

## Changes in the intrafamilial transmission of hepatitis B virus after introduction of a hepatitis B vaccination programme in Korea

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### SUMMARY

Hepatitis B virus (HBV) infections are endemic in Korea. The aims of this study were to determine the prevalence of HBsAg positivity in Korea and to evaluate the changes in intrafamilial transmission after introduction of HBV vaccination in 1983. This study was based on the 2001 Korea National Health and Nutrition Examination Survey. A total of 2512 study subjects, aged 10–29 years, were selected from across Korea using a stratified multi-stage probability sampling design. To identify the changes in intrafamilial transmission after the introduction of the HBV vaccination programme, 1850 subjects with parental serological markers were selected. These subjects were then grouped into two birth cohorts (cohort 1: born before 1983; cohort 2: born after 1983). Appropriate sampling weights were used for all analyses. The weighted age-specific prevalence of HBsAg was 4·9% in participants in their 20s and 1·9% in adolescents; the combined weighted prevalence was 3·2%. Of subjects with HBsAg positivity in either parent, 17·5% were HBsAg-seropositive. Of subjects with two HBsAg-negative parents, 1·5% were HBsAg-seropositive. The HBsAg positivity rate of offspring with HBsAg-positive mothers was higher than those with HBsAg-positive fathers (27·3% vs. 4·8%,  $P < 0·001$ ). The weighted HBsAg positivity rate of offspring with HBsAg-negative mothers was 2·3% for cohort 1 and 0·4% for cohort 2 ( $P < 0·01$ ), and for those offspring with HBsAg-positive mothers it was also significantly decreased compared to cohorts 1 and 2 (40·2% vs. 16·4%,  $P < 0·01$ ). However, the weighted HBsAg positivity rate of offspring with HBsAg-positive mothers was still high. Our results showed that introduction of HBV vaccination has resulted in a decline in the overall HBsAg positivity rate and a reduction in intrafamilial transmission in Korea, but further preventive measures for maternal intrafamilial transmission are needed.

**Key words:** Hepatitis B virus, intrafamilial transmission, vertical transmission.

### INTRODUCTION

Hepatitis B virus (HBV) infection is a major cause of chronic hepatitis, liver cirrhosis, and hepatocellular

carcinoma in many parts of the world [1–3]. It is estimated that 75% of the world's total HBV carriers live in Asian countries, including China and India. Chronic carriers of HBV are not only at risk of developing long-term progression of infection, but also represent a significant source of infection for others [4–6]. Like other endemic countries, the majority of

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chronic HBV carriers became infected early in life, particularly before age 2 years [7].

Korea is known to be one of the endemic areas in the world for HBV infection. In Korea, plasma-derived HBV vaccines have been available for commercial use since 1983. The first vaccination plan against HBV infection was strongly recommended, even for adults. Until the mid-1980s, about 6 million people were vaccinated throughout the country, including public service workers, offspring of low-income citizens, elementary school students, and children. As the importance of hepatitis prevention for newborns was emphasized, HBsAg screening of pregnant women and hepatitis B vaccination of newborns have been encouraged in public health centres. Furthermore, the national HBV vaccination programme for elementary school children was launched in 1988 and the universal vaccination programme was extended to include all neonates and infants in 1995 [8–11].

Since the introduction and extension of the national HBV vaccination programme, there have been many studies on the epidemiology of HBV infection in Korea. Most of the studies have been based on non-representative data and used small sample sizes from selected communities [12, 13]. Fortunately, the Ministry of Health and Welfare (MOHW) of Korea performed the Korea National Health and Nutrition Examination Survey (KNHANES) in 2001, which included selective serological markers for HBV infection. As the survey was based on a representative sample of the entire nation, this data has provided a more comprehensive assessment of HBsAg positivity in Korea.

The aims of this study were to determine the prevalence of HBsAg positivity in Korea and to evaluate the changes in intrafamilial transmission of HBV after introduction of HBV vaccination in 1983.

## MATERIAL AND METHODS

Our study was based on the KNHANES conducted in 2001. The study design and sampling have been described in detail elsewhere [14, 15]. Briefly, the survey consisted of four parts: the Health Interview Survey, the Health Examination Survey, the Health Behavior Survey, and the Nutrition Survey. Initially, 13200 households were selected from across the nation using a stratified, multi-stage probability sampling design. A total of 12183 households participated in the survey (participation rate 92.3%), and

thus the final sample consisted of 37769 persons from 12183 households.

With the exception of the Health Interview Survey, the other three surveys were carried out on a subsample, which was also randomly selected from the original sample. A total of 2512 subjects, aged 10–29 years (1080 participants in their 20s and 1432 adolescents) from the 2001 KNHANES subsample were extracted to identify the age-specific prevalence of HBsAg positivity. For analysis of intrafamilial transmission, subjects with no parental data for HBV serological markers of infection were excluded. Thus, 1850 subjects from 1210 families with serological data for 1210 mothers and 875 fathers were used. The study subjects were then grouped according to their birth years into one of two birth cohorts (birth cohort 1, 755 subjects aged 18–29 years, born before the introduction of HBV vaccination; and birth cohort 2, 1095 subjects aged 10–17 years, born after the introduction of HBV vaccination).

The blood samples were collected by trained specialists and were tested for HBsAg using enzyme-linked immunosorbent assay (ELISA) kits (CODA, Bio-Rad, USA) at a single laboratory. All procedures related to laboratory tests were thoroughly supervised by the quality control committee. Demographic data were selected from household interview questionnaires, which were administered by trained interviewers. Informed consent was obtained from all participants. This study using 2001 KNHANES data was approved by the Institutional Review Board of the Catholic University of Korea (CUMC08U044).

## Statistical analysis

Statistical analysis was performed using SAS, version 9.1 (SAS Institute Inc., USA). To make valid inferences accounting for the 2001 KNHANES complex survey design, sampling weights were incorporated to produce population estimates [14]. SAS PROC SURVEY procedures, which included weight, cluster, and strata statements, were used to address this issue [16, 17]. Appropriate sampling weights were used for all analyses. The weighted age-specific prevalence of HBsAg was calculated in 10-year blocks. Categorical variables were analysed using PROC SURVEYFREQ and are presented as a frequency (*n*) and a percentage of the weighted frequencies based on sampling weights. Continuous variables were analysed using PROC SURVEYMEANS and are presented as mean ( $\pm$ S.E.). In order to identify the changes after introduction

Table 1. General characteristics of 1850 study subjects for intrafamilial transmission from the 2001 Korea National Health and Nutrition Examination Survey

Variables	Birth cohort 1* (n=755)			Birth cohort 2† (n=1095)			P value
	n	%	Weighted %‡	n	%	Weighted %‡	
Gender							0.490
Male	380	50.3	51.1	569	52.0	51.6	
Female	375	49.7	48.9	526	48.0	48.4	
Residence							0.008
Metropolitan	375	49.7	52.9	464	42.4	45.8	
City	253	33.5	33.0	418	38.2	37.9	
Rural	127	16.8	14.1	213	19.4	16.3	
Standard of living							0.838
Good	50	6.6	6.4	67	6.2	6.4	
Normal	476	63.1	61.7	699	64.3	62.9	
Poor	229	30.3	31.9	321	29.5	30.7	
Family size (mean ± s.e.)		4.0 ± 0.0	4.0 ± 0.1		4.2 ± 0.0	4.2 ± 0.1	<0.001
HBsAg (father)							0.663
Positive	28	5	5.3	45	5.6	5.7	
Negative	528	95	94.7	762	94.4	94.3	
HBsAg (mother)							0.254
Positive	48	6.4	6.5	56	5.1	5.3	
Negative	707	93.6	93.5	1039	94.9	94.7	

\* Birth cohort 1: 755 subjects, aged 18–29 years, born before 1983.

† Birth cohort 2: 1095 subjects, aged 10–17 years, born after 1983.

‡ All weighted proportions were adjusted for sample weights.

of HBV vaccination, we compared the prevalence of HBsAg positivity according to the HBsAg status of the parents by birth cohort. Prevalence values for categorical variables were tested using the  $\chi^2$  test for proportions (using PROC SURVEYFREQ). *P* values <0.05 were considered statistically significant.

## RESULTS

The weighted age-specific prevalence of HBsAg was 4.9% in subjects in their 20s and 1.9% in adolescents; the combined weighted prevalence of HBsAg positivity was 3.2% (Fig. 1).

Birth cohorts 1 and 2 were not significantly different with respect to gender, standard of living, and HBsAg status of the parents. However, birth cohort 2 included more rural residents and had larger family sizes compared to birth cohort 1 (Table 1).

For offspring with either parent HBsAg-positive, the percent of weighted frequency for HBsAg positivity was 17.5%. Moreover, for offspring with both parents HBsAg-negative, the percent of weighted frequency for HBsAg positivity was 1.5%.

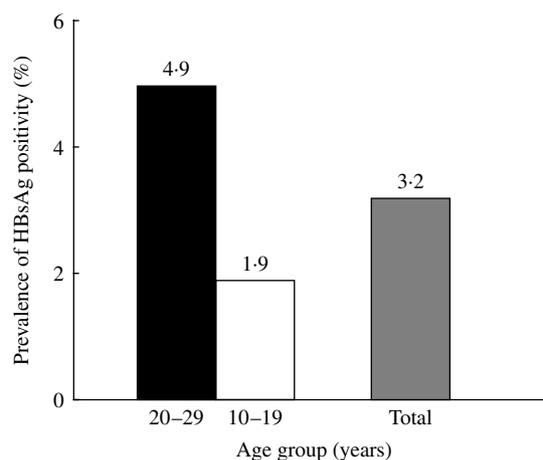


Fig. 1. Adjusted weighted age-specific prevalence of HBsAg positivity in the Korean population, aged 10–29 years, based on the 2001 Korea National Health and Nutrition Examination Survey.

Subjects with either parent HBsAg-positive had a significantly higher HBsAg positivity rate in cohort 1 (28.8%) than in cohort 2 (9.2%, *P* <0.001), and subjects with both parents HBsAg-negative had a

Table 2. Crude and adjusted weighted HBsAg-positive rate of offspring according to HBsAg status of the parents of 1850 study subjects from the 2001 Korea National Health and Nutrition Examination Survey

Variables	Birth cohort 1*		Birth cohort 2†		Total		P value
	%	Weighted %‡	%	Weighted %‡	%	Weighted %‡	
Offspring with either parent HBsAg-positive	29.0 (22/76)	28.8	8.7 (9/103)	9.2	17.3 (31/179)	17.5	<0.001
Offspring with both parents HBsAg-negative	2.2 (11/497)	2.8	0.6 (4/717)	0.6	1.2 (15/1214)	1.5	0.010

\* Birth cohort 1: 755 subjects, aged 18–29 years, born before 1983.

† Birth cohort 2: 1095 subjects, aged 10–17 years, born after 1983.

‡ All weighted proportions were adjusted for sample weights.

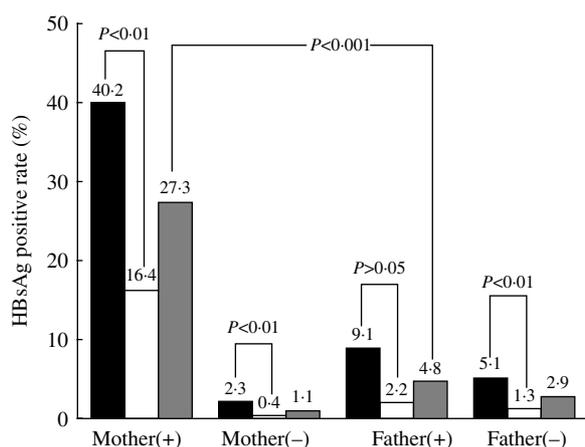


Fig. 2. Adjusted weighted HBsAg positivity rate of offspring according to HBsAg status of the parents from the 2001 Korea National Health and Nutrition Examination Survey (■, birth cohort 1: aged 18–29 years, born before 1983; □, birth cohort 2: aged 10–17 years, born after 1983; ▒, total).

HBsAg positivity rate of 2.8% for cohort 1 and 0.6% for cohort 2 ( $P=0.010$ , Table 2).

On analysis of the weighted HBsAg positivity rate of offspring according to the HBsAg status of the fathers and mothers, offspring of HBsAg-positive mothers had higher rates of weighted HBsAg positivity compared to offspring with HBsAg-positive fathers (27.3% vs. 4.8%,  $P<0.001$ ; Fig. 2).

The weighted HBsAg positivity rate of offspring with HBsAg-negative mothers was 2.3% for cohort 1 and 0.4% for cohort 2 ( $P<0.01$ ). Further, those offspring with HBsAg-positive mothers were significantly fewer in cohort 2 (16.4%) compared to cohort 1 (40.2%,  $P<0.01$ ). However, the weighted HBsAg positivity rate of offspring with HBsAg-positive mothers was still high (Fig. 2).

## DISCUSSION

The HBV vaccination programme, at least in part, has been in effect in Korea since 1983. A mass HBV immunization programme for elementary school children was started in 1988 and the universal vaccination programme was extended to include all neonates and infants in 1995. Indeed, the actual HBV vaccination coverage rate was 82.6% in 1993, according to the elementary school children’s survey, and increased to >95% through the universal vaccination programme of neonates and infants in 1995 [12, 13]. Furthermore, the programme for the prevention of HBV vertical transmission was implemented in July 2002 by the Korea Centres for Disease Control and Prevention (KCDC) [9].

This study is a report of the prevalence of HBsAg positivity and the vaccination effects on intrafamilial transmission in a representative young population in Korea about 18 years after the introduction of HBV vaccination. In our study, the subjects of each cohort could have received vaccination at a private clinic after the introduction of HBV vaccine in 1983 and they could have been exposed to the mass HBV immunization programme for elementary school children, which started in 1988, but the subjects in each cohort were not exposed to the national universal vaccination programme for neonates and infants, which started in 1995. We do not know if any of these study participants actually had HBV immunization or not, but we suspect that birth cohort 2 would have been exposed to HBV vaccine at an earlier age than birth cohort 1.

The weighted age-specific prevalence of HBsAg was 4.9% in participants in their 20s and 1.9% in adolescents; the combined weighted prevalence of HBsAg

was 3.2% in a representative young population. Compared to the data of the 1998 KNHANES, the age-specific prevalence fell from 5.4% in 1998 to 4.9% in 2001 in participants in their 20s, and from 2.2% in 1998 to 1.9% in 2001 for teenagers [15]. All these findings may reflect the effectiveness of Korea's vaccination programme. Considering the fact that a person who is infected at an earlier age more frequently becomes a HBsAg carrier, general exposure to HBV vaccine at an earlier age might be one of the reasons for the decreased prevalence of HBsAg [18].

Apart from parenteral and vertical transmission, HBV may also be transmitted through sexual, child-to-child, or household personal contact, and broad personal hygiene can also be a factor [19–21]. Generally, HBV transmission from HBsAg carrier mothers and fathers to their children is one of the important routes of infection.

Subjects with HBsAg positivity of either parent had significantly higher HBsAg positivity rates in cohort 1 (28.8%) than in cohort 2 (9.2%), and subjects with HBsAg negativity of both parents had a HBV infection rate of 2.8% in cohort 1 and 0.6% in cohort 2. After the introduction of HBV vaccination, the significant decrease in intrafamilial transmission was more likely to be explained in offspring with either parent HBsAg-positive, compared to offspring with both parents HBsAg-negative. Although all groups had a decreased rate in cohort 2, the prevalence of HBsAg positivity of either parent was still considerably higher in cohort 2. Reduction of HBsAg positivity suggests an overall effect of immunization, improved economic status and hygiene, although we could not ascertain their relative importance.

On analysis of the HBsAg positivity rate based on the HBsAg status of the fathers and mothers, offspring of HBsAg-positive mothers had higher rates of HBsAg positivity compared to those with HBsAg-positive fathers, and the HBsAg positivity rates of offspring with HBsAg-positive mothers were much higher in cohort 1 than in cohort 2. Our data have demonstrated that maternal HBV infection remains one of the most influential factors for HBV infection, even after the introduction of HBV vaccination. According to a study on the prevalence of HBsAg carrier mothers, the prevalence of HBsAg-positive parturients was 3.3% in 2001–2002 and the rate has been sustained around 3.5% since 1992 in Korea [22].

Previous studies have also reported similar results on the importance of the mother in HBV transmission [21, 23, 24]. This situation may also be explained by

the fact that in Korean families, mothers spend most of their time caring for their children. In Taiwan, universal HBV vaccination in Taiwanese newborns has not only reduced chronic HBV infection, but also prevented childhood hepatocellular carcinoma [25, 26]. The trend in HBV infections may be helpful in better understanding HBV infections in the vaccinated generation and the impact of the vaccination programme.

Despite the limitation in interpretation due to the cross-sectional study design, our results suggest that the introduction of HBV vaccination has resulted in a decline in the overall HBsAg positivity rate and a reduction in the influence on intrafamilial transmission in a young population. Nevertheless, maternal transmission is still important for further prevention of HBV infections in Korea.

We will continue to conduct prospective sero-epidemiological analyses using KNHANES data to establish the effectiveness of the HBV vaccination programme in Korea.

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#### DECLARATION OF INTEREST

None.

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