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Hepatitis B virus: Where do we stand and what is the next step for eradication?

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Abstract

Hepatitis B (HB) virus (HBV) infection, which causes liver cirrhosis and hepatocellular carcinoma, is endemic worldwide. Hepatitis B vaccines became commercially available in the 1980s. The World Health Organization recommended the integration of the HB vaccine into the national immunisation programs in all countries. HBV prevention strategies are classified into three groups: (1) universal vaccination alone; (2) universal vaccination with screening of pregnant women plus HB immune globulin (HBIG) at birth; and (3) selective vaccination with screening of pregnant women plus HBIG at birth. Most low-income countries have adopted universal vaccine programs without screening of pregnant women. However, HB vaccines are not widely used in low-income countries. The Global Alliance for Vaccine and Immunization was launched in 2000, and by 2012, the global coverage of a three-dose HB vaccine had increased to 79%. The next challenges are to further increase the coverage rate, close the gap between recommendations and routine practices, approach high-risk individuals, screen and treat chronically infected individuals, and prevent breakthrough infections. To eradicate HBV infections, strenuous efforts are required to overcome socioeconomic barriers to the HB vaccine; this task is expected to take several decades

to complete.

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Core tip: Hepatitis B (HB) vaccines, which are the first vaccines that have been proven to prevent cancer, have played a crucial role in preventing HB virus (HBV) infection worldwide since their development in the 1980s. In particular, the HB vaccines have been rapidly integrated into the national immunisation programs of low-income countries since the Global Alliance for Vaccine and Immunization was launched in 2000. However, we have still not eradicated HBV. More than 240 million people worldwide are carriers of HBV. The vaccine strategies, current status of HBV infection, and unresolved issues related to controlling HBV infection are discussed in this review.

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INTRODUCTION

According to the World Health Organization (WHO), two billion people (one-third of the global population) have been infected with the hepatitis B (HB) virus (HBV) worldwide, and more than 240 million are chronic carriers (4%-6% of the world population)^[1]. Chronically infected individuals have a 25% risk of dying from the

sequelae of chronic HBV infection, such as cirrhosis and hepatocellular carcinoma (HCC)^[2]. Approximately 600000 people die every year due to the consequences of HBV infection^[1]. Globally, chronic HBV infection accounts for 54.4% of the cases of liver cancer^[3]. HBV infection is one of the vaccine-preventable infectious diseases. In 1991, the WHO recommended the integration of the HB vaccine into the national immunisation programs in countries with an HBV carrier prevalence of 8% or higher by 1995 and in all other countries by 1997^[4].

In this review, the vaccine strategies for the control of HBV infection and the prospect of HBV eradication are summarised and discussed.

HB VACCINE

Discovery of the HBV

In 1963, Blumberg *et al*^[5-8] unexpectedly identified a protein in the blood of Australian aborigines, which was later named the Australia antigen. The investigators were examining serum from multi-transfused patients with conditions such as leukaemia or thalassemia compared to serum from a variety of healthy individuals from different parts of the world to identify genetic polymorphisms of serum proteins^[9]. The Australian antigen was initially thought to be associated with leukaemia and Down's syndrome^[5,10], but further observations revealed that the Australia antigen is a component of the infectious agent for HBV. In fact, two patients with Down's syndrome and a technician in Blumberg's laboratory became positive for the antigen after developing hepatitis^[6,8,10-12]. The Australia antigen was eventually confirmed to be correlated with viral hepatitis^[13-16]. In 1970, Dane *et al*^[17] discovered hepatitis B virions -double-coated particles approximately 42 nm in diameter- in the serum of patients with Australia antigen-associated hepatitis.

Development of the HB vaccine

After the discovery of the Australian antigen, it took over 10 years to make the HB vaccine commercially available. The virion of HBV (*i.e.*, the Dane particle) consists of an inner core and an outer membranous envelope, which contains the Australian antigen^[8,18]. Electronic microscopy analyses revealed that enormous numbers of spherical and tubular particles of 22 nm in diameter, which are clearly distinct from the virions, co-exist in the serum of HBV-infected patients^[11,17,19]. These particles are empty viral envelopes, containing only the Australian antigen and non-infectious agents^[6,8,18]. The first available vaccines consisted of purified and formalin-inactivated small empty HBV envelopes containing the hepatitis B surface antigen (HBsAg), which were harvested from the plasma of chronic HBV carriers^[20-23]. These plasma-derived HB vaccines first became commercially available in the United States in 1981 and in France in 1982^[24,25]. Since 1981, plasma-derived HB vaccines have been manufactured and used in many

countries. However, there were concerns about whether the supply of plasma was adequate to meet the demand for the vaccine and whether the safety of a vaccine derived from human blood could be verified. A recombinant expression system was developed to address these problems. The recombinant expression of HBsAg was achieved in HBV-transfected yeast^[26,27]. Electron microscopy revealed that the expressed HBsAg polypeptides showed the same appearance as the particles isolated from human plasma. In 1986, the recombinant HB vaccine (the second-generation vaccine) was approved by the United States Food and Drug Administration^[8,24]. Although new recombinant HB vaccines using HBV-transfected mammalian cells containing pre-S2+S envelope proteins (*i.e.*, third generation vaccines) were commercialised in the 1990s^[25,28,29], the majority of vaccine manufacturers are now adopting a yeast-system for recombinant expression^[30]. The complete vaccine series induces protective levels of anti-HBs antibodies in more than 95% of infants, children, and young adults^[1]. Although the duration of protection provided by the HB vaccine is controversial, the protection afforded by three or four doses of a monovalent HB vaccine persists for at least 20 years^[1,31].

Universal vaccination vs selective vaccination

Two vaccine programs are being conducted worldwide to control and eradicate HBV infection. The first program is universal vaccination, which integrates a three- or four-dose series HB vaccine into routine vaccination programs. The other is selective vaccination, which targets high-risk individuals identified by assessments of chronic diseases, lifestyle, and occupation. The WHO strongly recommends universal vaccination in all countries, and nearly all of the countries throughout the world are adopting such a program^[4]. In addition, high-income countries that can afford to perform screening of pregnant women give hepatitis B immune globulin (HBIG) to newborn babies born to HBsAg-positive mothers at birth. Because screening of pregnant women is costly and not feasible in low-income countries, the WHO does not recommend it for all countries. As shown in Table 1, the current HBV prevention strategies are classified into three groups: (1) universal vaccination without screening of pregnant women; (2) universal vaccination with screening of pregnant women plus HBIG; and (3) selective vaccination with screening of pregnant women plus HBIG.

In intermediate and highly endemic countries, universal vaccination without screening of pregnant women is clearly cost-effective^[32]. However, the protective efficacy rate of a three- or four-dose HB vaccine series alone is 70%-80% in perinatal transmission^[33-35]. In contrast, HB vaccine plus HBIG increases the protective efficacy rate to 95% in perinatal transmission^[35]. Although aspects of the healthcare infrastructure, such as medical personnel, hospitals, and careful follow-up programs, are indispensable for the screening of pregnant women, the adminis-

Table 1 Classification of hepatitis B vaccine prevention strategies

	Universal vaccination alone	Universal vac. + pregnant-women screening + HBIG	Selective vaccination + pregnant-women screening + HBIG
Low- and intermediate-income countries ¹	✓		
High-and intermediate-income countries ¹ (e.g., European countries, United States)		✓	
High-income countries (e.g., Scandinavian countries, United Kingdom, Japan)			✓

¹Intermediate-income countries are using a variety of vaccination strategies; HBIG: Hepatitis B immune globulin.

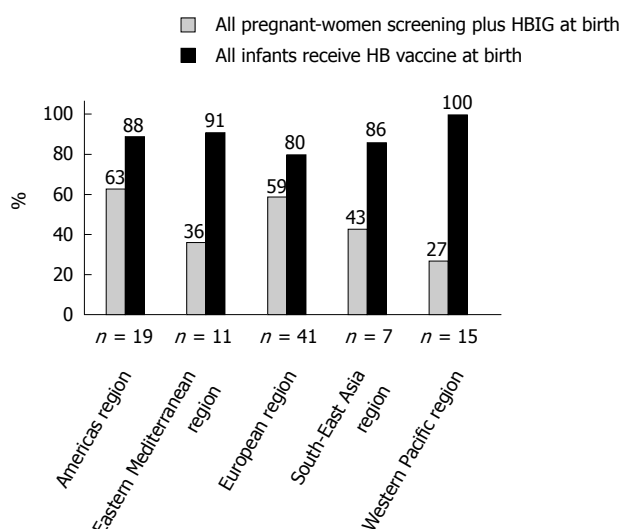


Figure 1 World Health Organization global and regional implementation of universal hepatitis B vaccination at birth and screening of pregnant women plus hepatitis B immune globulin administration at birth. The data were drawn from the WHO "Global policy report on the prevention and control of viral hepatitis"^[36]. HBIG: Hepatitis B immune globulin; HB: Hepatitis B.

tration of HBIG can definitely improve the prevention rate of perinatal transmission.

Universal vaccination with screening of pregnant women plus HBIG is the most effective strategy to reduce and eradicate HBV, if and when the financial condition of a country allows for the implementation of such a program. In fact, almost all high-income countries are conducting universal vaccination with screening of pregnant women plus HBIG. The number of countries providing selective vaccination with screening of pregnant women plus HBIG is small and has gradually declined. Because the prevalence of HBV carriers is low in these countries, universal vaccination is considered not to be cost-effective; instead, the government's target high-risk individuals for vaccination.

GLOBAL POLICY REPORT ON THE PREVENTION AND CONTROL OF VIRAL HEPATITIS

In 2012, a global survey of the efforts to prevent and control viral hepatitis was conducted on the behalf of

the WHO by the World Hepatitis Alliance, a non-government organisation that represents approximately 280 hepatitis B and hepatitis C patient groups around the world^[36,37]. Of the 194 WHO member states, 126 (64.9%) completed the surveys, which is not a sufficiently high response rate. The rates of response to WHO regional surveys were 26.1% (12/46) in the African Region, 77.1% (27/35) in the Americas Region, 77.3% (17/22) in the Eastern Mediterranean Region, 83.0% (44/53) in the European Region, 36.4% (4/11) in the South-East Asia Region, and 55.6% (15/27) in the Western Pacific Region.

The WHO member states are classified into five groups: "high income", "upper-middle income", "lower-middle income", "low income", and "other". The rates of response to the WHO/World Hepatitis Alliance survey in these groups were 80% (40/50: high income), 64.2% (34/53: upper-middle income), 68.0% (34/50: lower-middle income), 47.4% (18/38: low income), and 0% (0/3: other). The proportion of high- and upper-middle-income countries was 2% (1/46) in the African Region, 60% (21/35) in the Americas Region, 32% (7/22) in the Eastern Mediterranean Region, 68% (36/53) in the European Region, 18% (2/11) in the South-East Asia Region, and 26% (7/27) in the Western Pacific Region.

The rates of implementation of screening for all pregnant women plus HBIG at birth and programs administering the HB vaccine to all infants at birth in each WHO region (except for the African Region) are shown in Figure 1. According to this report, the rates of screening of pregnant women plus HBIG administration were 63% (Americas), 36% (Eastern Mediterranean), 59% (Europe), 43% (South-East), and 27% (Western Pacific), with more than half of the countries in the Americas and European Regions adopting HBIG administration after birth. Because high- and upper-middle-income countries are the majority in both the Americas and European regions, these regions can afford to provide screening of all pregnant women plus HBIG administration. In contrast, the Western Pacific Region shows the lowest rate (27%) of screening of pregnant women plus HBIG administration and the second-lowest ratio of high- and upper-middle-income countries.

In light of the low ratio of high- and upper-middle-income countries in the Western Pacific Region, the WHO Western Pacific Office strongly recommends the

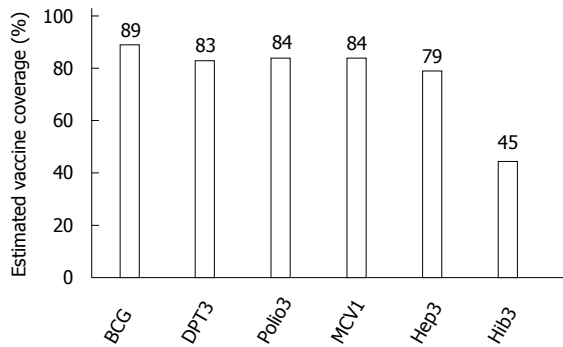


Figure 2 World Health Organization-estimated global coverage rates for the BCG, DPT3, polio, MCV1, Hep3, and Hib3 vaccines in 2012. The data are from^[47]. BCG: Bacille Calmette-Guérin; DPT3: Three-dose DTP; MCV1: Measles-containing vaccine; Hep3: Three-dose hepatitis B; Hib3: Three-dose Hib vaccine

universal administration of a dose of HB vaccine to all newborn infants rather than a targeted approach for infants born to HBsAg-positive mothers^[38]. The coverage of HB vaccine birth dose administration (within 24 h after birth) varies from 80% to 100% among the six WHO regions. The Western Pacific Region achieved 100% birth dose coverage, following sustained efforts by the Western Pacific Office over many years to improve the birth dose coverage in low-income countries^[38]. Conversely, the birth dose coverage rate is not high in the regions where high-income countries are implementing screening of all pregnant women, such as the European Region (80%).

GLOBAL ALLIANCE FOR VACCINE AND IMMUNISATION

Vaccine shortages began to emerge in the late 1990s^[39]. Vaccine manufacturers had begun phasing out the production of the traditional, less-expensive vaccines, such as the diphtheria-pertussis-tetanus (DPT) combination used in low-income countries. Between 1998 and 2001, 10 of 14 manufacturers partly or totally stopped their production of traditional vaccines. In 2001, the availability of the traditional DPT combination tuberculosis and measles vaccine dropped to the lowest level in 10 years. Moreover, the prices of these vaccines were increased.

Compared to traditional vaccines (*e.g.*, DPT, oral polio, measles), which cost (USD) \$0.06-0.10 per dose, the HB vaccine was expensive in the 1980s and 1990s^[40,41]. In 1981, the price of a plasma-derived HB vaccine at introduction was \$30 per dose. Although recombinant HB vaccines provide a safe and stable supply of HB vaccine, the price of the recombinant HB vaccine varied from USD \$30 to \$40, or nearly \$100 for the complete series of three shots. Therefore, the benefits of the development of HB vaccines were not experienced by low-income countries, where the vaccines were greatly needed to prevent HBV infection.

The Global Alliance for Vaccine and Immunization (the GAVI Alliance) is a public-private partnership whose partners include United Nations agencies, the WHO, the

World Bank, public health institutions, donor and recipient countries, the Bill and Melinda Gates Foundation, pharmaceutical manufacturers, and other members of the philanthropic and financial communities. The GAVI Alliance was launched in 2000 to establish vaccination programs in low-income countries. By bringing together low-income countries, donor governments, research and technical institutes, civil society organisations, vaccine providers, and private philanthropists, the dynamics of the global vaccine market have been changed by the establishment of sustainable supplies of vaccines, research, competition, and price reduction. During the first phase (2000-2005), hepatitis B became one of the three under-utilised vaccines [hepatitis B, *Haemophilus influenzae* type b (Hib), and yellow fever] immediately available for routine infant immunisation programs through the new and under-utilised vaccine flagship program^[42-44]. The HB vaccine was considered to have the greatest potential in the implementation of under-utilised vaccines. The widespread use of new and under-utilised vaccines has the potential to contribute to the United Nations Millennium Development Goal 4 of reducing global childhood mortality by two-thirds by 2015^[42,45,46].

GLOBAL COVERAGE OF TRADITIONAL VACCINES AND UNDER-UTILISED VACCINES

The global coverage in 2012 of traditional vaccines was as follows: Bacille Calmette-Guérin (BCG), 89%; the three-dose DTP (DPT3) vaccine, 83%; the three-dose polio vaccine (Polio3), 84%; and the first-dose measles-containing vaccine (MCV1), 84%^[47]. In contrast, as shown in Figure 2, the 2012 coverage of the three-dose HB (Hep3) vaccine and the three-dose Hib vaccine (Hib3) was 79% and 45%, respectively^[47]. A slight difference in the coverage between traditional vaccines and under-utilised vaccines remains. In the 2000s, the GAVI Alliance began introducing the combination pentavalent vaccine (DPT-hepB-Hib)^[48]. The GAVI Alliance increased the number of manufacturers and reduced the price of the pentavalent vaccine. Most GAVI-eligible countries thus switched to the pentavalent vaccine. By 2015, the GAVI Alliance aims to support the immunisation of an additional 230 million children with the combination pentavalent vaccine^[49]. Therefore, the immunisation status of HBV and Hib will soon become the same as that of DPT.

STATUS OF HB VACCINATION

Universal vaccination without screening of pregnant women

Almost all of the countries classified by the WHO as low-income use universal vaccination without screening of pregnant women. The WHO/United Nations Children's Fund and the GAVI Alliance have important roles in the prevention of HBV infection in these countries.

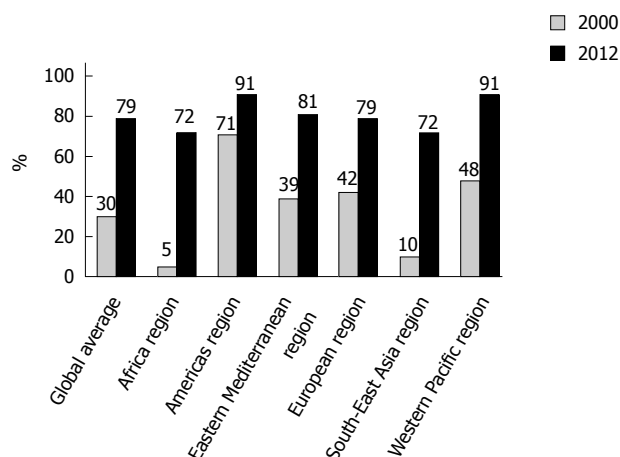


Figure 3 World Health Organization-estimated global coverage and coverage in each WHO region for the universal 3-dose hepatitis B vaccine in 2000 and 2012.

With the GAVI Alliance's support, many low-income countries were able to introduce an HB vaccine into their routine vaccine programs. As shown in Figure 3, the global average of the universal three-dose HB vaccine immunisation rate was 30% of the WHO member states in 2000^[47]. Very low introduction rates were revealed in the Africa Region (5%) and the South-East Asia Region (10%)^[50]. Only the Americas Region achieved above 50% in the universal three-dose HB vaccine immunisation rate in 2000^[50]. However, by 2012 the global average of the universal three-dose HB vaccine immunisation rates had more than doubled to 79%^[47]. In that year, the routine three-dose HB vaccination coverage was approximately 90% in the Americas Region and Western Pacific Region, and the coverage rates in the African Region and South-East Asia had increased by 14- and 7-fold, respectively.

African region: All of the African Region WHO member states except for Algeria are in Sub-Saharan Africa, which has two-thirds of all of the worldwide cases of human immunodeficiency virus (HIV)^[36]. The prevalence of HBV is estimated at 8% in West Africa and 5%-7% in Central, Eastern, and Southern Africa^[51,52]. Due to the lower prevalence of the serum hepatitis B e antigen (HBeAg) in Africa compared to that in Asia, HBV infection in Africa is thought to be acquired almost always in early childhood by horizontal transmission rather than by vertical transmission^[53-56]. In Sub-Saharan countries, a birth dose is not used; instead, a 6-, 10-, and 14-wk ("6-10-14") after birth vaccination schedule is common^[57,58]. Although universal infant HB vaccination was introduced in only 5% of the African Region member states in 2000, the introduction rate had increased to 72% by 2012^[50]. Although a birth dose might be beneficial for African infants^[58], no information about the birth dose or regional goals in Africa is available.

Americas region: In the WHO Americas Region, the

prevalence of HBV infection varies from low to intermediate^[59]. The prevalence of HBV infection is less than 2% in the central and tropical Latin America region, and it has remained between 2% and 4% in the Caribbean, Andean, and south Latin American regions^[36,52]. In 2000, the Pan American Health Organization (PAHO) recommended that universal infant HB vaccination should be the primary strategy to prevent HBV transmission^[59,60]. The decision to introduce a birth dose of HB vaccine depended on the prevalence of HBV carriers in each country. The PAHO recommended that a birth dose should be added to the vaccine program in the countries and territories where the prevalence of HBsAg exceed 8%^[59,61]; the majority of the countries had no birth dose in their routine vaccine schedules. Without a birth dose, a 2-4-6 mo after birth schedule is predominant^[59]. In 2012, however, the PAHO advised all of the region's countries to introduce a birth dose (within 24 h of birth) for universal infant HB vaccination^[62]. As shown in Figure 3, the universal three-dose HB vaccine immunisation rate of the Americas Region was 91% in 2012, the highest among the WHO regions.

Eastern Mediterranean region: The epidemiology of HBV infection in this region is complex. Before the introduction of the HB vaccine into the region's routine immunisation programs, the prevalence of HBV carriers ranged from 2% to 3% in several member states; however, the prevalence was more than 10% in the region members of Somalia and Sudan^[63]. Similar to other regions, the universal infant HB immunisation rate increased to 81% by 2012, which is double the figure in 2000^[50]. In 2009, universal infant HB vaccination, including a birth dose (within 24 h of birth), was recommended by the Eastern Mediterranean Regional Office, and a reduction in the prevalence of chronic HBV infection to less than 1% among children over 5 years of age by 2015 was set as a time-bound regional goal^[63].

European region: Although high- and upper-middle-income countries are the majority in the European Region, the rate of universal HB vaccination was only 79% in 2012, giving the region the rank of fourth highest among the six WHO regions^[50]. Although Italy was one of the first countries to begin universal HB vaccination for infants, northern European countries are still using selective vaccination programs. Three countries give the first shot of HB vaccine to school-aged children^[64]. It was reported that 13.3 million (1.8%) adults in the European Region had HBsAg; furthermore, two-thirds of the region's residents who are infected with HBV live in the countries that are not part of the European Union/Free Trade Treaty Association^[65], indicating that in the European Region one in 50 adults is an HBV carrier. As long as northern European countries continue selective vaccination, the universal immunisation rate will not reach 100%.

South-East Asia region: The universal HB immuni-

sation rate in the South-East Asia Region in 2000 was 9%, the second lowest figure among the WHO regions. Although universal immunisation reached 72% in 2012, this figure was the lowest among the WHO regions^[50]. Mirroring the universal HB vaccination rate, the 2012 DPT coverage rate of the South-East Asia Region was the second lowest (75%) among the WHO regions^[66]. These findings suggest that the implementation of the entire panoply of immunisation programs is insufficient in this region. The WHO Regional Office encourages the South-East Asia member states to intensify their routine vaccine immunisation programs^[67].

Western Pacific region: Although the Western Pacific Region comprises only 28% of the global population, the region bears a disproportionate burden of HB-related mortality and morbidity, accounting for almost half of all chronic HBV infections worldwide. An estimated 160 million people with chronic HBV infection live in this region, and the regional HBV-related mortality rate is comparable to that of tuberculosis^[68,69]. The control and prevention of hepatitis B infection is thus the top priority in this region. In 2005, the Western Pacific region became the first region to set a time-bound goal of reducing the chronic HBV infection rate to less than 2% among five-year-old children by 2012^[69]. This milestone influenced the individual countries' national policies^[70] and resulted in the highest coverage rate (91%) for universal HB vaccine immunisation among the WHO regions in 2012^[50].

Universal vaccination with screening of all pregnant women plus HBIG

The universal vaccination with screening of all pregnant women plus HBIG strategy is expensive and complicated, but it is the most powerful strategy to prevent and control HBV infection. High-income countries, such as the United States and Italy, are implementing universal vaccination, screening all pregnant women, and administering HBIG to babies born to HBsAg-positive mothers at birth.

In the United States in 1982, the Advisory Committee on Immunization Practices (ACIP) recommended that persons with a substantial risk of HBV infection should be vaccinated^[71]. The initial strategies for preventing HBV infection focused on the immunisation of high-risk groups: healthcare workers, men who have sex with men (MSM), drug users, recipients of certain blood products, and close contacts. However, many people who had no identifiable source for infection were infected with HBV^[72]. In 1991, the ACIP proposed, for the first time, that hepatitis B vaccination was recommended for all infants regardless of the HBsAg status of the mother^[73]. In Italy, an HB vaccine program for the high-risk groups began in 1983^[74]. Despite the decreasing circulation of HBV in the late 1980s, a compulsory universal vaccination against HBV was introduced for all newborns and for 12-year-old children (a double cohort

policy of mandatory immunisation) in Italy in 1991^[75-77]. In some counties, a birth dose (administration within 24 h after birth) is not given if the screened mother is negative for HBsAg^[78,79]. In the United States, a birth dose of the monovalent HB vaccine is given to babies born to HBsAg-negative mothers before discharge from the hospital^[80]. In Europe, a monovalent or polyvalent vaccine is given to babies born to HBsAg-negative mothers at 2 or 3 mo after birth as the first dose^[78,79]. As a birth dose, a monovalent vaccine should be used. In Germany, four doses are recommended for the hexavalent vaccine, and three doses are used for the monovalent vaccine^[77,78]. Serum HBsAg is usually used for the screening of pregnant women. However, serum HBeAg is also used for screening in a few countries^[81]. In Taiwan, free HBIG is administered to newborn babies born to HBs-positive and HBe-positive mothers^[81-83]. Because the risk of mother-to-child transmission is considered low in babies born to HBsAg-positive and HBe-negative mothers, the administration of self-paid HBIG is optional for the families of babies born to HBeAg-negative mothers^[82,83].

Selective vaccination with screening of pregnant women plus HBIG

Denmark, Finland, Iceland, Japan, Norway, Sweden, and the United Kingdom, which are low-endemic countries (prevalence of HBsAg < 1%)^[65], use selective vaccination^[77,78]. Of these seven countries, in 2012, five were among the 10 countries with the lowest mortality rates for children under 5 years of age, and all seven are among the 24 richest countries in 2013^[84,85]. In these countries, selective vaccination is considered more cost-effective than universal vaccination. In 2008, however, Ireland gave up selective vaccination and introduced a universal childhood vaccination program with a hexavalent vaccine^[86,87]; the Netherlands decided to implement universal vaccination in 2011^[88-90]. Selective vaccination targets individuals at high risk of HBV infection, but the definition of high risk varies from country to country. In 70% or more of the countries with selective immunisation programs, high-risk individuals include the following: injection drug users; non-injection users who are living with current injectors; sexual partners of injection users; children of injectors; MSM; close family contacts; healthcare workers; laboratory staff; police, fire, and rescue services; babies born to mothers who are chronically infected with HBV or to mothers who have had acute hepatitis B during pregnancy; people traveling to or going to reside in an area of high or intermediate prevalence; individuals receiving regular blood or blood products; and individuals in residential accommodations for those with learning difficulties^[77]. In these countries, HBIG is given to babies born to HBsAg-positive mothers. In England, the indications for HBIG are as follows: infants of mothers with acute hepatitis, mothers who are HBsAg-positive and HBeAg-positive, mothers who are HBsAg-positive and HBeAg/anti-HBe-negative, mothers whose HBeAg/anti-HBe status is unknown,

Table 2 Hepatitis B surface antigen prevalence before and after the introduction of universal vaccination for hepatitis B virus

Ref.	Region	Country	Subjects	Year of the introduction of infant universal vaccination	HBsAg positive rate			
					Before-vaccination program	Year	After vaccination program	Year
95	North America	United States	(Hawaii) School children	1992	1.6%	1989	0.04%	2001-2002
96	South America	Colombia	(Colombian Amazon) 5-9 yr of age	1992	7%	1992	2%	1999
97	Asia	Taiwan	(Taipei) ≤ 12 yr of age	1984	9.8%	1984	1.3%	1994
94	Asia	China	Young children	1992	9%-12%	1992	< 1%	2005
98	Europe	Italy	(Afragola) General population	1991	13.4%	1978	0.91%	2006
99	Africa	South Africa	(Gauteng Province) ≤ 24 mo after birth	1995	8%-9%	1995-1996	0.9%	2003-2004
100	Africa	Gambia	(Keneba) ≤ 24 yr of age	1984	13.3%	1984	0.6%	2003
100	Africa	Gambia	(Mandar) ≤ 24 yr of age	1984	35%	1984	1%	2003

Table 3 Incidence of acute hepatitis B before and after the introduction of universal vaccination for hepatitis B virus

Ref.	Region	Country	Subjects	Year of the introduction of universal vaccination	Annual incidence of acute hepatitis B cases per 100000 population			
					Before vaccination program	Year	After vaccination program	Year
101	North America	United States	0-19 yr of age	1992	3	1990	0.3	2002
102		United States (Alaska)	Under 20 yr of age	1984	19	1981-1920	0	1993-1994
103	Asia	Taiwan	Infants	1984	5.36	1975-1984	1.71	1993-1994
104	Europe	Italy	General population	1991	5.1	1991	1.3	2005

mothers whose serum HBV DNA levels are $\geq 1 \times 10^6$ IU/mL, and infants whose birth weight is less than 1500 g^[91,92]. Japan has a unique schedule of HB vaccines plus HBIG. Babies born to HBeAg-positive mothers are administered HBIG twice (48 h and 2 mo after birth) followed by a three-dose HB vaccine series without a birth dose^[93].

RESULTS OF UNIVERSAL VACCINATION

Prevalence of HBsAg

Since the introduction of infant universal vaccination, successful results of universal vaccination for HBsAg have been reported in many countries, although in almost all of the relevant studies the subjects are children and adolescents (Table 2). The report from China noted in Table 2 was a nationwide survey^[94], and the remaining data concern limited areas of the United States, Colombia, Taiwan, Italy, South Africa, and Gambia. With the introduction of infant universal vaccination, the prevalence of HBsAg declined from 1.6% to 0.04% in the United States^[95], from 7% to 2% in Colombia^[96], from 9.8% to 1.3% in Taiwan^[97], from 9%-12% to < 1% in China^[94], from 13.4% to 0.91% in Italy^[98], from 8%-9% to 0.9% in South Africa^[99], from 13.3% to 0.6% in Gambia (Keneba), and from 35% to 1% in Gambia (Mandar)^[100]. The highly endemic countries in particular showed a remarkable reduction in the prevalence of HBsAg.

Acute hepatitis B

The incidence of acute hepatitis B is shown in Table 3. Almost all cases of acute hepatitis B are asymptomatic.

All studies except a study that was performed in Alaska were nationwide surveys^[101-104]. The study from Taiwan evaluated the mortality from fulminant hepatitis, whose pathogen was not identified^[103]. The incidence of acute hepatitis B per 100000 people declined from 3 to 0.3 in the United States^[101], from 19 to 0 in Alaska^[102], from 5.36 to 1.71 in Taiwan^[103], and from 5.1 to 1.3 in Italy^[104]. Clear and sizable reductions in the incidence of acute hepatitis B were achieved after the introduction of universal HB vaccination programs.

HCC

It takes several decades for HCC to develop after an individual becomes an HBV carrier^[105]. Only approximately 25 years have passed since the first introduction of universal vaccination for HBV, and thus the number of studies evaluating the incidence of HCC is still limited (Table 4). HCC associated with HBV infection was often observed in young children in Taiwan^[106-108]; this finding was very useful for the evaluation of the effectiveness of universal vaccination in a short period. The study from Taiwan showed that nationwide universal vaccination reduced the incidence of HCC in children in 1997^[109], which was 13 years after the introduction of the universal vaccine program in that country. The annual incidence of HCC per 100000 people in Taiwan declined from 0.7 to 0.36 in children 6 to 14 years of age and from 0.52 to 0.13 in those 6 to 9 years of age^[109]. This was the first report proving that a vaccine could prevent cancer. Moreover, in Alaska, universal newborn vaccination coupled with a simultaneous catch-up vaccination program reduced the annual incidence of HCC

Table 4 Incidence of hepatocellular carcinoma before and after the introduction of universal vaccination for hepatitis B virus

Ref.	Country	Subjects	Year of the introduction of universal vaccination	Annual incidence of HCC cases per 100000 population			
				Before vaccination program	Year	After vaccination program	Year
102	United States (Alaska)	Under 20 yr of age	1984	3	1984-1988	0	1995-1999
109	Taiwan	6-14 yr of age	1984	0.7	1981-1986	0.36	1990-1994
109	Taiwan	6-9 yr of age	1984	0.52	1974-1984	0.13	1984-1986

HCC: Hepatocellular carcinoma.

per 100000 from 3 to 0^[102]. Since 1999, no cases of HCC have occurred in Alaska^[102].

NEXT STEPS

Further increase in vaccine coverage

The GAVI Alliance estimated that 3.7 million future deaths from HBV infection were averted by vaccine programs conducted during 2000 and 2011^[110]. The GAVI Alliance also estimated that 4.9 million future deaths will be averted during the years 2011 to 2020 in the 73 GAVI-eligible countries, compared to no vaccinations^[111]. Although the global coverage of HB vaccine lags behind the global coverage levels for DPT, which is an indicator of expanded immunisation programs, the continued introduction of pentavalent vaccines will improve this situation.

In the WHO Africa and South-East Asia regions, however, the coverage of the HB vaccine was still lower than 80% in 2012^[50]. Moreover, these two WHO regions had not reached 80% DTP3 coverage in 2012^[50], a coverage minimum set by the Global Immunization Vision and Strategy (GIVS) as a target at the national level to form the framework for strengthening national immunisation programs in 2006 and 2015^[112,113]. To improve the poor immunisation coverage and achieve the GIVS target, the South-East Asia Regional director declared 2012 as the year for intensifying routine immunisations^[67,114]. In the South-East Asia Region, the coverage of a three-dose HB vaccine increased from 56% in 2011 to 72% in 2012^[50].

Although inter-country differences exist, the Africa Region is facing a significant hurdle in its efforts to meet the GIVS goal^[52,113,115]. Among HIV-infected individuals in sub-Saharan Africa, the prevalence of HBsAg is 15%^[116]. HIV sero-positivity increases the risk of failure to respond to vaccines^[117-119]. Many researchers have noted that to increase the HB vaccine coverage rate, it is necessary to secure firm commitments from governments (political commitment), financial flow, consistent scheduling of vaccination outreach programs, stable vaccine supplies, strong infrastructures (e.g., cold chain, stock space for new vaccines, delivery points), inter-sectional coordination, adequate human resources (including educated and trained healthcare providers), the education of women and parents, and surveillance systems to determine the impact of vaccines^[120-126]. The GAVI Alliance is expected to have substantial public impacts on

vaccination coverage in both WHO regions in 2011 and 2020^[111,113].

A mathematical model predicts that 90% of the complete HB vaccine series coverage rate, including a birth dose, can achieve an 84% reduction in HBV-related deaths^[127]. On the basis of this mathematical model, a pessimistic view is that the HB vaccine alone might be insufficient to eradicate HBV^[128]. In addition, there is concern about the quality of immunisation coverage data. Inconsistencies in immunisation data have been observed in many countries. Although there are no data about such inconsistencies regarding the HB vaccine, the proportion of verified DPT-3 doses was found to be lower than 85% (after over-reporting) in 16 of 27 countries^[129]. In many cases, the survey-based DPT-3 immunisation coverage rates have not reached the level suggested by countries' official reports or WHO/UNICEF estimates^[130]. Immunisation data quality audits are needed to obtain accurate and timely data and to determine how best to improve immunisation programs.

Filling a gap between protocol and routine practice

Not only the coverage rate but also age-appropriate vaccinations (*i.e.*, timely vaccinations) are important to control infections. However, vaccinations are often delayed after the recommended ages^[131-134]. In 31 low- and middle-income countries, the median fraction of timely administered vaccinations was 65% for BCG vaccine, 67% for DPT-1, 41% for DTP-3, 68% for polio-1, 38% for polio-3, and 51% for MCV^[131]. The median delay in the 31 countries was 2.1 wk for BCG, 2.4 wk for DPT-1, 6.3 wk for DPT 3, 2.0 wk for polio-1, 6.6 wk for polio-3, and 4.1 wk for MCV^[131]. Although that study did not discuss the HB vaccine, an HB vaccination delay could presumably be occurring in low- and middle-income countries. For example, in Argentina only 33% of children were vaccinated on time with the HB vaccine by seven months of age in 2002^[135]. In Cambodia, the timely birth dose (within 24 h after birth) coverage was 66%^[136]. In the 2000-2002 National Immunization Survey for each state in the United States, the timely administration of a three-dose HB vaccine among children aged 24 to 35 mo ranged from 49.4% (Vermont) to 81.6% (Rhode Island)^[137]. Although the HB vaccine birth-dose coverage has increased year after year since 2000 in the United States, the nationwide coverage was still only 61.5% in 2007^[138]. These data suggest that delayed vaccinations occur frequently in high-income countries just as in low-

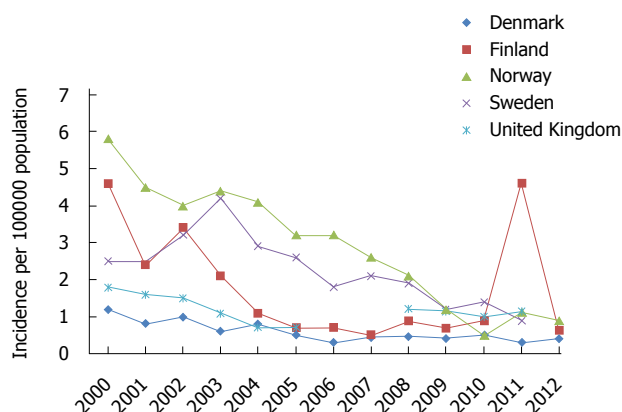


Figure 4 Incidence of acute hepatitis B in northern European countries with selective vaccination (◆: Denmark; ■: Finland; ▲: Norway; ×: Sweden; *: United Kingdom). The data for 2006 and 2007 in the United Kingdom were not available.

income countries.

The situation for programs providing for the screening of pregnant women plus HBIG, which is implemented in high-income countries, is more complicated. The screening rate of pregnant women varies from 96.5% to 98.8% in Puerto Rico, the United States, Italy, and Denmark^[139-142]. In the United States, perinatal HBsAg test results were documented in 92.6% of maternal medical records; 13.7% of the infants born to HBsAg-positive mothers were not administered an HB vaccine, and 20.1% of infants were born to mothers with unknown HBsAg status^[143]. Because the testing and reporting is incomplete in the United States, the true number of perinatal HBV cases per year is likely to be 10 to 20 times higher^[144]. In infants born to HBsAg-positive mothers in the United States between 1994 and 2008, the administration rates of HBIG and the HB vaccine at birth remained at the same levels (from 90.3% to 96.4%), and the rate of completed 3-dose series vaccinations by age 12 mo decreased from 86.0% to 77.7%^[145]. The reported rates of missed HBIG administration at birth were 4.0% in Denmark, 5.0% in Italy, 19.7% in the United States, and 62.4% in China^[141-145,146]. To eradicate HBV infection, closing and/or filling the gaps between the recommended protocol and routine practices are imperative in all countries.

Intensification of approaching high-risk groups

Because the awareness and knowledge of HBV infection and the HB vaccine are insufficient among people who engage in high-risk behaviours^[147], it is important to approach high-risk groups using both selective and universal vaccination strategies^[148-150]. The European Centre for Disease Prevention and Control reported that heterosexual transmission (23.4%), nosocomial transmission (23.2%), injected drug use (13.4%), and transmission among MSM (10.3%) were the most common routes for acute hepatitis B transmission in 2011^[151]. The coverage rates of HB vaccination among high-risk populations

were 6% to 39% (MSM, drug users, commercial sex workers, and heterosexuals; > three doses) in the Netherlands in 2007, 50.5% (> one dose), and 41.8% (> three doses) in the United States in 2009, and 22% (prisoners; > one dose) in England and Wales in 2010^[66,152,153]. Even among healthcare workers, the coverage rate of the HB vaccine was 84.9% in Belgium, 85.3% in Italy, 87.5% in Poland, 88.0% in Spain, 93.0% in the United Kingdom, and 75.0% in the United States^[154,155]. Household exposure and close family contacts of HBV carriers are another high-risk group. According to a survey of European countries, 90% of the countries with a universal vaccination program and all of the countries with a selective vaccination program recommended HB vaccination for individuals with close family contacts with HBV carriers^[77]. However, the vaccine coverage was found to be only 25%-34% among the household contacts of HBV carriers in Italy, the United Kingdom, and Denmark^[142,156,157].

If high-risk adults are not identified or approached, the health of the children in the area will continue to be threatened. This is a particularly serious problem in the countries implementing selective vaccination policies, where almost all children are susceptible to HBV. Thus, whether these countries with selective vaccination will change their policies has become the focal point of increasing attention^[158-163]. The incidence of acute hepatitis B in five northern European countries with selective vaccination is illustrated in Figure 4^[164-166]. For the past decade in these countries, the incidence of acute hepatitis B continued to decrease. However, there is no obvious trend of decline in the incidence of acute hepatitis B per 100,000 people, which fluctuates approximately 0.3-0.6 in Denmark and 0.7 to 1.0 in the United Kingdom. Because the burden of HBV has remained more or less the same over time since 1990 in the Netherlands despite the use of an intensified targeted approach, the Netherlands recognised the failure of the target vaccination strategy and decided to adopt universal vaccination^[89]. Many studies have reported that it is difficult to reach high-risk groups^[89,159,167-170], and the targeting of vaccinations for adults belonging to high-risk groups must be strengthened to eliminate HBV infection^[171].

Generations miss the benefit of the universal HB immunisation

More than two decades have passed since the first introduction of nationwide universal vaccination, which occurred in Taiwan^[172]. Unfortunately, the HB vaccine is not beneficial to individuals who are already chronically infected with HBV, and the majority of HBV carriers might have been born before the introduction of universal vaccination in their country. Some chronically infected individuals might miss the opportunities to receive an infant vaccination or a catch-up vaccination despite the implementation of vaccine programs. Most chronically infected people are unaware of their infection and thus do not receive appropriate treatment.

The WHO global action plan indicated that one of several remaining challenges is the fact that millions of chronically infected individuals do not have timely access to testing, care, and effective treatment to delay the development of the disease and to prevent disability^[51]. In the United States, the incidence of acute hepatitis B declined by as much as 80% between 1987 and 2004^[173]. However, this decline in acute hepatitis B did not diminish the burden of chronic HBV infection. The burden of HBV infection in the United States, as measured by inpatient and outpatient healthcare utilisation, waitlist registration for liver transplantation, and mortality related to HBV infection, increased substantially throughout the 1990s due to the immigration of a large number of persons from Africa and Asia^[173]. In the United States, over half of the individual members of racial/ethnic minority groups have not been tested for HBV, and only one-half of those who tested positive have ever received treatment^[174]. Similar to the United States, the United Kingdom also suffers from the burden of chronically infected individuals who were born outside the United Kingdom^[175-178]. Chronic HBV infection in migrants has been estimated to account for 96% of all newly added chronic HBV infections in England and Wales between 1996 and 2000^[175]. Because screening of the general population is unlikely to be cost-effective, the screening of high-risk populations has been introduced in high-income countries^[179-182]. In 2008, the United States Centers for Disease Control updated and expanded the guidelines for testing for chronic HBV infection, in which persons born in geographic regions with an HBsAg-positive prevalence > 2% are recommended for testing^[183]. The guidelines recommend the early testing and detection of chronic HBV infection. The 2% screening threshold for the prevalence of chronic HBV infection was demonstrated to be cost-effective^[184]. Recent studies in the Netherlands and Canada demonstrated that a selective HBV screening program targeted at all migrants followed by early treatment could be cost-effective^[180,185]. This “screen and treat” policy was reported to provide early disease detection, early antiviral treatment, the prevention of HBV-related advanced liver disease, and good quality of life^[185,186]. In contrast, low-income countries have no prospect of screening of the high-risk population, diagnosis, or effective treatment^[187,188]. The WHO estimates that less than 50% of the blood supply in sub-Saharan Africa is screened for HBV^[188]. The budgetary allocation for the implementation of health programs is critically important to identify and treat HBV carriers.

Breakthrough infections

There is no clear definition of “breakthrough infection.” Thus, the term is used in several varying contexts^[189,190]. In general, “breakthrough infection” means that an HBV infection occurs despite a history of HB vaccination. In the literature, “breakthrough infection” is often characterised by the seroconversion for anti-HBc antibodies or the detection of HBsAg. The pre-existence of anti-

HBs antibodies seems to not always be necessary for the diagnosis of “breakthrough infection”^[190]. Therefore, primary vaccine failure (non-responder), waning immunity after vaccination (decline of anti-HBsAb levels over time), the emergence of escape mutants, and inappropriate vaccine schedules can all be causes of “breakthrough infection”.

Although the evidence is insufficient, non-genotype A could be one of the causes of breakthrough infections^[191-193]. In the prophylactic treatment of mother-to-child transmission, a high maternal viral load is the highest risk factor for breakthrough infection^[82]. Of course, off-schedule treatment and escape mutants can also cause a breakthrough infection during prophylactic treatment in the perinatal period^[194]. The frequency of anti-HBc antibodies in vaccinated children born to HBV carrier mothers was 3.3% (HBsAg-positive carriers: 0.6%) in Italy^[195], 8.9% (HBsAg-positive carriers: 3.5%) in China^[196], 1.7% in the United Kingdom^[197], 25.5% (HBsAg-positive carriers: 2.9%) in Thailand^[198], and 6% (HBsAg-positive carriers: 2.9%) in Greenland^[199]. In all of these countries except Thailand, HBIG was administered at birth.

In vaccinated adolescent general populations, the frequency of anti-HBc antibodies was 1.8% in Alaska, 13.8% in Gambia, and 4.1% in Taiwan^[100,200,201]. Although the rate of breakthrough infection might be influenced by the prevalence of chronic HBV infection in each country, at least a few per cent of vaccinated children could experience a breakthrough infection. Nuclear acid amplification testing for the screening of blood donations, which was introduced for detecting the early window period of HBV infection, identified blood donors with vaccine breakthrough infections who had a history of vaccination and were positive for both HBV DNA and anti-HBs antibodies^[192,193,202]. The blood donors with vaccine breakthrough infections developed subclinical acute infection but not chronic infection. Similarly, adolescents and young adults vaccinated in infancy showed transient infection but no chronic infection^[203,204]. These findings suggested that a completed series of the HB vaccine cannot guarantee that HBV infection would be completely prevented^[205].

Booster doses

The need for booster doses in HB vaccine programmes remains controversial. The duration of vaccine-induced immunity is uncertain, but it is definitely long-term (> 15-20 years)^[172,203,206]. Several studies have reported that booster doses of infantile immunisation should be considered in adolescence^[207-209]. However, numerous studies have demonstrated that booster doses are not needed in immunocompetent individuals who have received a complete series of HB vaccines^[31,172,190,196,203,204,206,210,211]. At present, the WHO does not recommend the universal administration of booster doses. However, immunocompromised hosts, such as hemodialysis patients and HIV-positive patients, are known low responders to vaccines.

Although routine serologic examinations of anti-HBs antibody levels are not needed after HB vaccination, it is recommended that healthcare providers, chronic hemodialysis patients, HIV-infected patients, and other immunocompromised individuals should be monitored and receive booster doses if their anti-HBs antibody levels decrease to less than 10 mIU/mL^[190,211].

Low and non-responders

In 5%-10% of healthy individuals, a three-intramuscular-dose series of the HB vaccine fails to produce protective antibody levels (> 10 mIU/mL)^[212-214]. Increasing age, smoking status, male gender, and obesity are the risk factors for poor or no response to the HB vaccine^[212,213,215]. Specific human leukocyte antigen (HLA) types have been reported to be associated with the antibody response to the HB vaccine^[216,217]. The HLAs are coded by the major histocompatibility complex (MHC) group of genes located on chromosome six in the human genome. The MHC complex plays a central role in the development of the adaptive immune response to HBsAg.

In efforts to overcome the low and non-responsiveness to the HB vaccine, several approaches have been proposed. An additional dose, an additional three-dose series, an increased vaccine dose, changing the route of administration, new adjuvants, and granulocyte-macrophage colony stimulating factor (GM-CSF) have all been proposed to be influential factors for improving the seroprotection rate. The most common strategy for low responders and non-responders is to give an additional vaccine or a series of vaccines. The best injection site was confirmed to be the deltoid muscle, except in infants^[218,219]. Of low and non-responders to the initial three-dose series, 39%-91% and 61%-100% showed good responses after one additional dose (4th dose) and an additional three-dose series, respectively^[220,221]. An additional three-high-dose series vaccine could further improve the seroprotection rate^[222,223]. Moreover, an additional double dose of the combined hepatitis A and hepatitis B vaccine was shown to increase the seroprotection rate to 59% after the first dose and to 95% after the third dose in non-responders^[224]. The hepatitis A component might act as an adjuvant for the hepatitis B response. In the United States, chronic hemodialysis patients who had no response to an initial three-dose series are advised to receive a second series using the same dose and schedule^[225]. Clearly, the reduction in the numbers of non-responders depends on the number of additional doses^[226,227]. Because it is speculated that intradermal inoculation may activate dermal keratinocytes and Langerhan's cells, inducing an effective lymphocyte response^[226,228], intradermal vaccination is considered to be superior to intramuscular vaccination^[229]. However, a meta-analysis showed that intradermal vaccination was almost equivalent to intramuscular vaccination^[229]. The HB vaccine using a new adjuvant system (AS04), which is a combination of a fragment of the bacterial

lipopolysaccharide and alum, demonstrated more effective seroprotection rate results than a conventional HB vaccine^[215,229]. GM-CSF is a candidate cytokine adjuvant, and it is used for the revaccination of non-responders^[230]. A standard dose vaccine plus GM-CSF showed almost the same seroprotection rate as that provided by a high-dose vaccine in healthy non-responders^[231]. Although there are several options to overcome poor responsiveness to HB vaccines, no consensus protocol has been established.

CONCLUSION

HB vaccines are very effective against HBV infection and were shown to be the first useful tool for cancer prevention. Financial support for global immunisation, as encouraged by the GAVI Alliance, has become solid and stable. However, the path to the eradication of HBV presents further obstacles. The difficulties to overcome include identifying the best ways to increase coverage rates, closing the gap between recommendations and routine practices, approaching and treating high-risk individuals, screening and treating chronically infected individuals, and preventing breakthrough infections. HBV infection is one of the diseases considered to be a candidate for global eradication, similar to polio, but it is presumed that several decades of effort will be necessary to eradicate HBV. We must acknowledge that the war against HBV will not be over soon. The difference in the prevalence of HBsAg between high- and low-endemic countries is becoming small. Eventually, the countries implementing selective vaccination for HBV will make the wise decision to introduce universal vaccination for global eradication. Although it is uncertain whether the victory against HBV will be gained using only vaccines; at present, vaccines are the most cost-effective method for the control of HBV infections.

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