Table 5
Prevalence of hepatitis B surface antigen since 1978 in Japan.

Location	Subject group	Research Year							Citation Reference
		1978	1986[a]	1990	1997	2005	2007	2011	
Iwate prefecture	6-year-old children	0.94%	0.04%	0.02%					No. 9
Shizuoka prefecture	Elementary school students		0.2%		0.05%				No. 10
Iwate prefecture	5–9-year-old children					0.017%			No. 7
Nationwide	16-year-old first-time blood donors						0.01%		No. 6
Nationwide	4–8 years of age						0.16% (2005–2011)		This study
Nationwide	9–15 years of age						0.17% (2005–2011)		This study

[a] The nationwide prevention program of mother-to-infant infection of HBV has been operating since 1986, except for Iwate prefecture, where the prevention program was introduced in 1981.

study to evaluate the effect of the current hepatitis B prevention strategy. HBsAg is the earliest indicator of acute infection and is also indicative of chronic infection if its presence persists more than 6 months. It is useful for the diagnosis of HBV infection and for screening of blood. The design of the present study was cross-sectional surveillance using sera from healthy children, and considered the HBsAg-positive child as a healthy HBV carrier or an asymptomatic patient in the incubation period. HBcAb is the specific antibody to hepatitis B core antigen. HBcAb testing identifies all previously infected persons. The prevalence of the HBV serological markers describes the endemicity of hepatitis B in Japan.

We were able to obtain only limited information from the samples in compliance with the ethical agreement with the National Serum Reference Bank, National Institute of Infectious Diseases, Japan. Also, we should perform HBsAg or HBcAb research separately because of the limitation of sample volume (maximal 50 μL for each sample). Despite this limitation, we could obtain important findings.

Out of 3000 serum samples from healthy children, we found five HBsAg-positive sera (0.17%). These HBsAg-positive sera were found in the Southern area of Japan, except for one sample from Miyagi prefecture. The Miyagi sample was speculated to be derived from an HBV-infected child during early the incubation period. The reason for this conjecture was because the serological test result of this sample was HBsAg-positive (even though the OD value was lower than other positive samples), but HBcAb-negative, and its sequencing analysis failed due to low polymerase chain reaction (PCR) yield. HBsAg-positive sera found in Saga prefecture were collected in the same year, and these samples showed a closely related sequence of HBV-genotype B. There was a possibility that these sera were from siblings or members of the same community. The sequences of HBV-genotype B found in Saga were closely related to the domestic HBV-genotype B previously reported (GenBank number: AB010289, AB287327). HBsAg-positive sera found in Fukuoka prefecture showed the common sequence of HBV-genotype C, however, the sampling years of these samples were different (2006 and 2010). The sequence of them was closely related to the HBV-genotype C previously reported from Japan (GenBank number: AB195943, AB222729). All sequence-analyzed samples were thought to be infected with domestic HBV and imported infection cases were very negative.

The present study results showed that the HBsAg prevalence values among children aged 4–8 years and aged 9–15 years were 0.16% and 0.17%, respectively. There was no significant difference in the prevalence according to age ($P = 0.95$). This is compatible with the nature of HBV infection, in that persistent chronic HBV infection mainly results from transmission in early childhood [3].

HBsAg seroprevalence in both age groups was lower than 1%, which is the ultimate goal of hepatitis B control adopted by the WHO Western Pacific Region [3]. However, the prevalence was higher than we expected based on previous studies (Table 5). The reasons for this discrepancy may include issues of sample size and varying HBV endemicity by locality. According to the previous studies [9,10], HBsAg seroprevalence among children was 0.94% in Iwate prefecture and 0.2% in Shizuoka prefecture before the selective vaccination program began. After the introduction of the program, HBsAg prevalence among children drastically declined. The program resulted in a HBsAg prevalence in children of 0.04% and 0.05% in Iwate and Shizuoka prefectures, respectively. In the latest surveillance study in Iwate prefecture, HBsAg seroprevalence among children aged 5–9 years was found to have reached 0.017% in 2005 [7]. However, it must be remembered that Iwate and Shizuoka prefectures were the locations where the selective vaccination program had been ideally carried out by the prefectural governments [10]. According to the results of HBsAg screening in 16-year-old first-time blood donors, the prevalence of HBsAg was 0.01% [6]. From the pre-health interview before blood donation, most of the people with liver trouble were eliminated from the pool of blood donors; this caused underestimation of HBV sero-marker prevalence among blood donors.

The present study yielded 15 HBcAb-positive sera (2.5%, 95% confidence interval 1.25–3.75%). Of those sera, four sera were derived from teens including ages 10, 11 and 16 years. In comparison with HBsAg prevalence among children aged 9–15 years (2 out of 1163), HBcAb prevalence in teens (4 out of 200) showed a high tendency. This may indicate the existence of a subset of children who acquired HBV infection once, but did not become carriers or reach chronic status. There was no significant difference in HBcAb-positive status with or without the selective vaccination program. Thus, selective vaccination alone is not enough to control HBV transmission.

HBsAg and HBcAb test results clearly revealed the differences in HBV endemicity according to location. Both HBsAg and HBcAb were found mainly in the Southern area, including Saga and Fukuoka prefectures. HBV infection is one of the main factors in the development of liver cancer. According to the annual report of the Centre for Cancer Control and Information Services, National Cancer Centre, Japan [13], the frequency of death by cancer of the liver and intrahepatic bile duct was highest in Saga, and Fukuoka prefectures. The trend of the high distribution of HBsAg/HBcAb in the present study and the occurrence of liver cancer is consistent. Discussions about HBV control strategy must consider regional differences in HBV endemicity [14].

The rate of regular prenatal check-ups was so high that it facilitated the introduction of the mother-to-infant HBV transmission prevention program. The HBsAg prevalence among pregnant women has been estimated as approximately 1% [5,15], although this number includes gaps in some places, for example, 0.3% in Niigata in 2008 and 1.7% in Ehime in 2010. Only infants born to HBsAg-positive mothers were the targets of the selective vaccination program, which means that nearly 99% of newborn are excluded from the current HBV prevention strategy. The HBV-susceptible populations continue to accumulate year by year. On the other hand, hepatitis B carriers are still born to HBsAg-positive mothers within the mother-to-infant HBV transmission prevention program due to the failure of treatment such as inappropriate

immunization schedule or misunderstanding between doctors and guardians [14,16]. Additionally, horizontal transmission from family members (other than mothers) has been observed [17,18]. The findings of the present study showed that the opportunity to acquire HBV infection was more frequent than we thought, especially in some locations. Furthermore, in addition to Japan-dominant HBV-genotype B and C, HBV-genotype A has been increasing [19,20]. HBV-genotype B and C rarely induce chronic infection after acute hepatitis among adults; on the other hand, the risk of developing chronic infection from HBV-genotype A is higher than that of HBV-genotype B and C. This also supports the need for a HBV prevention strategy for susceptible populations, such as hepatitis B universal vaccination in early childhood.

Hepatitis B vaccination should be introduced into the routine child immunization program for susceptible populations, and selective vaccination, the mother-to infant HBV transmission prevention program, should be continued for high-risk children. Simultaneously, the continuous surveillance of illness and sero-epidemiological studies must be supported in order to determine an evidence-based vaccination program and associated policies.

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