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# Comprehensive Prevention of Hepatitis B Virus Transmission to Reduce Primary Liver Cancer

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Hepatitis B virus（HBV）belongs to the family of Hepadnaviridae and infects more than 2 billion people over the world. Children less than 5 years of age who become infected with the HBV are the most likely to develop chronic infection and eventually proceeds to liver cancer, which accounts for 33% cancer deaths. Prevention of HBV transmission is essential to reduce the risk of liver cancer. In order to reduce HBV transmission, it is necessary to apply a comprehensive prevention system to block vertical and horizontal transmission. Vertical transmission of HBV from mother to child is the most frequent cause in the developing countries. The HBV status of HBsAg, HBeAg, and HBV DNA in all pregnant women is screened to prevent transmission from the prenatal stage. Antiviral therapy should be considered, if HBV DNA exceeds 5 log10 copies/ml. Horizontal transmission in the postnatal period can be prevented by universal HBV vaccination. However, if the HBeAg status of the mother becomes positive during the pregnancy, additional treatment of hepatitis B immunoglobulin, HBIG is required. Unfortunately, in most countries, comprehensive prevention systems that block vertical and horizontal transmission are not applied due to cost issues and inconvenience of transportation for residents. The vaccination program has not been appropriately established in all countries, even though the universal HBV vaccination has been widely introduced. Because of such circumstances, the rate of HBV transmission is still at high level.

Key words: HBV, horizontal transmission, vaccine, liver cancer, prenatal stage, postnatal stage

## INTRODUCTION

Hepatitis B virus（HBV）is the most frequent cause of liver cancer. In 2015, HBV infection accounted for 265,000 cases（33%）among 810,000 global liver cancer deaths［1］. Infants infected with before 1 year of age develops chronic HBV infection in 90% of frequency［2］. Thus, the incidence of liver cirrhosis or cancer will reduce significantly by preventing infants from new HBV infection. Postnatal prevention is usually performed by either universal HBV vaccination or nonroutine human anti-HBs Immunoglobulin（HBIG）administration. However, comprehensive prenatal and postnatal intervention of HBV transmission to prevent new HBV infection is rarely applied［3］.

Nowadays, the most implemented HBV prevention all over the world is HBV vaccination due to financial supports from international organizations. HBV vaccine containing viral S protein will be injected for 3 times between the age of day 0, 1 month,

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and 6 months of the baby, to induce the antibody against HBV [4]. This vaccine is highly effective, but not powerful enough to show a complete block against HBV infection. HBV vaccination prevents HBV transmission only in the postnatal period. Prenatal prevention, the most important period for prevention, is usually overlooked.

This review explains the importance to perform both prenatal and postnatal prevention, especially emphasizing the importance of prenatal prevention. It can be part of the guidance for the health policy to halt the HBV transmission more effectively.

## Basic knowledge of HBV

### *HBV genome and protein*

HBV has a partially double-stranded DNA genome which is approximately 3 kilobase pairs (kbp) in size. Minus strand DNA is the template for the synthesis of the viral mRNA, however, plus- strand contains about 2/3 of the circular genome. HBsAg, HBeAg, HBVpol, HBcAg, and HBx are essential components for the HBV life cycle. The first three components are important for HBV transmission [5]. HBV uses reverse transcriptase during a part of replication process in productively infected hepatocytes. Once HBV enters the cell, viral DNA is converted to form stable covalently closed circular DNA (cccDNA) (Fig. 1), which contributes to persistent infection and serves as a target for antiviral therapy, but now it is still a difficult goal to achieve complete elimination [6-9].

HBsAg, used to be called as an Australian antigen, was discovered by Blumberg from Aboriginal sample in the mid-1960s [10]. HBsAg is the component of the envelope protein and classified into 3 types: S, M, and L. S consists of 226 amino acids (aa). M consists of S and an additional 55 aa. L consists of M and an additional 108 or 119 aa. Current vaccine is constructed from HBsAg, because HBsAg is more abundant than other proteins [11, 12].

HBeAg is an auxiliary protein synthesized during the HBV replication. HBeAg is not a component of the virus particle and is secreted to the outside of the infected cells. After two-times of proteolytic processes, the final size of HBeAg becomes 15 kilodaltons (kDa). The specific function of HBeAg is not clear but related to immune evasion [13-16]. The clinical implication of HBsAg indicates active viral replication inside the hepatocyte [17].

HBcAg is the subunit of viral nucleocapsid with a

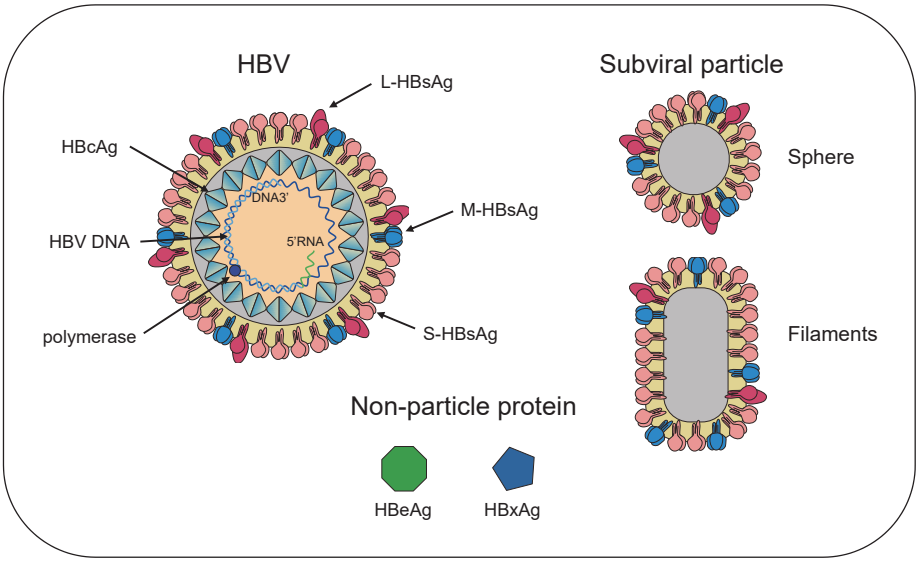


Fig. 1. Virion structure of HBV. HBV has L-HBsAg, M-HBsAg, and S-HBsAg as surface antigens. HBV genome is a partially double-stranded DNA, which exists in the core structure formed by HBc protein and binds to the polymerase. Other than infectious virion, spherical and filamentous particles lacking a core are produced from infected hepatocytes. Non-particulate proteins, HBeAg and HBxAg, are also produced.

molecular weight of 21 kDa. It encompasses 183 or 184 aa and is divided into two parts: 1) The N terminal 149 aa domain, essential for the self-assembly of capsids, and 2) the C terminal 34 aa domain, essential for the packaging of the pre-genome/HBV Pol complex [7, 18, 19].

HBV Pol is the product of the P gene and contains 832 or 845 aa. This protein has both DNA-dependent DNA polymerase activity and RNA-dependent DNA polymerase (reverse transcriptase) activity. In addition, HBV Pol has RNase H activity in the C-terminal domain and can degrade pregenomic RNA after synthesis of minus DNA strand. The full-length minus DNA strand serves as a template for plus strand DNA synthesis by the DNA-dependent DNA polymerase activity of the HBV Pol.

HBx is a 17 kDa regulatory protein encoded by the X open reading frame of HBV (Fig. 1). It is required for efficient transcription of cccDNA by interacting with Cullin4A-DDB1 [7, 20]. HBx is usually overexpressed in hepatocellular carcinoma (HCC) which eventually occurs after liver cirrhosis during chronic HBV infection. HBx promotes hepatocarcinogenesis by interfering the normal physiological function of the hepatocytes [21].

HBV induces many genetic and epigenetic alterations in infected hepatocyte and promotes the progression of hepatocellular carcinoma. HBV will damage host DNA and cause genomic instability by producing reactive oxygen species (ROS) and disturb the function of DNA repair enzymes [22]. HBV can also induce gene methylation, promote or repress several cellular signal transduction pathways, subsequently, suppress apoptotic process and improve viral replication [23, 24].

### *HBV infection and liver cancer*

Around the world, 2,000 million people are infected with HBV, and 350 million of them are suffering from chronic infection. More than 600,000 people die of HBV infection every year and cirrhosis and HCC account for 310,000 and 340,000 deaths, respectively [25, 26].

Chronic HBV infection is defined as more than six months' positivity of serum HBsAg [26]. About 25% of chronic HBV infection is estimated to progress HCC. The incident rate of hepatic cirrhosis by chronic HBV infection is annually 2-3% [27].

An association between the initial age of HBV infection and the incidence of chronic HBV infection was recognized. The risk to become chronic HBV infection after initial infection was 90% in newborn, 25-30% in children below five years, and < 5% in children above five years [28, 29].

### *Transmission of HBV to children*

HBV infects children during the prenatal as well as the postnatal period. In the prenatal period, HBV is transmitted from mother to child, which accounts

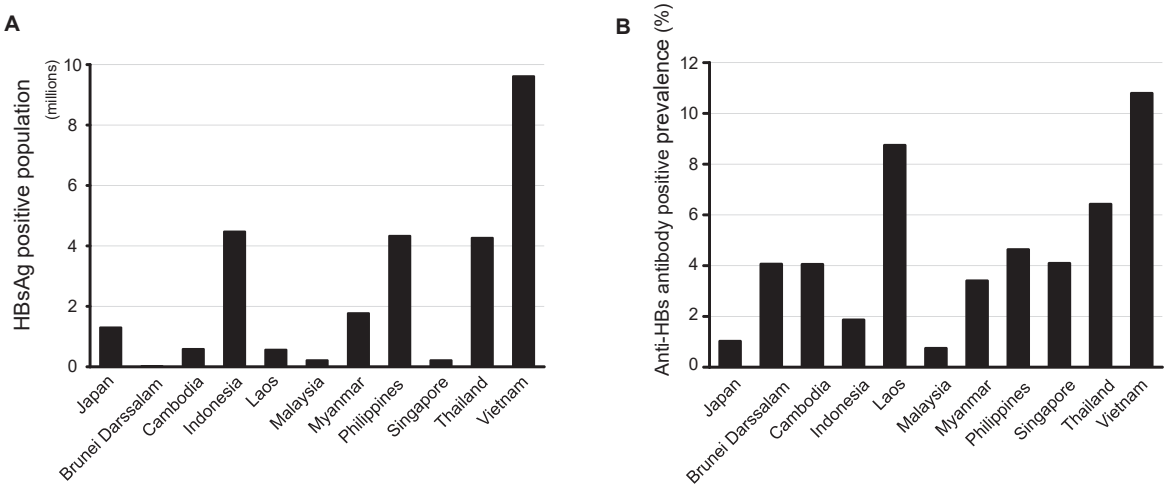


Fig. 2. (A) HBsAg positive population and (B) anti-HBsAg antibody positive prevalance in Southeast Asia and Japan [33].

for 50% of HBV chronic infection in endemic areas [26, 30]. In the postnatal period, transmission occurred from the environment, such as family members and the playmates [30]. Because HBV particle can survive under dry condition for more than a week, HBV can be transmitted horizontally among the family members [31]. The study in Alaskan families showed that HBsAg was positive in the 50% of the swab taken from toothbrush rack, 35.5% on baby bottles, 12,1% on the toys, and 7.1% from the kitchen, table, and benchtops [32].

***HBV infection in Southeast Asia and Japan***

The pooled analysis between Jan 1, 1965 and Oct 23, 2013 showed the number of people suffering from chronic HBV infection (Fig. 2A) and HBsAg (+) seroprevalence (Fig. 2B) [33]. Among countries in Southeast Asia, Malaysia showed the lowest rate of chronic HBV infection (0.74%), while Vietnam showed the highest rate (10.79%). Southeast Asia countries exhibited higher HBsAg seroprevalence than Japan (Fig. 2B). However, the number of people suffered from chronic HBV infection is relatively high in Japan, because it has more population than each country in Southeast Asia except Indonesia (Fig. 2A).

## Comprehensive prevention and its challenges

***Algorithm for the prevention system***

HBV infection in a pregnant woman poses a serious risk to her infant at birth, so the universal screening of HBV is necessary. If HBsAg is detected in a pregnant woman, both HBeAg and HBV DNA should be examined to confirm HBV infection (Fig. 3) [5].

The kits for detecting HBsAg have various sensitivity with relatively high accuracy. Mutations in the HBsAg genes sometimes happened, which cause failure of detection by kits using anti-HBsAg monoclonal antibodies [34]. In February 2019, 'Determine HBsAg 2' was introduced by Abbot as the most sensitive HBV rapid test with an analytical sensitivity of 0.1 IU/mL. The test can be applied to serum, plasma, or whole blood and only take 15 minutes [35].

Unfortunately, according to WHO, access to affordable hepatitis testing is limited. Only 9% of HBV-infected people can be diagnosed. Among those diagnosed, the treatment reaches only 8% [4]. HBs detection kit is also not sensitive enough to examine all pregnant women in the HBV epidemic area. For these reasons, mother-to-child HBV transmission still happens.

If a pregnant woman shows HBsAg and HBeAg double positive, HBIG should be provided to protect neonates from HBV infection. Combination of HBIG and HBV vaccine to the neonates from HBeAg positive mother enhanced the prevention efficacy up to 98% [36]. The effect of HBIG treatment to the neonates from HBeAg negative mother is still unclear. A retrospective study in Taiwan showed that there was no significant difference in HBsAg status of the children between HBIG treated (0.14%) and non-treated (0.29%) HBeAg negative mothers [37].

The concentration of HBV DNA in the serum represents the HBV status of the pregnant woman. The higher concentration of serum HBV DNA is detected, the higher frequency of HBV transmission to the fetus happens [38].

If the number of HBV DNA in a mother's serum exceeds 5 $\log_{10}$ copies/ml (20,000 IU/ml), the risk of HBV transmission to the neonates increases to 0.9%. In addition, if the serum HBV DNA level reached to 7 to 9 $\log_{10}$ copies/ml, transmission to the neonates dramatically increases [38]. Therefore, antiviral treatment in the mother showing a threshold level 20,000 IU/ml of HBV DNA is recommended. The daily treatment of tenofovir disoproxil fumarate (TDF) 300 from the 30th-32nd gestational week to 1 month after birth significantly reduced the rate of HBsAg positiveness in the children [39, 40].

HBV screening for pregnant women is conducted not all but in many countries. Thailand routinely conducts HBV screening and applies the universal HBV vaccination. However, the countries applying the HBV screening also have a different policy for the HBIG treatment to the children. The countries that apply HBIG treatment by only referred to HBsAg positive data are U.S.A., Italy, and Korea. The countries that apply HBIG treatment to the children born from both HBsAg and HBeAg double-positive mothers are Taiwan and Singapore [38].

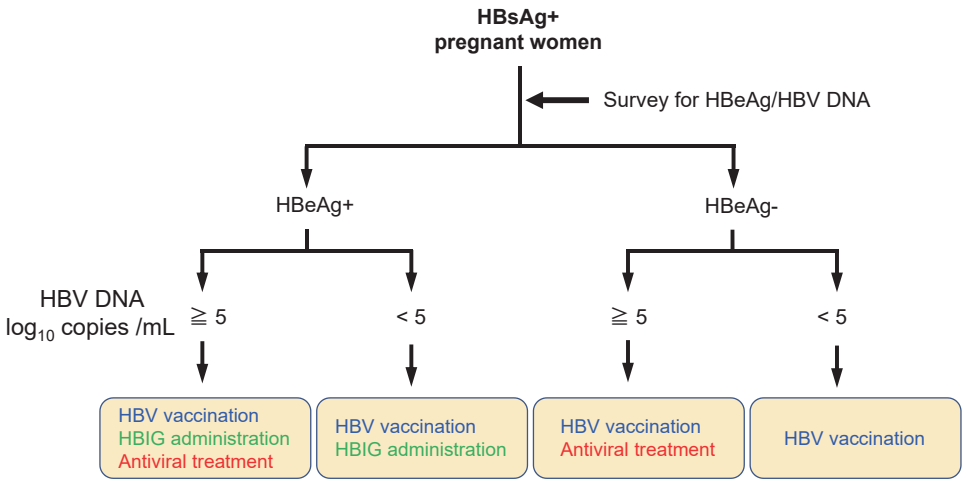


Fig. 3. HBV survey in pregnancy [5].

Japan is applying HBV screening to all pregnant women since 1985. The HBV vaccine and HBIG combination program for infants born from HBsAg (+) mother was adopted in 1986. Thirty years after the policy, the Japanese Ministry of Health, Labour and Welfare (MHLW) announced that the prevalence of HBsAg seropositive decreased to 0.033% among 27,240 children aged 0-15 years [41].

In Indonesia, HBV screening is not routinely administered to pregnant women. About 150,000 out of 5 million pregnant women possibly transmit HBV to the fetus each year. And 95% of fetuses may develop chronic infection [42].

### *HBV vaccination*

As of 2018, 189 countries have implemented universal HBV vaccination over the world [4]. However, the coverage of HBV vaccination varies depending on the country.

Taiwan is the first country that implemented the program since July 1984 [38, 43]. Taiwan succeeded to reduce the frequency of fetal HBV transmission from 38% to 4.6%. HCC incidence was also decreased from 0.92 to 0.23 per 100,000 people after vaccination [44].

In Indonesia, HBV universal vaccination was adopted since 1997. In 2012, the vaccination coverage was less than 50%. Children received three times of HBV vaccination were 73.9-94.1%. Among 967 children in five areas of Indonesia, HBsAg positive rate in preschool-aged children ranged from 2.1 to 4.2% and in school-aged children ranged from 0 to 5.9% [45].

Unfortunately, even in countries that are completely covered by HBV vaccination, the effectiveness does not reach 100%. Ten percent of the cases cannot be prevented by vaccination [38]. Several studies have shown an association between vaccine efficacy and maternal HBV status during pregnancy. The vaccine efficacy for children born from mother who was HBeAg (+) and HBeAg (-) was 89.5% and 95.6%, respectively [36, 46, 47]. In another study examining 2,356 children, children born from HBeAg (+) mother showed 9.26% of HBsAg positivity and 16.76% of anti-HBc positivity. In the study, children born from HBeAg (-) mother showed 0.23% of HBsAg positivity and 1.58% of anti-HBc positivity [38].

### *HBV therapy*

In order to reduce the morbidity and mortality related to chronic HBV infection, antiviral treatment is performed. The efficacy of HBV therapy is indicated by the reduction in HBsAg amount and/or HBV DNA load. In addition, the eradication of the virus, including cccDNA, is not an attainable goal, because cccDNA is highly stable and persists in the nucleus of hepatocytes [9].

## CONCLUSION

In order to reduce the risk of suffering from

HCC, comprehensive intervention for mother-to-child HBV transmission during the prenatal and postnatal period is required. Prenatal intervention can be achieved by conducting HBV screening on all pregnant women. Prenatal intervention can also be achieved by providing antiviral therapy to women showing plasma HBV DNA level more than 20,000 IU/ml. Subsequently, postnatal intervention can be achieved by HBV vaccination to all newborns. While indication for HBIG treatment depends on the seroprevalence of HBeAg and HBV DNA during maternity.

In the future, it is necessary to optimize the HBV prevention program. Even in developing countries, the coverage ratio of HBV vaccination is still low. Also, the application of additional intervention is still in progress. By following the WHO program, we expect hepatitis B will be successfully eliminated by 2030.

## *AUTHOR CONTRIBUTIONS*

AMH, HI, and HY wrote the manuscript. AVK, DD and YK[1)] prepared figures. YK[1,4)] edited English. KN, HI, and HY reviewed the manuscript. All authors read and approved the final manuscript.

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## *CONFLICTS OF INTEREST*

The authors declare no conflicts of interest.

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