Chapter 19
Immunoprophylaxis of Hepatitis B Virus Infection and Its Sequelae

Mei-Hwei Chang

Introduction

Hepatitis B virus (HBV) infection is a major health problem in human. It can cause acute, fulminant, or chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC). More than 780,000 people die every year due to the acute or chronic consequences of hepatitis B (http://wwww.who.int/mediacentre/factsheets/fs204/en/). It is estimated that 2 billion people had been infected by HBV, and *approximately 240 million people have chronic HBV infection worldwide* [1]. Liver cancer represents 6 % and 9 % of the global cancer incidence and mortality burden, respectively. With an estimated 746,000 deaths in 2012, liver cancer is the second most common cause of death from cancer worldwide [2]. Chronic HBV infection is a major risk factor for the development of HCC. The risk of HCC associated with seropositivity for HBsAg ranges from 5-fold to 98-fold with a population attributable risk of 8–94 % [3]. HCC is one of the five most common sites of cancer diagnosed. Unfortunately, the response to therapy for HCC is generally poor and the recurrence rate is high.

In spite of the progress of antiviral therapy in patients with chronic hepatitis B to suppress viral replication and to reduce liver inflammation and complication, the current result of viral and disease elimination is still very limited. To control hepatitis B virus infection and its sequelae, prevention is better than therapy. Immunoprophylaxis is the best method to prevent HBV infection. The development of HBV vaccine using HBsAg protein as the immunogen to induce the protective antibody (anti-HBs) against HBV infection shed light on the elimination of HBV infection and its sequelae. Through three decades' experience and cumulated data, we are confident that immunoprophylaxis is safe and successful to protect people from HBV infection and its related diseases.

M.-H. Chang, M.D. (✉)
Department of Pediatrics, and Hepatitis Research Center, National Taiwan University Hospital, No. 8, Chung-Shan S. Road, Taipei, Taiwan
e-mail: changmh@ntu.edu.tw

Y.-F. Liaw, F. Zoulim (eds.), *Hepatitis B Virus in Human Diseases*, Molecular and Translational Medicine, DOI 10.1007/978-3-319-22330-8_19

Transmission Routes of HBV: The Importance of Mother-to-Infant Transmission and Early Prevention

HBV infection is transmitted through either mother-to-infant route or horizontal route. An incubation period of 6 weeks to 6 months, mostly around 75 days, usually precedes the presentation of hepatitis B. In endemic areas such as Asia where mother-to-infant transmission is the major route of transmission, HBV infection develops mainly during infancy and early childhood. Even in endemic areas like Africa where horizontal transmission of HBV in early childhood was considered as the route of transmission previously, infants' HBsAg seropositive rates were reported to be 8.1 % among 0–6-months-olds, and 8.9 % among 6–12 months olds in one study [4], and 53.8 % among the live births of HBeAg positive mothers in another study [5]. The importance of early prevention against both mother-to-infant transmission and horizontal transmission of HBV is thus evident and stressed in Africa [6].

The age at which HBV infection occurs is an important factor affecting the outcome of HBV infection (Table 19.1). The earlier the infection occurs, the higher is the risk for chronicity. With no immunoprophylaxis, more than 90 % of infants who were infected by their HBeAg/HBsAg positive mothers will develop chronic HBV infection during follow-up [7] This may be explained by the very high virus amount transmitted to the neonate with physiologic immature immune system. The chronicity rate after HBV infection is decreased to approximately one quarter (23 %) in children infected at preschool age and in young adults to 2.7 % [8, 9]. Perinatal transmission decreased to <5 % if the mother was HBsAg positive but negative for HBeAg negative.

Intrauterine infection occurs rarely in <5 % of the infants to HBeAg and HBsAg positive mothers. In our study in Taiwan during 10 years, 2.4 % of the 665 infants of HBeAg and HBsAg positive mothers were seropositive for HBsAg at birth, suggesting intrauterine infection [10]. They remained HBsAg positive at 12 months of

Table 19.1 Maternal HBV sero-status and age at infection are important factors affecting the outcome of HBV infection in children born before versus after the HBV immunization program

	Without immunoprophylaxis	With immunoprophylaxis at infancy
Infant of HBsAg(+), HBeAg(+) mother	>95 % infected, ≥90 % chronicity rate[a] among infected infants [6]	Vaccine + HBIG → 10 % chronic infection [54]
Infant of HBsAg(+), HBeAg(−) mother	<5 % chronicity rate, with risk of FH or AH [11, 12]	0.29 % chronic infection if no HBIG at birth, 0.14 % if with HBIG, risk of FH or AH reduced [54]
Toddler	5.0 % infected, chronicity rate among infected 23 % [7]	–
Young adult	1.5 % infected, chronicity rate among infected 2.7 % [8]	–

FH fulminant hepatitis, *AH* acute hepatitis, *HBIG* hepatitis B immunoglobulin

[a]Chronicity Rate = rate of HBsAg(+) >6 months

age. Transplacental leakage of HBeAg-positive maternal blood, which is induced by uterine contractions during pregnancy and the disruption of placental barriers, is the most likely route to cause HBV intrauterine infection [11].

Acute or fulminant hepatitis B can occur in infancy. The incidence of fulminant hepatitis B is higher in infancy than in other age periods. Mother-to-infant transmission, mainly from HBeAg negative, HBsAg positive mothers, is the most important route of transmission for acute or fulminant hepatitis in infancy [12, 13].

Active and/or Passive HBV Immunization

HBV immunization can be classified into passive immunization and active immunization. Passive immunization using hepatitis B immunoglobulin (HBIG) provides temporary immunity, while active immunization by vaccine yields long-term immunity. Perinatal transmission is the most important transmission route of HBV, particularly in endemic areas, and therefore, prevention by active and passive immunization against HBV should be initiated at birth. Additional doses of HBV vaccine should be given during infancy.

Other prevention modalities, such as screening the blood products, proper sterilization of injection needles and syringes, and avoidance of risky behaviors, such as parenteral drug abuse, tattoo, or skin piercing to prevent horizontal transmission are also important. Many countries with low prevalence of HBV infection also have HBV vaccination program for adolescents to prevent the exposure to HBV by sexual contacts or other risk behaviors. But the program is not as successful as the infantile HBV immunization strategy.

Passive Immunization Against HBV Infection Using HBIG

HBIG is prepared from the pooled plasma of donors who have high levels of anti-HBs. During the process of extraction for anti-HBs, viruses are inactivated, and solvents used in the preparation are removed. It excluded the products tested positive for HBsAg, anti-HCV, and HIV. It is used for post-exposure prophylaxis (passive immunoprophylaxis) of HBV infection.

HBIG was given immediately after birth to infants of HBeAg-positive HBsAg carrier mothers. In comparison to the 91 % of HBsAg carrier rate among infants without immunoprophylaxis, the HBsAg carrier rate was 26 % among infants who received three doses of HBIG at birth, 3 and 6 months old, and was 54 % in those who received a single 1.0 ml dose of HBIG at birth. The prevention efficacy was 45 % by one dose of 1.0 ml HBIG and 75 % by three doses ofHBIG, respectively [14].

Active Immunization Against HBV Infection Using Hepatitis B Vaccine

Currently, there are two kinds of HBV vaccine on the market, the plasma-derived vaccine and the recombinant vaccine. The first HBsAg-based highly purified and inactivated vaccine was made by Dr. Maurice Hilleman from chronic HBV infected subject' serum [15]. In order to produce a safe vaccine, stringent treatments with pepsin, urea, and formaldehyde and rigorous filtration to destroy all viruses, and chimpanzees test was conducted [16]. The plasma vaccine was approved by FDA of the USA in 1981 [17]. By inserting the gene coding for HBsAg, HBsAg was expressed in yeast to develop the recombinant HBV vaccine [18] and was licensed in 1986 [19]. Gradually, recombinant vaccine replaced plasma vaccine, and becomes the main vaccine used worldwide.

Active immunization with three or four doses of HBV vaccine without HBIG was proved to be immunogenic in more than 90 % of infants of non-carrier mothers or HBeAg-negative carrier mothers. Pilot clinical trial revealed that for infants of HBsAg negative mothers, the first dose of vaccine at 1 week stimulated anti-HBs within 1 month in 48 % of the neonates, and in 91 % at 2 months after the second dose. By the age of 6 months and 7 months, 96 % and 100 % vaccinees developed anti-HBs after a third dose, respectively [20].

For infants of HBeAg and HBsAg seropositive mothers, 23 % was HBsAg(+) after three doses of HBV plasma vaccine given at 1 week, 1 month, and 6 months of age, while the HBsAg positive rate was 88 % in the unvaccinated infants. The prevention efficacy of using HBV vaccines was around 75 % (Beasley RP, et al. Unpublished data).

Active Plus Passive Immunization Against HBV Infection

Clinical trial combining HBIG immediately after birth followed by HBV vaccination for infants of HBeAg positive, HBsAg carrier mothers was conducted in Taiwan. The prevention efficacy was 94 %, which is superior to HBIG alone (71 %) or vaccination alone (74 %) [21, 22]. This best result of HBV prevention against perinatal transmission of HBV infection by highly infectious mothers established the ground of the later universal HBV immunization strategies and program used currently. A subsequent study using HBIG at birth and three 5-μg doses of recombinant HBV vaccine, only 4.8 % of the high risk infants became chronic carriers, with a >90 % level of protection and a rate comparable with that seen with HBIG and plasma derived hepatitis B vaccine [23]

The Timing, Strategies, and Global Status of the HBV Immunization Programs

Since the most common and important transmission route is mother-to-infant transmission during perinatal period, the most appropriate timing for HBV immunization should be started at birth, and additional doses of vaccine should be given in infancy to elicit early and long term protection. In the world first universal hepatitis B immunization program in Taiwan, immunization was given at birth with passive HBIG, and then three or four doses of hepatitis B vaccine. The strategy of universal HBV vaccination in infancy is more effective than selective immunization for high-risk groups.

There are three major strategies of HBV Immunization and screening of maternal HBV markers during pregnancy in different countries, depending on their epidemiologic features of HBV infection and available resources (Fig. 19.1):

Strategy 1. Combination of active and passive HBV immunization with maternal screening of HBeAg and HBsAg; this is conducted in highly endemic areas such as Taiwan.

Strategy 2. Combination of active and passive HBV immunization with maternal screening of HBsAg; it is conducted in areas with adequate resources, such as in the USA and Italy [24, 25].

Strategy 3. Active HBV immunization without maternal screening and HBIG. It is conducted in areas with limited resources.

The cost-effectiveness per case prevented by Strategy 2 was estimated to be highest; for Strategy 3 was lowest [26]. However, the protection for high risk mothers' infants is higher in Strategy 1 or 2 than strategy 3.

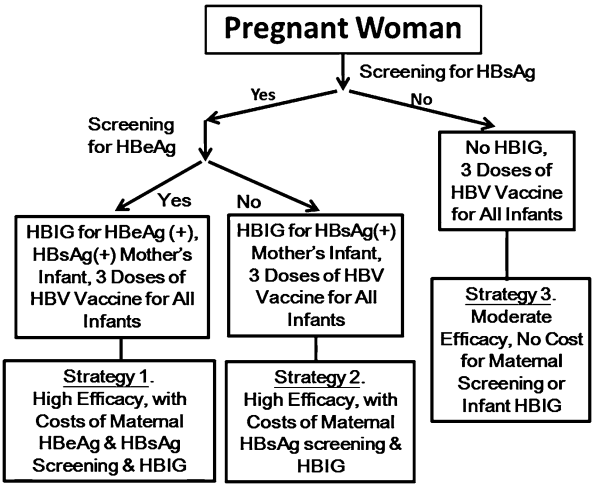

Fig. 19.1 Three major strategies of universal HBV immunization in the world countries

Universal Maternal Screening of HBeAg and HBsAg and Combining Active and Passive HBV Immunization for Infants (Strategy 1)

The world's first universal hepatitis B vaccination program was implemented in Taiwan using strategy 1 since July 1984. Screening for maternal serum HBsAg and HBeAg during pregnancy is conducted. Infants of highly infectious mothers with positive serum HBeAg and HBsAg received HBIG within 24 h after birth in addition to three or four doses of HBV vaccine during infancy. Infants of mothers with negative HBsAg, or positive HBsAg but negative HBeAg, or unknown HBV status received three or four doses of HBV vaccine only. The coverage rate of hepatitis B vaccine for neonates is around 94–99 % [27].

Universal Maternal Screening of HBsAg and Combining Active and Passive Immunization for Infants (Strategy 2)

In countries with low prevalence of HBV infection and better resources, HBIG is given to newborns of all HBsAg-positive mothers regardless of their HBeAg status, and three doses of HBV vaccine are given to all infants.

Since 1988, the Advisory Committee on Immunization Practices (ACIP), USA has recommended universal screening of pregnant women for HBsAg during the early prenatal period in each pregnancy. *All infants should receive HBV vaccination.* Infants of HBsAg seropositive mothers should receive appropriate immunization with HBIG and HBV vaccine to prevent perinatal transmission [24]. Although this strategy can save the cost of maternal screening for HBeAg, the wider use of HBIG in infants of HBsAg mothers regardless of maternal HBeAg status increases the cost.

Active HBV Immunization in Infancy Without Maternal Screening and HBIG at Birth (Strategy 3)

Using three or four doses of HBV vaccine to all infants without screening maternal HBV markers is a common practice of universal immunization program in the world. It can save the cost not only for maternal screening of HBV markers, but also the cost of HBIG. This policy is practically applicable in countries with limited resources. The results of prevention is good according the report of studies in Thailand and other countries [28].

In many endemic countries with limited resources, three doses of hepatitis B vaccine are given to all infants, regardless of the HBeAg status in HBsAg carrier mothers. This strategy offers an efficacy of around 75–80 % for infants of HBeAg-positive highly infectious mothers. Nevertheless, the cost of maternal screening and subsequent use of HBIG in the newborns can be avoided.

Global Status of the HBV Immunization Program

In 1992, the World Health Assembly passed a resolution to recommend global vaccination against hepatitis B. In 2009 WHO recommended that all infants receive the hepatitis B vaccine as soon as possible after birth, preferably within 24 h. The birth dose should be followed by two or three doses to complete the primary series.

Hepatitis B vaccine for infants was introduced nationwide in 183 countries by the end of 2013. Global coverage of infants with three doses of HBV vaccine in 1990 was only 1 %. It is gradually increased and was estimated to be as high as 81 % in 2013. A birth dose for hepatitis B vaccine was advocated by WHO, and was introduced in 93 countries by 2013, with a global coverage rate estimated as 38 %, reaching 79 % in the Western Pacific, but only 11 % in the African Region (WHO, Global immunization data) (http://www.who.immunization/monitoring_surveillance/data/en/).

The Preventive Effect of HBV Infection and Related Diseases by Immunization

Evidences support that hepatitis B vaccine provides effective protection against HBV infection and its complications, including fulminant hepatitis B, chronic hepatitis B, and its related HCC. It is the first successful cancer preventive vaccine in human [29]. It is also the first vaccine against a chronic disease [30].

Prevention of Acute Hepatitis B

Universal HBV immunization program has reduced the incidences of acute hepatitis B [31, 32]. After 25 years of universal HBV immunization in Taiwan, acute hepatitis B among adolescents and young adults ≤25 years old was reduced, making infants and the unvaccinated 25–39-year-old cohort additional targets for preventing acute hepatitis B (Fig. 19.2a). Vaccinated infants (0.78/100,000) had higher rates than those aged 1–14 years (0.04/100,000), due to breakthrough HBV infection from mother-to-infant transmission [32].

Prevention of Fulminant Hepatitis B

The mortality rateof fulminant hepatitis per 10^5 infants was reduced significantly from 5.1 in those who were born before the HBV vaccination program (1975–1984) to 1.71 in those born after the vaccination program in Taiwan (1985–1998) [33] *(Fig.19.2b). The mortality in vaccinated birth cohorts decreased further by more than 90 % from 1977–1980 to 2009–2011* [34].

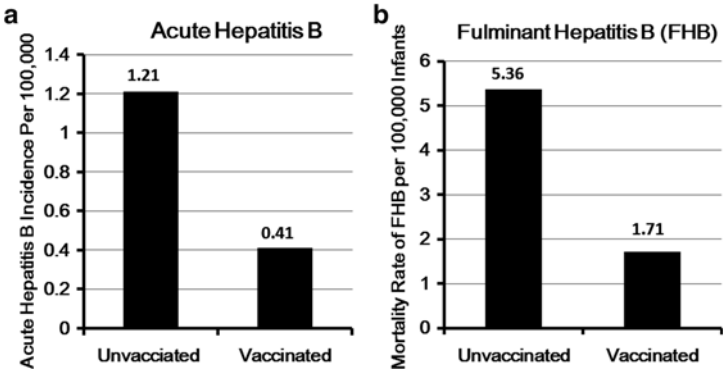

Fig. 19.2 (**a**) After universal hepatitis B immunization, the incidence rate of acute hepatitis B is also reduced in the vaccinated birth cohorts of 15–19 years old [32]; (**b**) the mortality rate of fulminant hepatitis (FH) B in infants is also reduced [33]

After universal HBV vaccination in Taiwan, HBV was found to very rarely cause fulminant hepatitis in children age ≥1 year, but remained a significant cause of fulminant hepatitis in infants [35]. The incidence rate ratio of patients age <1 year to those ages 1–15 years was 54.2 for HBV-positive fulminant hepatitis. HBV-positive fulminant hepatitis was prone to develop in infants born to HBeAg-negative, HBsAg-carrier mothers; these infants had not received HBIG according to the vaccination program in place. Maternal HBsAg was found to be positive in 97 % of the infants with fulminant hepatitis B, and maternal HBeAg was found to be negative in 84 % of these infants.

Reduction of Chronic HBV Infection Rate

Universal hepatitis B vaccination programs have effectively reduced the chronic HBV infection rate in many endemic countries. The protective efficacy of the hepatitis B vaccination program in infants born to highly infectious mothers and received HBIG and vaccine on schedule was approximately 85–90 %. The early mass survey data after the universal HBV vaccination program in Taiwan revealed that the protective efficacy was 86 % in the HBIG plus HBV vaccine group and 78 % in those with only three doses of HBV vaccine alone [36].

The HBsAg seropositive rates declined to below 1 % in most countries where universal vaccination programs have been successfully conducted [37]. Serial seroepidemiologic studies started just before the universal vaccination program and every 5 years in the post-vaccination era in Taiwan in the past three decades [38–42]. The results revealed that HBsAg seroprevalence rate among children declined from 9.8 % before the HBV immunization program to 0.5–1.2 % after the program. It implicates that Taiwan has been changed from an HBV endemic country to a low endemic coun-

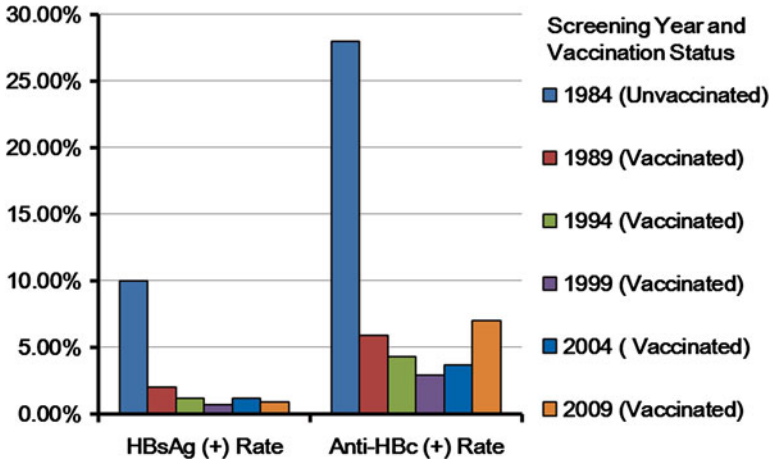

Fig. 19.3 Comparison of the HBsAg seropositive rates and anti-HBc seropositive rates among children born before versus after the launch of universal hepatitis B immunization program in Taiwan

try by the HBV immunization program (Fig. 19.3). The HBV infection rate (anti-HBc seropositive rate) declined from 38 to 16 % and further to 4.6 % in children 15–20 years after the HBV immunization program in Taiwan [42] (Fig. 19.3). Twelve years after integration of universal hepatitis B vaccine into the national expanded program on immunization (1992) in Thailand, the HBsAg and anti-HBc seropositive rate was reduced from 4.3 % and 15.8 % among those born before the program, to 0.7 % and 2.9 % among 6 months to 18 years old born after, respectively [28].

In Gambia, villages with good HBV immunization program, vaccine efficacies in 1993 against HBV infection and chronic HBsAg carriage were 94.7 % and 95.3 %, respectively [43]. During 1986–1990, the Gambia Hepatitis Intervention Study (GHIS) comparing fully vaccinated vs. unvaccinated GHIS participants among the allocated 125,000 infants. HBV infection was 0.8 % (2/255) vs. 12.4 % (59/475), suggesting a vaccine efficacy of 94 % [44]. Study in Gambia also showed a lower anti-HBc positive rate of 27.4 % (70/255) among vaccinated participants in comparison to 56.0 % (267/475) among the unvaccinated subjects.

Prevention of Liver Cancer by HBV Immunization

Prevention of chronic HBV infection by immunization can effectively reduce the incidence of liver cancer. HBV vaccine is the first human cancer preventive vaccine successfully preventing the development of liver cancer [29]. Taiwan has high incidence rates of HBV infection and HCC in both children and adults. Children with HCC in Taiwan are nearly 100 % HBsAg seropositive, 86 % of them are HBeAg negative, and their mothers are mostly (94 %) HBsAg seropositive [45]. The

Table 19.2 Impact of universal HBV immunization on HCC incidences among <20 Years old

	Diagnosed age of HCC	HCC incidence/100,000 person-year		% Reduction of HCC (after immunization)
		Before HBV immunization	After HBV immunization	
Taiwan [47][a]	6–9 Years 10–14 Years 15–19 Years	0.51 0.60 0.80	0.15 0.19 0.16	70 % 68 % 70 %
Khon Kaen, Thailand[b]	5–18 Years	0.097	0.024	75 %
Alaska Natives, USA[b]	<20 Years	0.5–3.0	0 after 1999	[c]Nearly 100 %

[a]Analysis for HCC incidences according to the birth year before versus after the vaccination program
[b]Analysis for HCC incidences according to the year of diagnosis before versus after the vaccination program
[c]Due to small population

histologic features of the HCC are similar to that in adult HCC. Most (80 %) of the non-tumor liver tissues have liver cirrhosis. Integration of HBV genome into host genome was demonstrated in the childhood HCC tissues [46].

The world first universal hepatitis B vaccination program in Taiwan has demonstrated significant reduction of the average annual incidence rate of HCC in children aged 6–14 years. It decreased from 0.52–0.54 cases per 100,000 children of the birth cohort born before the HBV vaccination program, to 0.13–0.20 cases in those born after the HBV vaccination program [47] (Table 19.2). According to a 20-year follow-up study of national cancer surveillance in Taiwan, the effect of HCC prevention by universal HBV vaccination was observed not only in children but also extended to adolescents, with an age- and sex-adjusted relative risk of 0.31 for persons vaccinated at birth [48]. Studies in Khon Kaen of Thailand also showed declines in the incidence of childhood HCC as a result of at-birth HBV immunization program [49]. Another study in Alaska, USA revealed effective reduction of HCC incidence, from 3 per 100,000 in 1984–1988 to undetectable after 1999 among Alaska Native children and adolescents under 20 years old, after 25 years of universal neonatal HBV immunization [50].

Remaining Problems for a Better Control of Hepatitis B and Its Sequelae

Low Vaccine Coverage Rate Due to Inadequate Resources or Ignorance

According to WHO global immunization data, global coverage rate of infants with three doses of HBV vaccine was estimated to be 81 % in 2013, as high as 92 % in Western Pacific Region, 89 % in Americas, 83 % in Eastern Mediterranean Region,

and 81 % in European Region, but lower rate as 74 % in South-East Asia Region, and 76 % in Africa. The coverage rate of a birth dose for hepatitis B vaccine reached 79 % in the Western Pacific, but only 11 % in the African Region (http://www.who.immunization/monitoring_surveillance/data/en/)

In some countries although universal HBV vaccination have been launched, the cost of vaccine is not covered by the government which may hamper the increase of immunization coverage rate. Further increase of the global coverage rates of neonatal dose and infantile HBV vaccination is important toward a better control of hepatitis B and related diseases. To provide free charged HBV vaccines for infants in developing countries may enhance effectively the vaccine coverage rate. It is particularly urgent in areas where HBV infection and HCC are endemic.

Poor compliance of the HBV vaccination due to ignorance or anxiety induced anti-vaccine act is still a problem in areas with adequate resources. *Incomplete vaccination had an independent effect on the mortality of FHF, showing an HR of 4.97 (3.05–8.11; $P \leq 0.0001$) after adjustment for maternal HBsAg serostatus* [51].

Education to enhance the understanding of the benefit and the extremely low vaccine-related adverse reactions of HBV vaccine is needed to improve the coverage rate. Previously an association between central nervous system demyelinating diseases and hepatitis B vaccine was implied [52]. Later evidence indicated that HBV vaccine does not increase the risk of onset or relapse of central nervous system demyelinating diseases [53].

HBV vaccination has not captured sufficient attention from the government in developed countries with relatively low prevalence of HBV infection, particularly under the competition of other new vaccines [54]. Competition of how to persuade the government of those countries to pay more attention to the low cost and very high efficacy of disease prevention is another important task to be done.

Breakthrough HBV Infection In Spite of Complete Immunization

In spite of complete immunization with combination of passive (HBIG) and active (vaccine) immunization, breakthrough infection may still occur. The most important risk factor is highly infectious mother with positive HBeAg and high viral load [10, 11]. The predictive breakthrough HBV infection rates of vaccinated infants at maternal viral load levels of 7, 8, and 9 log10 copies/ml were 6.6 %, 14.6 %, and 27.7 %, respectively [55].

In children born to HBeAg seropositive HBsAg carrier mothers, despite HBIG and three doses of HBV vaccine, 9.26 % still became HBsAg seropositive. In contrast, children born to HBeAg negative, HBsAg seropositive mothers, only 0.29 % became HBsAg positive if no HBIG was given at birth, and 0.14 % became HBsAg positive if HBIG was given at birth [56].

Another cause of breakthrough HBV infection is the emergence of hepatitis B surface gene mutants [57]. The prevalence rate of the hepatitis B surface gene *a* mutant increased from 7.8 % in the unvaccinated to 22–28 % among vaccinated HBsAg positive school children. The prevalence rate of the mutants among the total population has remained stationary for 20 years after the launch of the HBV immunization program because HBV vaccination reduced the HBsAg seropositive rates in the vaccinated population.

The natural course of surface gene mutant infected subject remains unclear. A recent study revealed that HBsAg-mutant HBV was detected in three of eight (38 %) HBV DNA-positive children with HCC. Higher frequency of HBV genotype C and a higher ALT level during surface mutant viremia were observed in codon 110–129 surface gene mutants than in codon 144–145 mutants. Immunized children carrying HBsAg-mutant HBV may develop hepatitis activity, HBeAg seroconversion, and a low viremic state earlier than those carrying wild-type HBV [57, 58].

Genetic hypo-responsiveness to vaccine, and immune compromised hosts are other causes of breakthrough HBV infection [59]. Immunosuppressive conditions, such as advanced HIV infection, chronic liver disease, chronic renal failure and diabetes have been demonstrated to be associated with reduced immunogenicity of hepatitisB vaccine.

The Possibilty of Blocking Mother-to-Infant Transmission of HBV Using Antiviral Agent in Addition to Immunoprophylaxis

Continuing efforts are ongoing to seek for other method to prevent breakthrough HBV infection by highly infectious mothers. Preliminary clinical trials using nucleoside analogue during the last trimester of pregnancy to prevent mother-to-infant transmission have been reported [60–62]. Lamivudine or telbivudine during late pregnancy in mothers with high viral load may reduce, but cannot prevent all the mother-to-infant transmission of HBV. It appeared safe in short term follow-up for mothers and infants [63]. *A study in pregnant cohorts with HBV DNA ≥7 log IU/ml showed significant reduction of perinatal transmission to 2 and 0 % in tenofovir disoproxil fumarate or lamivudine treated, compared with 20 % in untreated cohort* [64]. Tenofovir disoproxil fumarate for highly viremic mothers at 30 to 32 weeks of pregancy was also studied. The results indicated a significant reduction of HBV DNA sero-positive rate at birth and HBsAg sero-positive rate at 6 month old in their children, in comparison to non-treated control group [65].

In addition to the cost for screening viral load before enrolment and the cost for antiviral agent, the problems of discontinuation of oral antiviral agent in postpartum mothers need to be addressed. Further studies to clarify the long term safety, benefit, and efficacy of nucleoside analogue in the prevention of intrauterine infection are needed.

Future Prospects

Existing data already demonstrated the remarkable effectiveness of HBV immunization in preventing approximately 90 % of chronic HBV infection and 65–70 % of acute/fulminant hepatitis B. To eliminate HBV infection and its sequelae in the world, further increase of the global coverage rates of HBV vaccine particularly in areas with limited resource and countries with no universal HBV immunization program, and better strategies against breakthrough HBV infection mainly from mother-to-infant transmission are of vital importance.

Hepatitis B vaccine is the first cancer preventive vaccine in human. With the success of HBV vaccination to prevent liver cancer, the concept of a cancer preventive vaccine can be extended further to prevent the infection of other microorganisms and their related cancers.

Acknowledgement Grant support from National Health Research Institute (NHRI-EX103-10001BI)

References

1. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012;30:2212–9.
2. Theise ND. Liver cancer. In: Stewart BW, Wild CP, editors. World cancer report 2014. Lyon, France: IARC, WHO press; 2014.
3. Chen CJ, Yu MW, Liaw YF. Epidemiological characteristics and risk factors of hepatocellular carcinoma. J Gastroenterol Hepatol. 1997;12:s294–308.
4. Vardas E, Mathai M, Blaauw D, et al. Preimmunization epidemiology of hepatitis B virus infection in South African children. J Med Virol. 1999;58:111–5.
5. Sangare L, Sombie R, Combassere AW, et al. Antenatal transmission of hepatitis B virus in an area of HIV moderate prevalence, Burkina Faso. Bull Soc Pathol Exot. 2009;102:226–9.
6. Howell J, Lemoine M, Thursz M. Prevention of materno-foetal transmission of hepatitis in sub-Saharan Africa: the evidence, current practice and future challenges. J Viral Hepat. 2014;21:381–96.
7. Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. N Engl J Med. 1975;292:771–4.
8. Beasley RP, Hwang LY, Lin CC, et al. Incidence of hepatitis B virus infections in preschool children in Taiwan. J Infect Dis. 1982;146:198–204.
9. Beasley RP, Hwang LY, Lin CC, Ko YC, Twu SJ. Incidence of hepatitis among students at a university in Taiwan. Am J Epidemiol. 1983;117:213–22.
10. Tang JR, Hsu HY, Lin HH, Ni YH, Chang MH. Hepatitis B surface antigenemia at birth: a long-term follow-up study. J Pediatr. 1998;133:374–7.
11. Lin HH, Lee TY, Chen DS, et al. Transplacental leakage of HBeAg-positive maternal blood as the most likely route in causing intrauterine infection with hepatitis B virus. J Pediatr. 1987;111:877–81.
12. Shiraki K, Yoshihara N, Sakurai M, et al. Acute hepatitis B in infants born to carrier mother with the antibody to hepatitis B e antigen. J Pediatr. 1980;97:768–70.
13. Chang MH, Lee CY, Chen DS, Hsu HC, Lai MY. Fulminant hepatitis in children in Taiwan: the important role of hepatitis B virus. J Pediatr. 1987;111:34–9.

14. Beasley RP, Hwang LY, Stevens CE, et al. Efficacy of hepatitis B immune globulin for prevention of perinatal transmission of the hepatitis B virus carrier state: final report of a randomized double-blind, placebo-controlled trial. Hepatology. 1983;3:135–41.
15. Hilleman MR. Overview of the needs and realities for developing new and improved vaccines in the 21st century. Intervirology. 2002;45:199–211.
16. Buynak EB, Roehm RR, Tytell AA, et al. Vaccine against human hepatitis B. JAMA. 1976;235:2832–4.
17. Maupas P, Chiron JP, Barin F, et al. Efficacy of hepatitis B vaccine in prevention of earl HBsAg carrier state in children. Controlled trial in an endemic area (Senegal). Lancet. 1981;1: 289–92.
18. Valenzuela P, Medina A, Rutter WJ, Ammerer G, Hall BD. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature. 1982;298:347–50.
19. Hilleman MR. Yeast recombinant hepatitis B vaccine. Infection. 1987;15:3–7.
20. Lee GC, Hwang LY, Beasley RP, Chen SH, Lee TY. Immunogenicity of hepatitis B virus vaccine in healthy Chinese neonates. J Infect Dis. 1983;148:526–9.
21. Beasley RP, Hwang LY, Lee GC, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. Lancet. 1983;2: 1099–102.
22. Lo KJ, Tsai YT, Lee SD, et al. Combined passive and active immunization for interruption of perinatal transmission of hepatitis B virus in Taiwan. Hepatogastroenterology. 1985;32:65–8.
23. Stevens CE, Taylor PE, Tong MJ, et al. Yeast-recombinant hepatitis B vaccine. Efficacy with hepatitis B immune globulin in prevention of perinatal hepatitis B virus transmission. JAMA. 1987;257:2612–6.
24. Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. MMWR Recomm Rep. 2005;54:1–31.
25. Bonanni P. Implementation in Italy of a universal vaccination programme against hepatitis B. Vaccine. 1995;13 Suppl 1:S68–71.
26. Vimolket T, Poovorawan Y. An economic evaluation of universal infant vaccination strategies against hepatitis B in Thailand: an analytic decision approach to cost-effectiveness. Southeast Asian J Trop Med Public Health. 2005;36:693–9.
27. Chen DS, Hsu NHM, Sung JL, et al. The Hepatitis Steering Committee, The Hepatitis Control Committee: A mass vaccination program in Taiwan against hepatitis B virus infection in infants of hepatitis B surface antigen carrier-mothers. JAMA. 1987;257:2597–603.
28. Chongsrisawat V, Yoocharoen P, Theamboonlers A, et al. Hepatitis B seroprevalence in Thailand: 12 years after hepatitis B vaccine integration into the national expanded programme on immunization. Trop Med Int Health. 2006;11:1496–502.
29. Chang MH. Prevention of hepatitis B virus infection and liver cancer. Recent Results Cancer Res. 2014;193:75–95.
30. Lavanchy D. Viral hepatitis: global goals for vaccination. J Clin Virol. 2012;55:296–302.
31. Wasley A, Miller JT, Finelli L, Centers for Disease Control and Prevention (CDC). Surveillance for acute viral hepatitis—United States, 2005. MMWR Surv Summ. 2007;56:1–24.
32. Su WJ, Liu CC, Liu DP, et al. Effect of age on the incidence of acute hepatitis B after 25 years of a universal newborn hepatitis B immunization program in Taiwan. J Infect Dis. 2012;205:757–62.
33. Kao JH, Hsu HM, Shau WY, Chang MH, Chen DS. Universal hepatitis B vaccination and the decreased mortality from fulminant hepatitis in infants in Taiwan. J Pediatr. 2001;139: 349–52.
34. Chiang CJ, Yang YW, You SL, Lai MS, Chen CJ. Thirty-year outcomes of the National Hepatitis B Immunization Program in Taiwan. JAMA. 2013;310:974–6.
35. Chen HL, Chang CJ, Kong MS, et al. Pediatric fulminant hepatic failure in endemic areas of hepatitis B infection: 15 years after universal hepatitis B vaccination. Hepatology. 2004;39:58–63.

36. Hsu HM, Chen DS, Chuang CH, et al. Efficacy of a mass hepatitis B vaccination program in Taiwan: studies on 3464 infants of hepatitis B surface antigen-carrier mothers. JAMA. 1988;260:2231–5.
37. Chen ST, Chang MH. Epidemiology and natural history of hepatitis B in children. In: Jonas M, editor. Viral hepatitis in children. New York: Humana Press; 2010. p. 13–28.
38. 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.
39. Chen HL, Chang MH, Ni YH, et al. Seroepidemiology of hepatitis B virus infection in children: ten years of mass vaccination in Taiwan. JAMA. 1996;276:906–8.
40. Ni YH, Chang MH, Huang LM, et al. Hepatitis B virus infection in children and adolescents in a hyperendemic area: 15 years after mass hepatitis B vaccination. Ann Intern Med. 2001;135:796–800.
41. Ni YH, Huang LM, Chang MH, et al. Two decades of universal hepatitis B vaccination in Taiwan: impact and implication for future strategies. Gastroenterology. 2007;132:1287–93.
42. Ni YH, Chang MH, Wu JF, et al. Minimization of hepatitis B infection by a 25-year universal vaccination program. J Hepatol. 2012;57:730–5.
43. Whittle HC, Maine N, Pilkington J, et al. Long-term efficacy of continuing hepatitis B vaccination in infancy in two Gambian villages. Lancet. 1995;345:1089–92.
44. Peto TJ, Mendy ME, Lowe Y, Webb EL, Whittle HC, Hall AJ. Efficacy and effectiveness of infant vaccination against chronic hepatitis B in the Gambia Hepatitis Intervention Study (1986–90) and in the nationwide immunisation program. BMC Infect Dis. 2014;14:7.
45. Chang MH, Chen DS, Hsu HC, et al. Maternal transmission of hepatitis B virus in childhood HCC. Cancer. 1989;64:2377–80.
46. Chang MH, Chen PJ, Chen JY, et al. Hepatitis B virus integration in hepatitis B virus-related hepatocellular carcinoma in childhood. Hepatology. 1991;13:316–20.
47. Chang MH, Chen CJ, Lai MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. N Engl J Med. 1997;336:1855–9.
48. Chang MH, You SL, Chen CJ, et al. Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: a 20-year follow-up study. J Natl Cancer Inst. 2009;101:1348–55.
49. Wichajarn K, Kosalaraksa P, Wiangnon S. Incidence of HCC in children in Khon Kaen before and after national hepatitis B vaccine program. Asian Pac J Cancer Prev. 2008;9:507–9.
50. McMahon BJ, Bulkow LR, Singleton RJ, et al. Elimination of hepatocellular carcinoma and acute hepatitis B in children 25 years after a hepatitis B newborn and catch-up immunization program. Hepatology. 2011;54:801–7.
51. Chien YC, Jan CF, Chiang CJ, et al. Incomplete hepatitis B immunization, maternal carrier status, and increased risk of liver diseases: a 20-year cohort study of 3.8 million vaccinees. Hepatology. 2014;60:125–32.
52. Herroelen L, de Keyser J, Ebinger G. Central-nervous-system demyelination after immunisation with recombinant hepatitis B vaccine. Lancet. 1991;338:1174–5.
53. Martínez-Sernández V, Figueiras A. Central nervous system demyelinating diseases and recombinant hepatitis B vaccination: a critical systematic review of scientific production. J Neurol. 2013;260:1951–9.
54. van Herck K, Vorsters A, Van Damme P. Prevention of viral hepatitis (B and C) reassessed. Best Pract Res Clin Gastroenterol. 2008;22:1009–29.
55. Wen WH, Chang MH, Zhao LL, Ni YH, Hsu HY, Wu JF, Chen PJ, Chen DS, Chen HL. Mother-to-infant transmission of hepatitis B virus infection: significance of maternal viral load and strategies for intervention. J Hepatol. 2013;59:24–30.
56. Chen HL, Lin LH, Hu FC, et al. Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV. Gastroenterology. 2012;142:773–81.
57. Hsu HY, Chang MH, Ni YH, et al. No increase in prevalence of hepatitis B surface antigen mutant in a population of children and adolescents who were fully covered by universal infant immunization. J Infect Dis. 2010;201:1192–200.

58. Hsu HY, Chang MH, Ni YH, et al. Long-term follow-up of children with postnatal immunoprophylaxis failure who were infected with hepatitis B virus surface antigen gene mutant. J Infect Dis. 2013;207:1047–57.
59. Kruskall MS, Alper CA, Awdeh Z, Yunis EJ, Marcus-Bagley D. The immune response to hepatitis B vaccine in humans: inheritance patterns in families. J Exp Med. 1992;175:495–502.
60. van Zonneveld M, van Nunen AB, Niesters HG, et al. Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. J Viral Hepat. 2003;10:294–7.
61. Xu WM, Cui YT, Wang L, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. J Viral Hepat. 2009;16:94–103.
62. Han GR, Cao MK, Zhao W, et al. A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. J Hepatol. 2011;55:1215–21.
63. Zhang H, Pan CQ, Pang Q, Tian R, Yan M, Liu X. Telbivudine or lmivudine use in late pregnancy safely reduces perinatal transmission of hepatitis B virus in real-life practice. Hepatology. 2014;60:468–76.
64. Greenup AJ, Tan PK, Nguyen V, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of HBV. J Hepatol. 2014;61:502–7.
65. Chen HL, Lee CN, Chang CH, et al. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. Hepatology 2015;62:375-86.