has begun on a required basis since 1983⁹⁾ and the prevalence of HBV infection might be different from that in the past. However, there are no nationwide epidemiologic data on HBV infection. Therefore, we performed this study to investigate the recent, real prevalence of HBV infection in South Korea.

METHODS

Collection of Data

Korea Association of Health (KAH) is not a medical center or hospital but an examination center under the Ministry of Health and Welfare of the Korean Administration to check the health and nutritional status of the general population, including students, by means of conducting a variety of health tasks on behalf of the government. Various kinds of tasks associated with the health status of students and the general population have been performed by 13 branches of KAH, which are evenly distributed throughout the country, and by specialized mobile examination buses.

We analyzed the test results of HBsAg and HBeAg pooled in KAH and obtained from January 1, 1995 to December 31, 1999. Study population was composed of: 1) children or students between 6 and 18 years old who were attending preschools, elementary or secondary schools, and university freshmen 19 years old, whose serum samples were collected for assessing the Korean students' health status as a national public health task and 2) employees of private companies, public officials of the administration and people who were affiliated with 'Korean National Health Insurance' (that is not optional

but compulsory for all the people of South Korea). In the cases of elementary and secondary school students, education committees and public health officials ordered the tests as a mass screening test and then acquired the informed consent from them and their parents.

We used remaining serum samples to test HBeAg positivity after HBsAg testing. Some samples had sufficient volume for HBeAg, but the others did not. Although we could not randomly select serum samples for HBeAg positivity, technicians not only sampled serum from subjects, with having no information about whether or not they were HBsAg positive, but also had no information on serum samples except for those being tested on HBsAg positive serum while the tests were being processed.

Serologic methods and statistics

Testing for HBsAg and HBeAg was performed on serum samples collected from subjects. Blood samples collected were stored in a refrigerator after being centrifuged within 2 hours of blood drawing, and serologic tests were performed within 12 hours of being stored. Serum samples were tested for HBsAg and HBeAg with the use of reversed passive hemagglutination (RPHA) method (Fujirebio Inc., Tokyo, Japan). If HBsAg and HBeAg positivity had been equivocal in RPHA method, the results were confirmed with repeated RPHA and enzyme-linked immunosorbent assay (ELISA) (HBsAg; Korean Green Cross Corp., Seoul, Korea, HBeAg; Roche Diagnostics Corp., Indianapolis, U.S.A.).

For comparisons among subgroups of the population, chi-square (χ^2) test was used. A two-sided *p* value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Serum samples from 603,735, 639,465, 621,476, 612,705 and 650,398 subjects in 1995, 1996, 1997, 1998 and 1999 respectively, were tested for HBsAg. Men were 49.7 percent, 51.4 percent, 52.2 percent, 52.2 percent and 51.3 percent in each year. The distribution of the study population according to the sex and the age is shown in table 1. Table 2 shows the number of HBsAg positive persons according to their age in each year. Of HBsAg positive serum samples, 4.8 to 46.9 percent were available for HBeAg positivity (Table 3).

Table 1. Composition of the study population according to their age and sex

	1995		1996		1997		1998		1999	
	M	F	M	F	M	F	M	F	M	F
Sum	299,986	303,749	328,671	310,794	324,673	296,803	319,745	292,960	333,486	316,912
6-19	203,318	202,516	213,907	201,684	209,678	198,243	229,844	217,862	217,539	222,712
20-29	21,048	19,984	29,735	29,071	46,627	32,540	20,215	19,319	30,166	21,025
30-39	26,587	25,837	35,028	29,382	25,424	22,522	25,503	20,441	27,000	21,181
40-49	21,657	23,512	28,165	22,688	19,416	20,005	23,176	16,540	26,837	22,610
50-59	16,980	18,461	13,917	17,697	15,049	13,797	15,637	12,444	20,410	18,930
> 60	10,396	13,439	7,919	10,272	8,479	9,696	5,460	6,354	11,534	10,454

M, male ; F, female

Table 2. Distribution of HBsAg positive persons according to their age

	1995		1996		1997		1998		1999	
	Total	HBsAg (+) (%)	Total	HBsAg (+) (%)	Total	HBsAg (+) (%)	Total	HBsAg (+) (%)	Total	HBsAg (+) (%)
Sum	603,735	50,184 (8.3)	639,465	30,602 (4.8)	621,476	21,134 (3.4)	612,705	20,646 (3.4)	650,398	17,176 (2.6)
6-19	405,834	33,104 (8.2)	415,591	16,338 (3.9)	407,921	8,600 (2.1)	447,706	11,761 (2.6)	440,251	5,893 (1.3)
20-29	41,032	2,817 (6.9)	58,806	4,740 (8.1)	79,167	4,189 (5.3)	39,444	2,029 (5.1)	51,191	2,381 (4.7)
30-39	52,424	5,395 (10.3)	64,410	4,253 (6.6)	47,946	3,164 (6.6)	45,944	2,682 (5.8)	48,181	2,964 (6.2)
40-49	45,169	4,697 (10.4)	50,853	2,901 (5.7)	39,421	2,492 (6.3)	39,716	2,298 (5.8)	49,447	3,232 (6.5)
50-59	35,441	2,967 (8.4)	31,614	1,648 (5.2)	28,846	1,785 (6.2)	28,081	1,458 (5.1)	39,340	1,902 (4.8)
> 60	23,865	1,204 (5.0)	18,191	722 (3.9)	18,175	904 (4.9)	11,814	418 (3.5)	21,988	804 (3.7)

Table 3. Distribution of HBeAg positive subjects among HBsAg positive persons

	1995		1996		1997		1998		1999	
	Total	HBsAg (+) (%)	Total	HBsAg (+) (%)	Total	HBsAg (+) (%)	Total	HBsAg (+) (%)	Total	HBsAg (+) (%)
Sum	7,597	2,910 (38.3)	6,500	2,800 (43.1)	6,631	2,878 (43.4)	9,698	3,857 (39.8)	6,410	2,034 (31.7)
6-19	1,599	636 (39.8)	2,980	1,876 (62.9)	3,500	2,059 (58.3)	4,853	2,619 (53.9)	2,739	1,362 (49.7)
20-29	1,862	924 (49.6)	919	352 (38.3)	1,115	384 (34.4)	1,068	411 (38.5)	957	407 (42.5)
30-39	2,500	921 (36.8)	1,179	332 (28.2)	923	244 (26.4)	1,615	459 (28.4)	1,099	311 (28.3)
40-49	1,492	374 (25.1)	938	163 (17.4)	639	108 (16.9)	1,207	218 (18.1)	892	163 (18.3)
50-59	390	41 (10.5)	356	55 (15.4)	358	50 (13.9)	663	100 (15.1)	490	58 (11.8)
> 60	114	14 (12.3)	128	22 (17.2)	96	33 (34.4)	292	50 (17.1)	233	13 (5.6)

The positive rates of HBsAg among all subjects in each year were 8.3 percent, 4.8 percent, 3.4 percent, 3.4 percent and 2.6 percent, respectively, and there was sustained decline from 1995 to 1999 ($p < 0.001$), except for that between 1997 and 1998 ($p = 0.34$) being very lower than that in the past.

In subgroup analysis, the positive rates of HBsAg among subjects between 6 and 19 years old in each year were 8.2 percent, 3.9 percent, 2.1 percent, 2.6 percent and 1.3 percent, which were shown in figure 1A ($p < 0.001$). That is, the positive rate of HBsAg steeply declined from 8.2 percent in 1995 to 1.3 percent in 1999. During the same periods, the positive rates of HBsAg among subjects above 20 years old were 8.9 percent (17,080 out of 197,901), 6.4 percent (14,264 out of 223,874), 5.9 percent (12,534 out of 213,555), 5.4 percent (8,885 out of 164,999) and 5.4 percent (11,283 out of 210,147), respectively, and a decreasing tendency, from 8.9 percent in 1995 to 5.4 percent in 1999, was also observed, as shown in figure 1A ($p < 0.001$), but not between 1998 and 1999 ($p = 0.83$). The positive rates of HBsAg among subjects between 6 and 19 years old from

data in all years were significantly lower than those among subjects above 20 years old ($p < 0.001$). As demonstrated in figure 1A, the decreasing tendency was more prominent among subjects between 6 and 19 years old than that among subjects above 20 years old.

As shown in figure 1B, since 1996, the positive rates of HBeAg among subjects between 6 and 19 years old, which were 62.9 percent in 1996, 58.8 percent in 1997, 53.9 percent in 1998 and 49.7 percent in 1999, were significantly higher than those among persons above 20 years old, 26.3 percent, 26.2 percent, 25.6 percent and 18.3 percent ($p < 0.001$), except for that in 1995, 39.8 percent and 37.9 percent, respectively ($p = 0.37$). In each year, the positive rate of HBeAg tended to decline as the age increased.

DISCUSSION

This study was performed to estimate the reliable prevalence of HBV infection in South Korea. Some domestic surveys about the positive rate of HBsAg in South Korea have been reported. However, they were limited to that among adults who had lived in specific areas, employees in specific occupations, residents in certain institutions, or some students who were attending schools¹⁰⁻¹⁵. Prevalence of HBV infection is thought to be so different from that in the past but there have been no epidemiologic data surveyed nationwide, particularly in the late 1990s. Our study population was almost composed of relatively healthy adults and students evenly distributed over the country.

Prevalence of HBV infection was much lower than that of domestic articles in the past. And the decreasing tendency of HBsAg seroprevalence was distinctly observed, though it was a relatively short period. In the subgroup between 6 and 19 years old, the decrease of HBsAg seroprevalence was more conspicuous. In 1995, the positive rate of HBsAg among them was very high, 8.2 percent but, since then, there has been a sustained decline to as 3.9 percent, 2.1 percent, 2.6 percent and 1.3 percent in each year. Oh et al²⁾ reported in 1990 that the prevalence of HBV infection among 173,342 elementary and secondary school students (7 to 18 years old) in the area of Kwangju City and Chonnam Province, who were born before the vaccination programme was introduced, was 5.27 percent. Comparing their results with ours, though the time and the area surveyed were so different, there might be a marked decline in the number of HBV

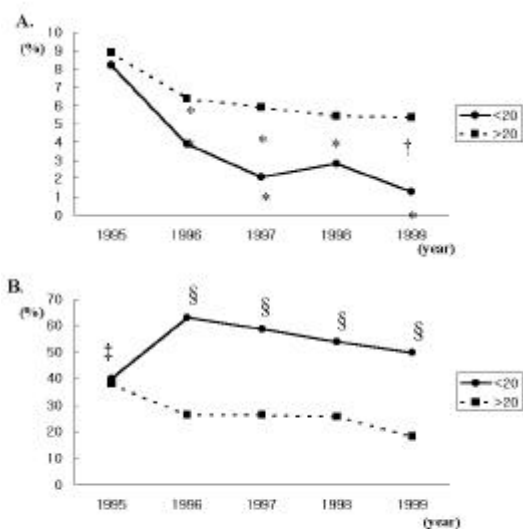


Figure 1A, B. The changes of HBsAg (A) and HBeAg (B) seroprevalences among groups between 6 and 19 years old and above 20 years old are demonstrated. The positive rate of HBsAg in more recent years was lower than that in the past in both subgroups (*; $p < 0.001$), except for that among subjects above 20 years old in 1999 ($p = 0.83$), and that among those between 6 and 19 years old in 1998. The positive rates of HBeAg among subjects between 6 and 19 years old were always higher than those among persons above 20 years old since 1996 ($p = 0.34$, §; $p < 0.001$).

carriers in recent years. We recently reported that, in Kangwon Province in South Korea, the positive rate of HBsAg among elementary school children (7 to 12 years old) was 1.4 percent and that was significantly lower than those of the past reports above¹⁵. Regrettably, it is impossible to acquire serum samples or the information about prevalence in the early 1990s. However, according to the domestic articles published from the 1980s through the early 1990s, the prevalence of HBV infection has been reported variably from 8% to above 10%^{10, 11}. With consideration of the beginning year of vaccination, 1983, and age of the study population, prevalence of HBV infection far above 10% is thought to decline after the 1990s. We think that before 1996 the prevalence declined steeply but after 1996 it did so gently because the pools themselves decreased. Some studies lately presented demonstrated that the HBV carrier state could be prevented in over 80 percent of neonates by using vaccination^{4, 16-19}. In South Korea, the national HBV vaccination programme was begun in 1983 on a required basis⁹ with a 3-doses schedule. According to the reports from Taiwan and Saudi Arabia, after executing a vaccination programme actively for over 90 percent of neonates, HBsAg seroprevalence of elementary schoolers declined from 8-10 percent to 0.16-1.3% in 9-10 years^{4, 16, 18, 19}. In South Korea, according to the report released by the Government, the percentage of vaccinees among neonates born after 1983 reached 79.7% and that among neonates born after 1990 was 98.9%, nationwide²⁰. Considering that most HBV infections in Asians occurred vertically and nearly all neonates would be vaccinated for HBV, the vaccination programme is thought to be the main contributor to the steep reduction of the number of chronic HBV carriers.

The decreasing tendency of HBsAg seroprevalence was also observed in the subgroup above 20 years old. KAH has no information on intravenous drug abuse and iatrogenic contamination. Although vaccination during the school period and the immunization that followed it are able to prevent the spread of infection within the family and through direct contacts during the adult period, the possibility of the reduction of horizontal transmission should be considered and a study about that is warranted.

There have been no data on the positive rate of HBeAg among HBsAg seropositive subjects in South Korea. In other countries, the positive rate of HBeAg was reported to be from 5 percent in Italy²¹ to 46 percent in Taiwan²². In our analysis, the positive rates of HBeAg among subjects between 6 and 19 years old varied from

39.8 percent to 62.9 percent in each year, and they were significantly higher than those among persons above 20 years old in each year, 18.3 to 37.9 percent, except in 1995. In hyperendemic areas such as North East Asia, chronic HBV infection in children is known to be commonly associated with HBeAg seropositivity and we think that our result, similar to that in Taiwan, proved it. Maternally derived HBeAg crossing the placenta may induce immune tolerance or eliminate T helper cells responsive to HBeAg in neonates, and HBeAg to anti-HBe seroconversion occurs very rarely²³. That subjects between 6 and 19 years old in South Korea have a higher proportion of HBeAg seropositivity in our study is thought to be due to the fact that they acquired HBV infection from their mothers during the perinatal period²⁴.

Our analysis is subject to some limitations. First of all, we retrospectively evaluated only serum data pooled in KAH and there was no information on the exact percentage of vaccinees or other medical information, such as intravenous drug abuse, because KAH only evaluated whether or not they have HBsAg and HBeAg since 1995. Since 1983, vaccination for HBV at 0, 1, 2 months or 0, 1, 6 months after birth has been compulsory for all neonates born in South Korea and that policy has not been changed until now. As described above, the percentage of vaccinees in South Korea was 79.7% since 1983 and above 98.9% since 1990²⁰. Although it was impossible to exactly separate persons who were born before 1983 from those who were born after 1983, we have thought that the vaccination was the main contributor to this decrease, especially in the population below 19 years old, based on the assumption that transmission by iatrogenic routes or intravenous drug abuse was not the important problem in Korea like the other countries in Asia. To confirm exactly the effect of vaccination for HBV on the prevalence of HBV infection, we think an investigation about various factors associated with HBV infection is warranted. Secondly, KAH preferentially performed the test with RPHA method. RPHA method and ELISA method have been most commonly used for serum HBsAg and HBeAg testing. ELISA method is more sensitive and specific, but more expensive and time-consuming than RPHA method. So RPHA method has been preferentially used in mass screening^{25, 26}. In our study, ELISA method was selectively performed to overcome such drawbacks of RPHA, if positivity of the results had not been obvious.

In conclusion, although there are no reliable data of the past on the real prevalence of HBV infection in South

Korea, we believe that there has been a considerable decrease of the HBsAg seroprevalence in South Korea, mainly thanks to the nationwide vaccination programme. It is expected that there will be a sustained decline of HBV infection and, in the long run, South Korea will have a prevalence of HBV infection as low as that in the Western countries along with a positive attitude for perinatal vaccination and prevention of percutaneous infection during adult periods.

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