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Review

Hepatitis B vaccination: The key towards elimination and eradication of hepatitis B☆

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Hepatitis B virus infection is a global health problem. Worldwide, about 360 million people are chronically infected with the virus. They continue to spread the virus to others and are themselves at risk of chronic liver diseases and hepatocellular carcinoma. The infection can now be treated by antivirals or interferons and the transmission route can be interrupted. Nevertheless, the most effective means is to immunize all susceptible individuals, especially young children, with safe and efficacious vaccines. The combined efforts of vaccination, effective treatment and interruption of transmission make elimination of the infection plausible and may eventually lead to eradication of the virus. Because hepatitis B vaccination has a key role in the control of hepatitis B, properties of this vaccine, its effectiveness in pre-exposure and post-exposure settings, duration of protection after vaccination and the need of booster doses are discussed. Mass hepatitis B vaccination in children decreases the carriage of the virus, and the diseases associated with acute and chronic infection, including hepatocellular carcinoma. Challenges that need to be solved to expand mass vaccination, and the strategies towards elimination and eventual eradication of hepatitis B in the world are also discussed.

***Keywords*: Hepatitis B virus; Hepatitis B vaccine; Universal hepatitis B vaccination; Elimination of hepatitis B; Eradication of hepatitis B**

1. Introduction

Hepatitis B virus (HBV) infection is one of the most common and important human viral infections. The infection can cause acute and chronic liver diseases, ranging from fulminant hepatitis to cirrhosis and eventually hepatocellular carcinoma (HCC) [1]. Worldwide, as many as 360 million people are chronically infected with HBV, and ~1 million deaths are attributed to its infection [2]. Hence, control of HBV infection is extremely important. Strategies to fight against the infection comprise interrupting the route of transmission, treating chronically infected patients as well as treating susceptible individuals with immunoproplylaxis [3].

As we enter the fifth decade of the fight against HBV following its discovery, advances in vaccine development/implementation and antiviral therapies have shed more light on the elimination and eradication of HBV infection [4]. Although current antiviral treatments using pegylated interferons or nucleos(t)ide analogs are effective for chronic hepatitis B, chronic HBV carriage is not easy to eliminate, as shown by the frequent persistence of hepatitis B surface antigen (HBsAg) in those who have responded well to the available treatments [5]. On the other hand, from the very beginning, the hepatitis B vaccine has proved to prevent HBV infection effectively [6,7]. Vaccination of infants against hepatitis B, especially those born to HBV carrier mothers [8] is the most effective way to control the spread of HBV. And thus, universal infant vaccination will be the key

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to the elimination and subsequent eradication of hepatitis B. Elimination and eradication of hepatitis B require long-term commitment all over the world to continue the vaccination as well as interrupting the routes of transmission, treating the chronic HBV carriers, so that the infection is completely stopped. Because of the important role of hepatitis B vaccine in the control of hepatitis B, the current status of hepatitis B vaccination is reviewed.

2. The hepatitis B vaccine

In 1982, two hepatitis B vaccines from France and the United States were licensed. They were subunit vaccines containing 22-nm HBsAg particles made from plasma of chronic HBsAg carriers. The preparations undergo vigorous inactivation steps and are highly purified, and aluminum hydroxide is added as an adjuvant. The vaccine is preserved with thimerosal.

Millions of doses of the first-generation plasma-derived vaccines have been used, and the effectiveness and safety records are excellent. However, concerns on the safety of human blood products always exist, especially after the discovery of human immunodeficiency virus (HIV) in the early 80's [9]. Meanwhile, recombinant DNA technology has matured to such an extent that it has led to the satisfactory production of HBsAg in the yeast, *Saccharomyces cerevisiae*. The yeast-derived HBsAg was then used for vaccination, also showing excellent effectiveness and safety. Nowadays, it has generally replaced plasma-derived vaccines. Recombinant DNA vaccines can also be produced by inserting plasmids containing HBsAg genes into mammalian cells.

Although the current vaccines are highly effective with a rate of 94–98% in protecting from chronic HBV infection for at least 20 years [10], they are far from perfect. There are still some populations in which the non-response rate is substantial, such as the elderly, smokers, obese individuals, those with chronic hepatic or chronic renal diseases. This resulted in more immunogenic hepatitis B vaccines being developed by incorporating HBV DNA sequences coding for pre-S_1 and pre-S_2 protein into the vector used for recombinant DNA technology in manufacture [11,12]. Additionally, improvement of the adjuvants to make the vaccine more immunogenic has also been tried [13].

To decrease the number of injections that are needed in routine immunizations to infants, combination vaccines containing HBsAg have been produced. The components of these combination vaccines include diphtheria, tetanus toxoids and acellular pertussis or whole-cell pertussis; *Hemophilus influenzae* type b; inactivated poliovirus; and hepatitis A virus. Any combination vaccine should demonstrate adequate efficacy as compared with individual vaccines. Pentavalent [14,15] and hexavalent [16] combination vaccines have been developed successfully recently. The combination vaccine not only decreases the number of injections but also increases the coverage rates of vaccination [17]. The development of hepatitis B vaccines and the public health strategy of hepatitis B vaccination have been reviewed recently [18,19].

The vaccine should be kept at 2–8 °C and should never be frozen. It is relatively heat-stable [20], the immunogenicity does not change when the vaccine is stored for up to one month at ambient temperature [21] or even at tropical temperature [22]. The heat stability helps greatly to deliver the vaccine in places where refrigeration is not available.

3. Effectiveness of vaccination

Hepatitis B vaccination is highly effective in both pre-exposure and post-exposure prophylaxis. Antibody to HBsAg (anti-HBs) is neutralizing and serum levels of $\geq$10 mIU/mL are protective.

3.1. Pre-exposure settings

The most extensively studied populations for pre-exposure prophylaxis are homosexuals and health-care workers. Randomized, double blind, placebo-controlled clinical trials have demonstrated a protective efficacy of 80–88% in male homosexuals [6,23–25]. In health-care workers, hepatitis B vaccine appears to be efficacious [26], especially in high-risk health-care workers, such as staff of renal hemodialysis units [27–29]. Patients with end-stage renal disease (ESRD) on hemodialysis are also protected by the vaccine [29–31], however, not all studies demonstrated that ESRD patients receiving hemodialysis benefit from hepatitis B vaccination [32,33]. Part of the reason may be the lower immune response to the vaccine in these patients. The poor response is attributed to malnutrition, uremia and the generalized immunosuppression state in this population. Patients with serum creatinine $\geq$4 mg/dL have been shown to respond less effectively after hepatitis B vaccination (86% vs. 37%) [34]. Those with glomerular filtration rate $<$10 mL/min, $>$60 years of age, and diabetes mellitus are less likely to seroconvert after immunization [35]. Efficient hemodialysis improves the response to hepatitis B vaccine [36,37]. A coexisting hepatitis C virus infection may reduce the effectiveness of the vaccine in patients on maintenance hemodialysis [38]. The poor response to hepatitis B vaccine can be rescued with reinforced vaccination protocols by increasing the dose or number of the vaccines [39,40]. Changing the route of vaccine administration from intramuscular to intradermal injections has also been claimed to improve the immunogenicity and may be cost-effective [41,42]. However, other studies

did not reach the same conclusion. The results of intradermal or intramuscular injections are almost the same, although the dose of hepatitis B vaccine can be reduced [43,44]. Because the dosage and number of intradermal injections differed in different studies, and how long the anti-HBs induced by the inoculation will last is unclear, a firm conclusion cannot be drawn.

For subjects infected with HIV, the responses after hepatitis B vaccination are suboptimal, either to plasma-derived vaccines or recombinant vaccines [45–48, reviewed in 49]. Based on a total of 447 subjects, relatively adequate $CD4^+$ T-cells of $\geq 500/mm^3$ and lower HIV viral loads of ≤ 1000 copies/mL ensure immune responses to hepatitis B vaccine [49]. Nevertheless, those whose $CD4^+$ T-cell counts and HIV viral loads are less favorable should not be denied the vaccination. A reinforced protocol as that used for those with other types of immune suppression can be employed and post-vaccination monitoring can also be conducted [49]. The response to hepatitis B vaccine in patients with acquired immune deficiency syndrome (AIDS) treated with highly active anti-retroviral therapy (HAART) may recuperate in adults [49,50] and children [51].

Patients with chronic liver disease also have suboptimal responses to hepatitis B vaccination. In addition to age and genetic predisposition, the severity of liver disease and the underlying etiology also play a critical role. For example, chronic alcoholics have inadequate responses to the hepatitis B vaccine, especially when the liver disease is overt [52,53]. In patients with non-hepatitis B chronic liver disease who receive liver transplant, the anti-HBs seroconversion rate is low after hepatitis B vaccination [54–56]. The responses in those transplanted for HBV-related cirrhosis are especially poor, even after a reinforced triple course of vaccination [57] or a double course of recombinant vaccine containing pre-S_1, pre-S_2 and S protein [58], only few patients have adequate levels of anti-HBs.

Hepatitis B active immunization after liver transplant, if responsive in the transplant recipient, can prevent HBV recurrence following withdrawal of hepatitis B immune globulin (HBIG) [59]. Protection was especially evident in Taiwanese pediatric patients in a recent study [60]. In the study, all the 60 patients had received hepatitis B vaccination previously in a national infant hepatitis B vaccination program [61]. The results imply that in the future, after universal infant vaccination against HBV is widely implemented, pre-transplant booster with HBV vaccines will very likely prevent the occurrence of post-transplant *de novo* or recurrent HBV infection.

Responses to hepatitis B vaccine are also low in the recipients of renal transplant [62,63]. Increased dose and intradermal route of vaccination have also been tried to improve the immunogenicity with some success [64]. Because age of the patient has been shown to correlate with immune response to hepatitis B vaccine in patients with ESRD [65], and the immunogenicity is much higher if the vaccine is given before renal transplantation [66], hepatitis B vaccination should be given as early as possible for patients with ESRD, preferably before renal transplantation.

The poor response to hepatitis B vaccine can be improved by a different route of vaccine administration (see above), increased dose and frequency of vaccination [39,40,67,68]. The adjuvant can also be improved. A new adjuvant system containing 3-deacylated monophosphoryl lipid A and a natural saponin molecule from *Quillaja saponaria* in an oil/water emulsion has been claimed to yield a better immune response of the vaccine, although the protective antibody declines rapidly [69]. Unfortunately, the results could not be reproduced in another study [70].

Another approach is to use the biologically active molecules like granulocyte macrophage colony-stimulating factor as the adjuvant. A meta-analysis favors a significant effect in the antibody response rate and the achievement of an earlier seroconversion to the vaccine [71]. Other approaches include hepatitis B DNA vaccination with plasmid DNA encoding HBsAg [72], or administration of HBsAg-pulsed blood dendritic cells [73], preliminary results in hepatitis B vaccine non-responders showed some promising results. More studies are needed to confirm these findings. The use of DNA immunization with oligodeoxynucleotides containing CpG motifs attempting to enhance the immune response, although successful in mice, was not effective in chimpanzees [74].

3.2. Post-exposure settings

The most thoroughly studied population for post-exposure prophylaxis is infants born to hepatitis B e antigen (HBeAg)-positive HBsAg carrier mothers. To bridge the gap between exposure to HBV and active production of anti-HBs induced by the hepatitis B vaccine, HBIG is given as soon as possible in these newborns no later than 24 h after birth. The efficacy of protecting from chronic HBV infection in these individuals is >90% [8,75–80]. If HBIG is skipped, the efficacy is slightly lower, but can still be >83% [78,80–83]. These findings form the basis in support for the use of vaccine alone in countries where pregnant women are not screened for HBsAg and HBeAg [84]. Another important issue is the timely birth dose which should be given within 24 h after delivery, because a delay in this initial dose has been shown to lead to an increased risk of infection in children whose mothers are HBsAg carriers [85,86]. The heat stability of hepatitis B vaccines renders the administration of a timely birth dose feasible also in rural and remote areas [21,22,87,88].

Although HBeAg is a good marker of infectivity for us to judge whether to give or to skip administration

of HBIG to the newborns of mothers who are HBsAg carriers [61], despite hepatitis B vaccination, about 3% of infants born to HBeAg-negative HBsAg carrier mothers will still become persistently infected [89], indicating that defining infectivity by HBeAg in HBsAg carriers is not perfect. Actually, measurements of serum HBV DNA levels of HBsAg carrier mothers have been explored for the prediction of perinatal mother-to-infant transmission after immunoprophylaxis [90–93]. However, the results of these studies were confounded by hepatitis B immunoprophylaxis in the infants, and the roles of maternal serum HBV DNA and HBeAg in predicting infectivity were difficult to compare.

In a cohort of 773 Taiwanese HBsAg-positive mothers and their infants in 1972–1980, it was documented that the maternal serum HBV DNA level is a stronger independent predictor of the infant's persistent HBV infection than HBeAg [94]. In 22 HBeAg-positive HBsAg carrier women with undetectable serum HBV DNA, only 1(4.5%) of their infants became HBsAg carriers, in contrast to 82 HBV DNA-positive women's infants in whom 53 (64.6%) became carriers. In 107 HBeAg-negative women, the persistent HBV infection in infants of 99 HBV DNA-negative and 8 HBV DNA-positive mothers was 5 (5.1%) and 3 (37.5%), respectively. The study also showed a linear relationship between maternal viral load and the likelihood of persistent HBV infection in their infants [94]. Hence, to decide whether HBIG should be used in newborns of HBsAg carrier mothers, serum HBV DNA rather than HBeAg appears to be more logical. However, further studies are needed [92].

Because maternal hepatitis B viral load is the most critical factor in causing HBV infection in the newborns even after passive-active immunoprophylaxis, by analogy with the situation in HIV infection [95], lowering the maternal viral load by antiviral therapy may reduce perinatal HBV infection. Indeed, in a pilot study [96], eight highly viremic HBsAg carrier mothers (serum HBV DNA $\geq 1.2 \times 10^9$ geq/ml) received lamivudine (150 mg per day) in the last month of pregnancy from week 34 on, one of 8 (12.5%) immunized infants became chronically infected. In the untreated historical controls, the chronic infection occurred in 7 of 25 (28%) children. Nevertheless, the data investigating whether addition of anti-HBV antivirals to near-term pregnant HBsAg carrier women will yield additional decrease of perinatal HBV infection are limited, and thus needs to be addressed further with randomized control trials. In addition, the issues of cost as well as safety in the mothers and newborns also require careful consideration.

Preterm infants have decreased antibody response to hepatitis B vaccine [97], especially those with low birth weights (<1800 gm) [98,99] or premature gestation ages (<34 weeks) [99]. It has been recommended to defer the first dose of the vaccine in HBsAg-negative mother's infants weighing <2000 gm until they reach 2000 gm, or alternatively, until one month old [100,101].

3.3. Duration of protection and the need of booster doses

Vaccine-induced anti-HBs declines rapidly in the first year and then more gradually (reviewed in [102]). As time passes, the anti-HBs frequently becomes undetectable. Nevertheless, the vaccine-induced immunologic memory is maintained for at least 12 years despite the decline of anti-HBs [103]. Although, by testing humoral and cellular immunological parameters after a vaccine booster, we found a substantial proportion of fully vaccinated adolescents seem to lose immune memory conferred by hepatitis B vaccine given in infancy 15–18 years previously [104], whether these findings represent susceptibility to HBV infection remains to be seen. Actually, a booster vaccination is not needed for at least 20 years in Taiwan, because surveillance did not reveal any increase of acute hepatitis B [105] or chronic HBV infection [10] in adolescents vaccinated 20 years ago. For endemic areas like Taiwan where the primary goal of hepatitis B immunization is to prevent hepatitis B chronic carriage in infancy [61], even if the immunity conferred by the vaccine given in early childhood disappears, when the unprotected vaccine contract HBV infection in adulthood, the risk of becoming HBsAg carriers is far lower [106]. In this case, the primary goal has already been achieved then. A global universal infant immunization will postpone HBV infection in any given population to an older age when HBV infection will result in much less chronic HBsAg carriage worldwide. This will be a significant step towards the eradication of HBV infection. Nonetheless, after chronic HBV infection is well-controlled, the need of preventing acute hepatitis B in young adults will become evident. Therefore prolonged follow-up and surveillance of the vaccinees who received immunization in early childhood should continue. A booster vaccination will be considered only when the cohort start to have clinically significant acute hepatitis B. So far, in the endemic areas for hepatitis B, breakthrough HBV infections in the vaccinees who received the immunization in infancy occur infrequently, ranging from 0.008% to 0.19% per year (Table 1) [107–112]. In the rare cases of these breakthrough infections, they are subclinical and rarely become chronic.

4. Hepatitis B mass vaccination

After the hepatitis B vaccine became available, it was found that targeting at populations at risk of HBV infection, such as homosexuals, sex workers, drug abusers or teenagers was not easy [113]. On the other hand, universal vaccination against HBV in newborns was found to be easier and cost-effective [114,115].

Table 1
Breakthrough hepatitis B virus infections in the vaccinees who received hepatitis B immunization in childhood.

Author [Ref.]/year/country	No. of subjects studied	No. with HBV infection[a]	Observation period (years)	Average annual incidence (%)
Lin et al. [107]/2003/Taiwan	1200	11	7	0.13
Boxall et al. [108]/2004/UK, Asian	64	1	15.1	0.10
	52	1	11.8	0.16
Yuan et al. [109]/2004/China, Hong Kong	88	3	18	0.19
McMahon et al. [110]/2005/US, Alaska	1578	16	15	0.08
Dentinger et al. [111]/2005/US, Alaska	334	6	10	0.18
Zanetti et al. [112]/2005/Italy	1212	1	10.6	0.008

HBV: hepatitis B virus.
[a] The infections were asymptomatic and rarely became chronic.

Incorporation of hepatitis B vaccine into the routine Expanded Program on Immunization (EPI) of infants has been shown to be feasible and practical [84,116,117]. As of 2007, according to World Health Organization (WHO) 71 (89%) of the 193 member states had initiated a hepatitis B vaccination program. The global coverage of completing three doses of hepatitis B vaccine was 65% on average, ranging from 89% in the American Region to 28% in the Southeast Asian Region [http://www.who.int/immunization_monitoring/data/en/].

Due to the fact that chronic HBsAg carriage has been shown to correlate with the age when HBV infection occurs, the younger the age, the higher the chronicity [106], and because of the very high prevalence of chronic HBV infection in Taiwan as well as the extremely heavy disease burden caused by HBV [118], a national hepatitis B vaccination program was launched in 1984 [61], soon after the hepatitis B vaccines became available. As this is the earliest nationwide hepatitis B mass vaccination in the world, much important information can be obtained from it and I will use Taiwan's experience to elucidate some of the issues in this review. Briefly, pregnant women were screened for HBsAg and then HBeAg. If they were positive for HBeAg, their newborn infants received HBIG immediately after birth, followed by hepatitis B vaccine given within the first week of life. In more than 90% of infants, the first dose was given in the first or second day after birth. In those carrier mothers who were negative for HBeAg, the infants receive hepatitis B vaccines only, so did infants of non-carrier mothers. The program was carefully planned and has been supported strongly by Taiwan's Government [61]. Mass immunization against hepatitis B is very well accepted by the people and the coverage rate of vaccination in infants is >96% [10].

Worldwide, there are four different strategies of universal hepatitis B vaccination in newborns (Table 2). The most simple one is to give the vaccine to all newborns regardless of the maternal HBV status. Because screening of pregnant women is not necessary and HBIG is skipped in newborns, this strategy incurs the lowest costs. However, the efficacy may be jeopardized [78,80–83,119]. The most expensive yet most efficacious strategy is to give hepatitis B vaccine to all newborns, and to screen the pregnant women and add on HBIG to the newborns if the mother is positive for HBsAg, regardless of the HBeAg status. Each country can choose its own strategy depending on its own needs after considering epidemiology, disease burden, readiness of the public health system and economic constraint. Any approach in implementing hepatitis B vaccination will help to control hepatitis B in the country.

Table 2
Four different strategies of universal hepatitis B immunization in infants.[a]

Maternal screening	Infants receive		Efficacy	Cost	Example
	Vaccine	HBIG			
Yes (HBsAg and then HBeAg)	Yes	HBeAg-positive mothers' infants only	Higher	Higher	Taiwan
Yes (HBsAg only)	Yes	All HBsAg-positive mothers' infants	Highest	Highest	US
Yes (HBeAg only)	Yes	HBeAg-positive mothers' infants only (2 doses)	High	Highest	Japan[b]
No	Yes	No	Modest	Low	Thailand

HBsAg: hepatitis B surface antigen.
HBeAg: hepatitis B e antigen.
HBIG: hepatitis B immune globulin.
[a] Modified from Chang [120].
[b] Before 1995.

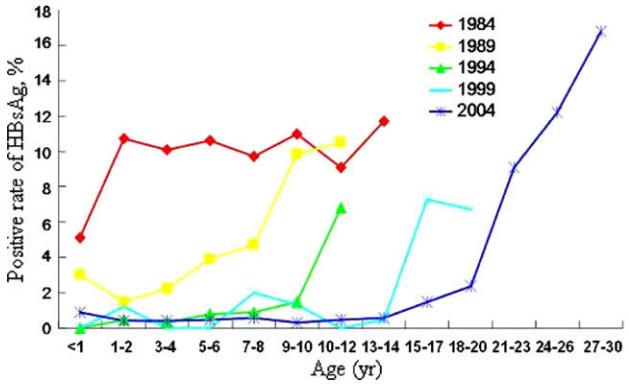

Fig. 1. Prevalence of hepatitis B surface antigen (HBsAg) in healthy children in Taipei from 1984 to 2004 [10]. The mass hepatitis B vaccination started in July 1984.

4.1. Decrease of chronic HBsAg carriage

After implementation of the universal hepatitis B vaccination in infants, seroepidemiologic studies soon reveal a steady and remarkable decrease of chronic HBsAg carrier rate in children, as shown in serial surveys in Taipei City in 1989, 1994, 1999 and 2004 (Fig. 1) [10]. The decrease has been confirmed in other parts of Taiwan (Table 3). Once hepatitis B vaccination is implemented in early childhood, there is always an evident effectiveness of protecting from chronic HBV infection (Table 3). In less endemic areas, the post-vaccination HBsAg carrier rate can even reach zero, harbingering the elimination and eventual eradication of HBV in the population.

Table 3
Effectiveness of protecting from HBsAg carriage after hepatitis B immunization.[a]

Country	HBsAg (%)		Efficacy (%)
	Before	After	
China, rural	14.6	1.4	90.4
China (Shanghai)	11	0.63	94.3
Egypt (Alexandria)	2.2	0.8	63.6
Gambia	12	0.9	92.5
Indonesia (Lombok)	6.2	1.4	61.1
Italy (Afragola)	13.4	0.9	93.3
Japan (Iwate)	0.9	0.03	96.7
(Shizuoka)	0.3	0.03	90.0
Korea	7.5	0.38	94.9
Malaysia	2.5	0.4	84.0
Micronesia	12	2.9	75.8
Polynesia	6.5	0.7	89.2
Saipan	9	0.5	94.4
Samoa	7	0.5	92.9
Saudi Arabia	6.7	0.3	95.5
Senegal	19	2	89.5
Singapore	4.1	0	100
South Africa	12.8	3.0	76.6
Taiwan (Taipei)	10	0.7	93.0
(Hualien)	9.3	1.9	79.6
(Taichung)	14	1.2	91.4
Thailand	4.3	0.7	83.7
US (Alaska)	16	0	100

[a] Reference list will be provided on request.

4.2. Decrease of diseases associated with acute HBV infection

After universal hepatitis B vaccination in infants, the mortality rate of fulminant hepatitis in infants decreases remarkably. In our study, fulminant hepatitis in infants reduced 70% (from $5.36/10^5$ in pre-vaccination era to $1.71/10^5$ post-vaccination) [121]. In addition, fulminant hepatitis B in children older than one year of age is then nearly wiped out [122]. In Italy where HBV is intermediately endemic and universal vaccination of infants and adolescents was launched in 1991, besides decrease of chronic HBV infection, the incidence of acute hepatitis B decreased 50-fold, from $1/10^5$ in pre-vaccination era to $0.02/10^5$ post-vaccination [123]. Nevertheless, it was found that HBV infection through household contacts of chronic HBsAg carriers, injection drug use, and iatrogenic procedures still needed to be interrupted to eradicate the residual HBV infection in the country. An anticipated bonus after universal hepatitis B vaccination in Italy is the marked decrease of acute hepatitis D infection [124]. In Singapore, a similar decrease of acute hepatitis B was also noted after hepatitis B vaccination [125].

4.3. Decrease of diseases associated with chronic HBV infection

After hepatitis B vaccination in South Africa, a hospital-based study clearly demonstrated a sharp decline in the incidence of HBV-associated membranous nephropathy [126]. Another hospital-based study from China also revealed that the incidence of HBV-associated glomerulonephritis decreased steadily after nationwide hepatitis B vaccination program [127].

4.4. Decrease of hepatocellular carcinoma

In endemic areas of chronic HBV infection, HCC is always prevalent and occurs usually after middle age [2,118]. If one wants to see the impact of hepatitis B vaccination on the occurrence of HCC, one would have to wait for 4–5 decades after the vaccination. Fortunately, we found a proxy to serve this purpose. In endemic areas of HBV, HCC in children can be seen occasionally, and is almost always related to chronic HBV infection which was transmitted to the patient from their mothers [128]. To investigate whether or not universal hepatitis B vaccination in newborns has impacts on the occurrence of HCC in Taiwan, we studied the incidence of HCC in children 6–9 years of age. It declined 4-fold from $0.52/10^5$ in the cohort born before implementation of the uni-

versal vaccination program to $0.13/10^5$ in those born after the program [129]. Another study that included Taiwanese children 0–9 years of age also reached the same conclusions [130].After some time, the studies were extended to children of 14 years of age, and the decrease of HCC was again evident [131,132]. Our most recent observations in adolescents (up to 19 years old) have shown that the effect has extended from childhood to early adulthood (unpublished observations). A cohort study from Korea suggested that hepatitis B vaccination in men can reduce the risk of HCC [133]. After large-scale hepatitis B vaccination, a similar trend of decrease in the incidence of HCC has also been reported form Singapore [125], China [134] and Saudi Arabia [135]. However, whether the decrease of HCC in these countries was associated with hepatitis B vaccination could not be ascertained, because the decrease was also seen in adult populations who were not vaccinated.

5. Safety and adverse events

To date, more than one billion doses of plasma-derived or recombinant DNA vaccines have been used, and the safety records of the hepatitis B vaccines are excellent. Besides reactogenicities that include mild fever in 1–6% of vaccinees and soreness at the injection site in 3–30%, there is a remote risk of anaphylaxis (1.1 per million doses) [136]. In addition, the following outcomes have been claimed to be the adverse reactions after hepatitis B vaccination, namely, chronic fatigue syndrome, multiple sclerosis, sudden infant death syndrome, rheumatoid arthritis, leukemia, macrophagic myofasciitis, type I diabetes, vasculitis, immune thrombocytopenic purpura, central retinal vein occlusion, lichenoid, lichen planus, cutaneous lupus, Guillain–Barré syndrome, transverse myelitis, optic neuritis, fluctuating hearing loss, hair loss, etc. Many of them are rare and occur also in the absence of hepatitis B vaccination. The causal association of these disorders with the vaccination is not established (reviewed in [137] recently). A similar situation also occurred in alleged suspicion of ethyl mercury-containing vaccine preservative – thiomersal in causing adverse reactions. Actually thiomersal has long been a safe and effective preservative [137]. Nevertheless, to avoid laborious yet unproductive defence against repeated alleged accusations, many pharmaceutical companies have avoided using it in their vaccines. In making decisions, it should be borne in mind that the benefit of hepatitis B vaccination far outweighs the alleged adverse reactions.

6. Vaccine escape mutants

Under immune pressure of hepatitis B immunization, especially when HBIG is combined, HBV with mutations in the *a* determinant can be selected [138]. The most common is a glycine to arginine change at amino-acid position 145. In Taiwan, the baseline prevalence of the *a* mutants was 7.8% in HBsAg carrier children, and was kept around 20% among HBsAg carrier children in the first 15 years of the universal mass vaccination program [139]. In the last 10 years, there has been no steady increase of the vaccine escape HBV mutants in Taiwanese carrier children who failed in the mass vaccination program, and there has been no evidence of the spread of this virus, likely because of the weakness of the mutant virus [140]. Despite the increased percentage of surface gene mutants after mass hepatitis B vaccination, the actual number of children infected with this mutant is small and is not increasing [139]. The results in Italy also concurred with the same conclusions [141]. Therefore, the presence of vaccine escape mutants does not seem to threaten the ongoing hepatitis B control strategies in Taiwan and Italy, and perhaps, worldwide. Worthy of note is the fact that the current hepatitis B vaccines can protect chimpanzees from the infection with this *a* mutant virus [142]. Hence, the currently available hepatitis B vaccines can be continued.

7. Challenges that need to be solved to expand hepatitis B mass vaccination

Although the hepatitis B vaccine has been available since 1982, and more than one billion people have been vaccinated, there are still many people who are not immunized. According to WHO, in 2006, 40% of infants worldwide had not yet received three doses of hepatitis B vaccine. The causes of failing to offer large-scale hepatitis B vaccination in each country are complicated.

7.1. Improving infrastructure of public health delivery system

In the absence of an effective system of public health delivery, basic regular immunization for infants is impossible, not to mention hepatitis B immunization. Usually such countries are poor and have limited resources for creating and maintaining regular operational facilities for public health. The well-trained public health personnel necessary to carry on the immunization program are also inadequate or even lacking. And thus, it is of vital importance to support these countries, so that vaccinations can be given as much as possible, including the hepatitis B vaccine. Integration of hepatitis B vaccination to the EPI will facilitate the vaccination in children [84,116,117].

Besides the constant endeavors on behalf of governments and WHO, efforts from non-government organizations are also needed. Among them, Global Alliance on Vaccines and Immunization (GAVI) is most note-

worthy. The GAVI was founded in 2000, and is a global coalition of international organizations, philanthropic foundations, private sectors including vaccine industry representatives as well as research and public health institutions [143]. It targets the world's poorest countries to help improve child health by extending the reach and quality of immunization coverage with strengthened health services. The hepatitis B vaccine has been included in the GAVI since 2000. Millions of children since then have received hepatitis B vaccine through the help of GAVI. In 2004, the coverage rate was 37.9% in 52 of the 75 counties eligible for GAVI support. By the end of 2008, 71 countries are expected to have introduced the hepatitis B vaccine [Hepatitis B. GAVI Alliance. www.gavialliance.org].

7.2. Public education

The public should be educated about the importance and necessity of hepatitis B prevention by vaccination. In Taiwan, we dedicated a lot of time and efforts in public education for nearly three years prior to the implementation of our universal vaccination program in 1984 [61]. Because of the importance of giving immunization immediately after birth, young people, especially women of reproductive age, are targeted for this education. At the same time, education of medical personnel is also necessary, because iatrogenic HBV infections are an important mode of HBV transmission. The key role of education can be seen in the Italian experience. Despite the success of universal vaccination against HBV since 1991, household contacts of HBsAg carriers, injection drug use, unprotected sexual behaviors and invasive medical procedures are still evident in transmitting HBV [123].

8. Strategies towards eradication of hepatitis B

As depicted in Fig. 2, HBV infection has three components, an infectious source, a susceptible host and an established route of transmission [3]. Because humans are the only reservoir of HBV, it is not impossible that a comprehensive control can eventually lead to the eradication of the virus. To begin with, the existing HBV carriers can now be treated effectively [5] and viral load can decrease to undetectable levels, so that infection does not spread rampantly. However, prolonged use of current nucleos(t)ide analogs against HBV still poses the problem of viral resistance and the cost of long-term treatment is still high [5]. Another important strategy is to interrupt the transmission route which can be reduced after education of the public and medical personnel as mentioned above although changes in high-risk human behaviors are often difficult. The most effective strategy is to immunize all susceptible individuals with the hepatitis B vaccine, especially children [2,3].

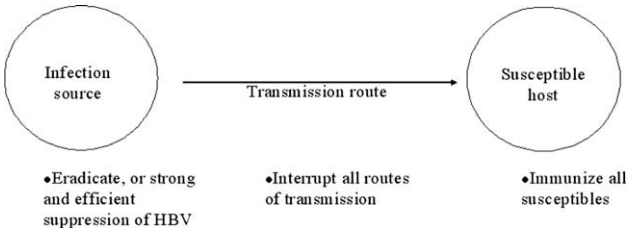

Fig. 2. Components of hepatitis B virus (HBV) infection and the relation to eradication of the infection.

In the modern globalized world, international travel and immigration are frequent, and adoption of children from HBV high-endemicity countries is not uncommon. Countries where the incidence of HBV infection is low should seriously consider shifting their immunization policy from targeting at-risk population to universal childhood hepatitis B vaccination [144–146]. Universal hepatitis B vaccination in childhood can prevent not only chronic HBV infection in high endemic areas, but also acute HBV infection in low endemic areas. Therefore, it should be recommended for all countries, regardless of HBV endemicity [147]. The combined efforts of universal vaccination, antiviral treatment and interruption of transmission make elimination of HBV infection plausible and eventually may result in the eradication of HBV. To reach this goal, all the efforts need to be supported adequately, and a long-term commitment from each government, WHO or non-government organizations is a must. The support should sustain and overcome the existing backlog of HBV carriers in the population. The goal of eradicating HBV is plausible, but every endeavor has to be pursued to make it become a reality.

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