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EDITORIAL

Unsolved problems and future perspectives of hepatitis B virus vaccination

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Abstract

Hepatitis B virus (HBV) infection is still a serious worldwide problem, and vaccination is the most effective strategy for primary prevention of the infection. Although universal vaccination may be required for total eradication, several countries, including Japan, have not yet adopted universal vaccination programs. Some individuals are non-responders to HBV vaccine and several mechanisms responsible for their poor response have been proposed. To overcome non-response, third generation vaccines with pre-S proteins have been developed. These vaccines have shown better anti-HBs responses and may also be effective in preventing infection by HBV with S mutant. Improvement of vaccine efficacy by intradermal administration, or co-administration with cytokines or adjuvants, may also be effective in non-responders. The necessity, timing and method of booster vaccination in responders with decreased anti-HBs responses, and effective vaccination against S-mutant HBV, are issues requiring resolution in the global prevention of HBV infection.

Key words: Escape mutant; Immunology; Hepatitis B virus vaccination; Non-responder; Universal vaccination

Core tip: Hepatitis B virus (HBV) infection is still a serious worldwide problem, and vaccination is most effective for primary prevention of infection. This review summarizes current unsolved issues and future perspectives on vaccination required for global prevention of HBV infection.

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INTRODUCTION

About 400 million people worldwide are chronically infected with hepatitis B virus (HBV), with about half being infected perinatally or during early childhood via

Table 1 Prevalence and transmission of hepatitis B virus

Prevalence	High	Intermediate	Low
Carrier rate	≥ 8%	2%-7%	≤ 1%
Region	Southeast Asia	Mediterranean basin	United States
	China	Eastern Europe	Canada
	Pacific islands	Central Asia	Central Asia
	Sub-Saharan Africa	Japan	Western Europe
	Alaska (Eskimos)	Latin and South America	Australia
		Middle East	New Zealand
Predominant age at infection	Perinatal	Early childhood	Adult
	Early childhood		
Predominant mode of infection	Maternal to infant	Percutaneous	Sexual contact
	Percutaneous	Sexual contact	Percutaneous

vertical and/or horizontal routes[1]. HBV infection can induce acute hepatitis, which may result in fulminant hepatitis, and chronic hepatitis, which may eventually lead to liver cirrhosis and/or hepatocellular carcinoma (HCC)[1]. HBV infection is responsible for 500000 to 1.2 million deaths per year due to chronic hepatitis, cirrhosis, and HCC[2], as well as being responsible for 60% to 80% of HCCs worldwide[3]. Treatment with antiviral agents, including nucleotide analogues and interferon, has been effective in some, but not all, patients with chronic HBV. Therefore, prophylactic approaches are essential to prevent viral infection. Many countries have introduced universal prophylactic vaccination programs, and some individuals, especially those who are immunocompromised, are unable to develop anti-HBs antibody following conventional vaccination. Moreover, HBV in vaccinated subjects may develop mutants, allowing them to escape the effects of vaccination. Attempts have been made to improve the immunogenicity of HBV vaccines. This review describes the current status and unresolved issues of HBV vaccination.

PREVENTION OF HBV INFECTION BY HBV VACCINES

Transmission route of HBV

Methods of HBV transmission at an early age include perinatal, vertical from mother to infant, and horizontal from an infected household member to the child[4]. Perinatal infection occurs in 70% to 90% of babies born to HBeAg-positive mothers, and in less than 15% of babies born to HBeAg-negative mothers[5,6]. The risk of vertical transmission was significantly increased by high serum levels of maternal HBV-DNA[7], and the rate of infection increased from 0% in mothers with serum HBV-DNA < 5 $\log_{10}$ copies/mL to 50% in those with HBV-DNA ≥ 9 $\log_{10}$ copies/mL[8]. Moreover, some reports from China have shown that the reductions of serum HBV DNA in the 3rd trimester of HBsAg-positive pregnant women by the administration of hepatitis B immunoglobulin (HBIG)[9] or nucleoside analogue[10,11] significantly decreased the neonatal intrauterine HBV infection. These data suggest that the serum level of HBV DNA in pregnant women is the major determinant in the occurrence of mother-to-infant transmission.

In infected persons, HBV is found not only in blood but in body fluids, including saliva, semen and vaginal secretions, all of which are capable of transmitting the virus. Furthermore, HBV remains viable for 7 d or longer on environmental surfaces at room temperature.

The World Health Organization (WHO) has classified countries into three categories according to the prevalence of chronic HBV carrier: high (8% or greater); intermediate (2%-8%); and low (less than 2%) (Table 1)[12]. In high endemic areas, the life risk of acquiring HBV infection is greater than 60% and most infections are transmitted vertically/perinatally or horizontally during early childhood. In intermediate endemic areas, the life risk of HBV ranges from 20% to 60%, and infections are found in all age groups. In low endemic areas, the life risk is low, especially in normal living environments, and infections occur primarily in adults through sexual or parenteral transmission[12]. Regardless, vaccination should be considered to prevent HBV infection.

Hepatitis B vaccine

The first plasma-derived HB vaccine, containing highly purified 22 nm HBsAg inactivated by urea, pepsin, formaldehyde, and heat, was introduced in 1982[13]. Subsequently, yeast-derived recombinant HB vaccines were introduced in the mid-1980s because of the potential risk of blood-borne infection in plasma-derived vaccines[14]. Yeast-derived vaccines were manufactured by cloning the HBV S gene in yeast cells, yielding nonglycosylated HBV small S protein but not the pre-S region[15]. Due to the potential neurotoxicity of the preservative thimerosal, two yeast-derived recombinant thimerosal-free vaccines (Recombivax HB® and Engerix-B®) were developed and have been widely available[16]. The third generation HB vaccines are mammalian cell-derived recombinant vaccines containing the pre-S region. These vaccines may be more immunogenic in a controlled trial[17], but are not widely available at present.

HB vaccines used for primary prophylaxis have been shown to reduce the risk of infection in most

populations[18]. A combination vaccine (Twinrix®), containing Engerix-B and HAVRIX (hepatitis A vaccine), is also available[19,20]. The HepB3 hepatitis B vaccination program, consisting of a series of three doses, the second administered one month and the third six months after the first dose, resulted in the production of anti-HBs in about 95% of recipients[21]. No significant side effects have been observed, except for pain at the injection site and mild to moderate fever[22].

Although HBV is transmitted at a high rate by parenteral, percutaneous and sexual contact, a study from the United States showed that vaccination of high-risk groups had little impact on the incidence of HBV infection[23]. In contrast, since perinatal or early postnatal transmission is the primary cause of chronic infections worldwide, the first dose of HB vaccine should be given as soon as possible after birth (< 24 h) even in low-endemic countries. Primary protection regardless of maternal HBsAg status has been recommended[24].

Prophylaxis of HBV-related diseases by hepatitis B vaccine

To prevent HBV infection, the WHO advocated HBV vaccination of all infants in 1992, or universal vaccination (UV). By the end of 2013, UV had been introduced nationwide in 183 countries. In Japan, UV has not yet been introduced, but will be introduced in the near future. Global coverage with HepB3 is estimated at 81% and is as high as 92% in the Western Pacific[25] (Figure 1). A meta-analysis of randomized controlled trials of HB vaccination of newborns showed that vaccinated infants born to HBV-positive mothers were 3.5-fold less likely to become infected with HBV (RR = 0.28, 95%CI: 0.20-0.40)[26].

In Taiwan, a high endemic area, UV of all newborns was implemented in 1986, reducing the HBsAg prevalence rate from 9.8% in 1984 to 0.6% in 2004[27]. Furthermore, the prevalence of HCC in childhood decreased from 0.7 per 100000 in 1981-1986 to 0.36 per 100000 in 1990-1994[28]. After 20 years of this program, the risk of HCC has been decreased by 70% in young adults, indicating that HB vaccine was the first vaccine to successfully prevent a major human cancer[27,29]. Furthermore, almost 30 years later, the prevalence of HBV infection was markedly lower, with HBsAg positivity decreasing from 10% to 0.9% and anti-HBc positivity from 28% to 7%[30]. In the Gambia, HBsAg prevalence in childhood decreased from 10% to 0.6% 10 years after UV introduction[31,32]. In Alaska, the incidence of acute hepatitis B was decreased to almost zero and the prevalence of chronic hepatitis among children and young adults was also decreased[33,34]. Furthermore, the incidence of HCC in patients under 20 years of age decreased from 3 per 100000 in 1984-1988 to zero in 1995-1999[33,34]. These findings showed that UV can prevent vertical and horizontal transmission of HBV infection, reducing rates of chronic HBV infection, especially in high endemic areas.

In the United States, a low endemic area, the incidence of acute hepatitis B has declined 82%, from 8.5 per 100000 in 1990 to 1.5 per 100000 in 2007[35]. In Malaysia, HBsAg prevalence in children decreased from 1.6% in 1997 to 0.3% in 2003[36]. In Italy, the morbidity of acute hepatitis B in patients aged 15 to 24 years old decreased from 17 per 100000 in 1990 to less than 0.5 per 100000 in 2005[37,38].

Despite vaccination at birth, however, 5% of babies become HBV carriers[39-41]. The precise mechanism is unclear, but vaccinated individuals, especially in HBV endemic areas, should be carefully monitored for HBV infection.

UNRESOLVED PROBLEMS IN HB VACCINATION AND RECENT ADVANCES

Non-responders to HB vaccine

Mechanisms of nonresponse to HB vaccine: Three conditions have been shown associated with nonresponse to HB vaccine (Table 2). In addition, around 10% of the general population shows poor responses. Antibody response rates decline gradually after age 40 years, with age being a factor determining response to HB vaccine[42]. The mechanism of nonresponse is not fully understood, but several hypotheses have been proposed.

Human leukocyte antigen

Because human leukocyte antigen (HLA) alleles are one of the determinants of the repertoire of peptides presented to T cells, HLA alleles are associated with response to HBV vaccine.

A report from eastern Turkey demonstrated that high frequencies of HLA-A11 and HLA-A24 and a low frequency of HLA-CW6 were associated with nonresponse to HB vaccine[43]. Another report from Turkey showed an association between HLA-DR (HLA-DRB1*04X, DRB1*0401X, DRB1*11/13, and DRB1*0401X0201) haplotypes and non-response, whereas Class-I (HLA-B13) was associated with a good response to HB vaccine[44]. A report from Italy showed that the haplotypes HLA-B8, DR3, and DQ2 were associated with nonresponse to HB vaccine, both in patients with celiac disease and healthy subjects[45]. A recent report from Korea showed that B62, DRB1*07 and DRB1*08(-) were significantly associated with poor responses to vaccine[46]. A meta-analysis of the association between HLA alleles and response to HB vaccine in 2308 subjects, including responders, non-responders, and healthy subjects, found that the DRB1 alleles DRB1*01, DRB1*1301, and DRB1*15 were associated with good responses whereas DRB1 *03 (DRB1*0301), DRB1*04, DRB1*07, and DRB1*1302 were associated with poor responses[47]. Furthermore, evaluations of DQB1 alleles showed that DQB1*05

Table 2 Factors associated with poor response to hepatitis B virus vaccination

Factors
Underlying medical conditions
Chronic HBV infection
Hemodialysis
Immature neonates
HIV infection
Immunosuppressor administration
Genetic factors
HLA haplotypes
Celiac disease
SNPs (cytokine, chemokine)
Technical errors
Intra-gluteal injection
Inappropriate storage conditions

SNPs: Single nucleotide polymorphisms; HLA: Human leukocyte antigen; HBV: Hepatitis B virus.

(DQB1*0501), DQB1*06, and DQB1*0602 were associated with good responses, whereas DQB1*02 was associated with poor response[47].

Cytokine and chemokine gene polymorphisms

Associations between single nucleotide polymorphisms (SNPs) at the interleukin (IL)-2 and IL4 loci, along with insertion/deletion variants at the IL12B locus, have been associated with responses to HB vaccines[48]. Moreover, three SNPs (rs497916, rs3922, rs676925) in CXCR5 and one SNP (rs355687) in CXCL13 were associated with response to HB vaccine. These findings indicate that cytokines and chemokines are actively involved in responses to HB vaccine[49].

Regulatory T-cells

The poor responses of HIV-infected patients to HB vaccine were thought to be due to low numbers of $CD4^+$ T cells[50]. However, the percent of regulatory T-cells was found to be negatively associated with response to HB vaccine in HIV-infected patients, suggesting another mechanism for low anti-HBs production in response to HB vaccine[51].

T cell immunoglobulin mucin-domain-3

Hepatitis C virus (HCV)-infected patients have been reported to show a poorer response to HB vaccine than healthy subjects[52]. This may be due to the differential regulation of IL-12/IL-23 production secondary to over-expression of T cell immunoglobulin mucin-domain-3 on monocytes[53].

Attempts to improve the efficacy of HB vaccine: Because the existence of non-responders to HB vaccine is a serious social problem, several attempts have been made to improve the efficacy of vaccine. Persons unresponsive to a first series of three injections (*i.e.*, anti-HBs < 10 mIU/mL) are recommended to complete a second 3-dose vaccine series, with about 50% of these individuals showing an anti-HBs response[16,54]. Non-responders to the second course should be evaluated for underlying chronic HBV infection. Response in patients on hemodialysis may be improved using double-dose vaccine[55]. However, some individuals are non-responsive to multiple series of vaccinations, suggesting the need for other strategies to induce anti-HBs production in these subjects.

Third generation HB vaccine

New HB vaccines have been developed to improve anti-HBs response in non-responders. Hepagene™, a third generation vaccine containing pre-S1 and pre-S2 proteins in addition to S protein, has been shown to induce anti-HBs in 76% of previously non-responsive individuals[56]. Another third generation HB vaccine, Sci-B-Vac™, was recently shown to induce anti-HBs in 20 of 21 non- or low-responders, with 12 non-responders and all 6 low responders showing a high anti-HBs response (> 100 mIU/mL)[57]. Moreover, the preventive effect of Sci-B-Vac™ has been assessed in newborns[58,59].

Vaccination plus cytokine

Granulocyte-colony stimulating factor: Recently, HB vaccine was administered together with granulocyte-colony stimulating factor (G-CSF) to patients with liver cirrhosis[60]. However, adjuvant G-CSF did not significantly enhance anti-HBs production.

Granulocyte-macrophage colony stimulating factor: The effect of granulocyte-macrophage colony stimulating factor (GM-CSF) on the response to HBV revaccination in non-responders has been evaluated[61]. Although the combination of GM-CSF (150 μg) and HB vaccine (20 μg) induced a higher anti-HBs response than HB vaccine (20 μg) alone, a higher dose (40 μg) of HB vaccine induced a higher response than the combination. GM-CSF was effective in patients with end-stage renal disease[62], but was ineffective during booster vaccination of HIV-infected patients with low anti-HBs antibody titer[63]. Thus, the stimulatory effect of GM-CSF has not yet been determined.

Other adjuvants

Interleukin (IL)-2 was not effective as an adjuvant[64,65]. In contrast, levamisole used as an adjuvant in HB vaccination has shown promising results[66,67]. New chemical adjuvants [AS02(v) and AS04] have also been found to increase response to HB vaccine[68-70].

Intradermal vaccination

HB vaccine is usually given intramuscularly, but intradermal vaccination was shown to be superior[71]. Intradermal vaccination induced higher anti-HBs positivity rates or a similar rate as intramuscular vaccine with smaller doses of vaccine[72]. The ability of intradermal administration to improve the effectiveness of vaccination has been tested, but intradermal vaccination is

Table 3 High risk individuals for hepatitis B virus infection and recommendations for booster vaccination

Individuals	Booster recommendation
Health-care workers	Single dose if anti-HBs < 10 mIU/mL
Men who have sex with men	Ensure primary vaccination, boosters are unnecessary
Persons with multiple sexual partners	Ensure primary vaccination, boosters are unnecessary
Injection drug users	No evidence to support booster vaccinations
Patients with hemodialysis	Additional boosters to maintain anti-HBs > 10 mIU/mL
Institutionalized patients	Not recommended
Public safety workers	Single dose if anti-HBs < 10 mIU/mL
Spouse, sexual partners and household members of HBV carriers	Receive primary vaccination, boosters are unnecessary
Recipients of liver transplantation	Additional boosters to maintain anti-HBs > 10 mIU/mL

HBs: Hepatitis B surface antigen.

technically difficult[73].

Intradermal administration every two weeks into non-responders to conventional intramuscular vaccination induced anti-HBs responses in 94% of the subjects[74]. Intradermal vaccination has induced better responses to HB vaccine than conventional intramuscular vaccination in healthcare workers[75,76], dialysis patients[77-79], HIV infected patients[80], and patients with celiac disease[81]. A comprehensive review of the efficacy of intradermal HB vaccination in non-responders found that this method induced a superior response compared with intramuscular vaccination under various conditions[82].

Booster immunization

Several studies have shown that the protective effects of HB vaccination may continue for at least 10 to 15 years[83,84] or even beyond 15 years, especially in subjects with a high anti-HBs titer after the initial course of vaccination[85]. Routine booster vaccinations have been regarded as unnecessary, due to the immunological memory acquired after the initial round of HB vaccination[86,87], and booster vaccination of previously vaccinated individuals has shown to result in a rapid increase in anti-HBs antibody[88]. However, the long-term protective effects of HB vaccination have not been fully investigated. Of 6156 high school students vaccinated during infancy, approximately 10% to 25% lost immune responses to HBsAg[86,87]. A recent report showed that 17.8% of vaccinated students born to highly infectious mothers positive for HBeAg became HBsAg-positive, compared with 11.1% of those born to maternal HBeAg-negative (P = 0.014), suggesting that booster vaccination may be needed for complete prevention of HBV infection[41].

Policies regarding booster vaccination vary among countries. In patients on hemodialysis, vaccine-induced antibody protection may persist only at anti-HBs titers above 10 mIU/mL, suggesting that a booster be administered if the antibody level declines to below 10 mIU/mL[89]. A European consensus statement also recommended booster vaccination if antibody concentration declines to below 10 mIU/mL, depending on the risk of exposure to HBV (Table 3)[90].

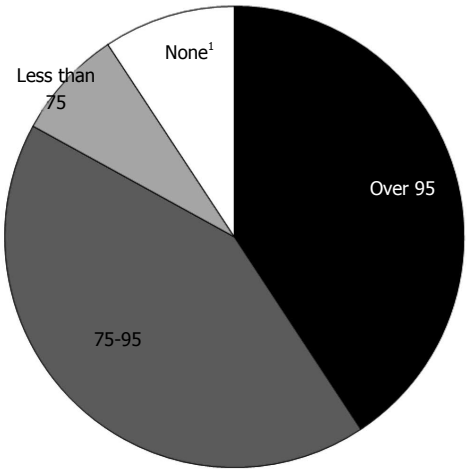
In liver transplantation, it was shown that 18 out of 23 recipients from isolated anti-HBc-positive donors developed HBV infection after liver transplantation[91], suggesting a recommendation of booster vaccination to acquire anti-HBs levels above 10 mIU/mL in all HBsAg-negative recipients before transplantation even if the donors are negative for HBsAg.

Escape mutants

Mutations in the small-S protein, most frequently a glycine to arginine substitution at codon 145 (G145R), have been found in some children born to HBV-infected mothers who were found to be infected despite previous vaccination[92,93]. Viruses containing the G145R mutant have been shown to be infectious in chimpanzees[94]. Other S-gene mutations have been identified in codons 120-147, and these mutations may evade neutralizing anti-HBs and infect vaccinated people[95-97]. In Italy, S-gene mutations, such as G145R, P120S and P127S, have been identified in liver transplant patients and in children born to HBsAg carriers and treated with HB vaccine. Although these mutants have been found in many regions around the world, including Taiwan[95], their prevalence appears to be low and constant, and reductions in the efficacy of HB vaccine have not been observed[97,98]. However, a recent report showed that HBV containing G145R had been transmitted by sexual contact to a subject who had received universal HB vaccination[39]. Recently, a vaccinated individual was found to have developed acute hepatitis B, caused by a vaccine-escape mutant[99]. Mathematical modeling predicted that over 50 years were required before any vaccine-escape mutants become predominant[100]. Continued monitoring is necessary to determine if the prevalence of these mutants is increasing and if the protective efficacy of conventional vaccines is maintained. Strategies for practical application of HB vaccine containing pre-S protein should be investigated.

Cross-genotype preventive effect in HBV vaccination

HBV strains have been classified into eight genotypes[101,102], with the prevalence of different genotypes varying geographically[103]. However, infection with an HBV genotype different from the native strain has increased in various regions, resulting in the progressive globalization of HBV infection. For example, infection with HBV genotype A strains from foreign countries and subsequent acute hepatitis are increasing in Japan, in which HBV genotype C is the major strain[104]. Infections of Japanese individuals with non-native strains have mainly occurred in adults through sexual contact[104], and UV has not yet been introduced in Japan (Figure 1). Recombinant vaccines



[1]Countries without the introduction of UV

Austria
Barbados
Bosnia and Herzegovina
Botswana
Brunei Darussalam
Bulgaria
Democratic People's Republic of Korea
Denmark
Equatorial Guinea
Finland
Hungary
Iceland
Japan
Monaco
Norway
South Sudan
Switzerland
United Kingdom of Great Britain and Northern Ireland

Figure 1 Universal vaccination coverage rate among World Health Organization member nations at the end of 2013. [1]Countries in which universal vaccination (UV) has not yet been introduced.

generated from HBsAg of HBV genotype A2 have been used worldwide. Although these A2-type vaccines were suggested to be effective in preventing non-A2 HBV infection[105], this cross-genotype preventive effect has not been fully investigated. Using an animal model, we recently showed that monoclonal antibodies derived from vaccines with genotype C could prevent infection by HBV genotype A[106]. Further investigations and careful observation are required for cross-genotype prevention of HB vaccine.

FUTURE PERSPECTIVES ON HB VACCINE

Several issues require future resolution

First, 5% to 10% of vaccinated healthy subjects are non-responders, and dialysis patients, HIV-infected patients and patients with celiac disease show poorer response to HB vaccine than healthy subjects. Booster vaccination overcomes the non-response in some of these subjects, but a third generation HB vaccine, intradermal vaccination or vaccination with adjuvants may be more effective. Methods are therefore needed to develop anti-HBs responses in non-responders.

Anti-HBs response gradually decreases after a single course of vaccination. However, there are no standard guidelines for the necessity, timing, or method of booster vaccination under various situations.

S-gene mutant HBV may escape from HB vaccination with S-protein alone. To prevent infection and spread of HBV with S-mutation, the effectiveness of third generation HB vaccines containing pre-S proteins in addition to S-protein should be determined.

Several countries have not yet introduced UV. Promotion of UV in these countries is mandatory for global eradication of HBV infection.

The significance of co-administration of HBIG with HB vaccine for prevention of mother-to-infant transmission of HBV needs to be fully evaluated. Although the administration of HBIG was shown to prevent intrauterine transmission of HBV and reduce overt infantile hepatitis[107,108], appropriate randomized control trials should be performed in the future.

CONCLUSION

HBV infection remains a serious problem worldwide, and vaccination is the most effective strategy for primary prevention of the infection. Although UV is needed for global eradication of HBV infection, it has not yet been introduced in many countries, including Japan. Third generation vaccines with pre-S proteins have shown better anti-HBs responses even in non-responders, but data on their efficacy are limited. Third generation HB vaccines may also be effective in preventing infection with HBV containing an S-mutation. Strategies are needed to improve vaccine efficacy in non-responders, whether with new vaccines or adjuvants, or by intradermal vaccination. Moreover, guidelines are needed regarding the necessity, timing and method of booster injection of responders with decreased anti-HBs response.

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