

## Three decades of hepatitis B control with vaccination

Liliane C Meireles, Rui Tato Marinho, Pierre Van Damme

Liliane C Meireles, Rui Tato Marinho, Department of Gastroenterology and Hepatology, Centro Hospitalar Lisboa Norte, 1649-035 Lisbon, Portugal

Pierre Van Damme, Centre for the Evaluation of Vaccination, Vaccine and Infectious Disease Institute, University of Antwerp, 2610 Antwerp, Belgium

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**Correspondence to:** Liliane C Meireles, MD, Department of Gastroenterology and Hepatology, Centro Hospitalar Lisboa Norte, Avenida Egas Moniz, 1649-035 Lisbon, Portugal. [lilianeenailil@gmail.com](mailto:lilianeenailil@gmail.com)  
Telephone: +351-91-6747892  
Fax: +351-21-7805610

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### Abstract

Hepatitis B virus (HBV) continues to represent a major health problem and can lead to acute liver failure, acute hepatitis, chronic carriage, chronic hepatitis of HBV, liver cirrhosis, liver cancer, liver transplantation and death. There is a marked difference in the geographic distribution of carriers. More than 240 million people worldwide are chronic HBV carriers. Mother-to-child transmission remains the most important mechanism of infection in countries with a high prevalence of HBV. Percutaneous/parenteral transmission and unsafe sexual practices are important mode of spread transmission of HBV in other countries. Vaccination against HBV is the gold measure for primary prevention and control of the disease. Currently, 179 countries have added HBV vaccination to their routine vaccination programs with great results. Neonatal immunization with HBV vaccine has been one of the most highly effective measures in public health and the first anti-cancer program to be launched. In this paper we review the achievements for the last three decades.

**Key words:** Cirrhosis; Vaccination; Primary prevention; Hepatocellular carcinoma; Hepatitis B

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**Core tip:** It is now 50 years since the discovery of the hepatitis B virus (HBV). Effective vaccines have been available since the 80s and vaccination has proved to confer lifelong protection against hepatitis B and was highly successful in reducing the disease burden. However, the occurrence of breakthrough infections, the immunological effect of natural boosting and the effectiveness of universal hepatitis B vaccination remains a challenge. The fight against HBV is not over

yet, but the broad use of vaccination is the cornerstone and the most important measure to control HBV and all its consequences.

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## INTRODUCTION

Hepatitis B is a major global health problem, that can cause chronic liver disease and it is associated to a high risk of death from cirrhosis and hepatocellular carcinoma (HCC)<sup>[1,2]</sup>. Hepatitis B virus (HBV) is an oncogenic virus according World Health Organization (WHO). Roughly 30% of the world's population (more than 2 billion people) show serological evidence of current or past infection and among them 240 million are chronic HBV carriers with an incidence of 500000-700000 per year<sup>[3-8]</sup>. Adults who have had a chronic HBV infection since childhood develop HCC at a rate of 5% per decade, which is 100-300 times the rate among uninfected people<sup>[3]</sup>. HBV is a worldwide infection but there is a marked difference in the geographic distribution of carriers. Southeast Asia and Sub-Saharan Africa has one of the world's highest rates of HBV carriership ranging from 10% to 20%, while it is less than 1% in Northern Europe and America<sup>[1,3,9]</sup>.

In areas of high endemicity, the infection is often acquired during the preschool years. HBV is found not only in blood but also in saliva, semen and vaginal secretions, all of which are capable of transmitting the virus. The most common route of transmission is perinatal in Asiatic countries and horizontal during childhood in African countries<sup>[3]</sup>. Other routes of transmission are transfusions of infected blood products, contaminated injections, sharing of needles among injecting drug users, unsafe sexual practices and intra-familial transmission involving non-sexual interpersonal contact over a long period of time<sup>[10,11]</sup>. It is estimated that 33% of the 16 billion annual injections administered worldwide, are unsafe, leading to approximately 20 million new HBV infections each year<sup>[12,13]</sup>.

Despite advances in antiviral therapy, the primary prevention by vaccination is the gold measure of public health and the most cost-effective. Over the past 30 years, there were investments in primary prevention to increase coverage of the universal vaccination programs and consequently the herd immunity<sup>[1,12]</sup>. Due to successful vaccination programs, the epidemiology of HBV disease have been changing<sup>[14]</sup>. Thus, the burden of HBV infection for health systems can potentially be controlled through global vaccination.

## VACCINATION-GLOBAL PERSPECTIVE-HISTORY OF SUCCESS

It has been 50 years since the discovery of the HBV, and, despite the availability of a prophylactic vaccine for about 30 years, HBV remains a disease of significant worldwide and global health burden<sup>[15]</sup>. For the occurrence of infection with HBV, we need: an infectious source, a susceptible host, and an established route of transmission. HBV is not entirely cytopathic; both liver damage and viral control depend on the complex interplay between virus replication and host immune response.

Humans are the only significant reservoir of HBV, so a comprehensive control strategy could eventually lead to the eradication of the virus<sup>[3]</sup>. A major obstacle to the introduction of HBV vaccination has been the high cost of HBV vaccines-but this cost has decreased due to economies of scale, local production of vaccines, competition among vaccine manufacturers, involvement of donors and bulk discounts obtained by the WHO permitting many developing countries to initiate HBV vaccine programs. The price of monovalent vaccine for developing countries has decreased from United States \$3.00 per dose in 1990 to United States \$0.30 per dose in 2001<sup>[16]</sup>.

In the eighties, the vaccine was considered for use only in high risk individuals for acquiring HBV infection. The recognition of HBV as a serious disease burden and the availability of safe and effective HBV vaccines led WHO in 1991 to set 1997 as the target for integrating the HBV vaccine into national immunization programs worldwide<sup>[17]</sup>. WHO added a disease reduction target for HBV in 1994, calling for an 80% decrease in new HBV carrier children by 2001<sup>[1]</sup>. Progressively, it has become more widely used and recommendations for HBV vaccination have been extended to all infants in an attempt to achieve protection against HBV infection. It is the so called universal vaccination<sup>[18]</sup>. In spite of these recommendations, 6 countries in Northern Europe (Denmark, Finland, Iceland, Norway, Sweden, and the United Kingdom) have yet to implement such a policy<sup>[4,19]</sup>.

Currently available HBV vaccines are extremely safe and have an efficacy of > 90% and are effective against all HBV serotypes and genotypes. The vaccination coverage is measured only after the completion of the third dose of vaccine.

In Asia, for example, HBV vaccination has been recommended for all neonates in China since 1992 and the Hepatitis B Immunization Project was initiated in 2002. The immunization coverage with three doses of vaccine increased from 71% in 2002 to 93% in 2009 among infants<sup>[20]</sup>. The surface antigen (HBsAg) prevalence in the general population decreased to 7.2% in 2006. This impact was more significant in children. In addition, the administration of the HBV vaccine have

reduced the risk of HCC among adults, nevertheless up to 10% of the adult population remain chronic carriers of HBV and prevention of HCC and cirrhosis remains a challenge for China<sup>[3,20-23]</sup>.

Another history of success: prior to universal vaccination, Taiwan used to be a high endemic area for HBV, around 90% of the population aged 40 years were estimated to have been infected with HBV. At that time, about 15%-20% of the adult population was estimated to be HBV carriers. Chronic HBV is responsible for about 80% of liver cirrhosis and HCC, which are among the leading causes of mortality in Taiwan<sup>[18,24]</sup>. The vaccination of newborns of carrier mothers was implemented in 1984 and extended to all neonates in 1986. At the start of the program, the HBV carrier rate among children younger than 15 years of age was 9.8%<sup>[25]</sup>. Almost 30 years after the introduction of universal vaccination, the prevalence of HBsAg has decreased to 0.9%.

Before 1984, Alaska was an area with high HBV endemicity. However, as a consequence of the introduction of universal newborn HBV vaccination in 1984, the region was re-classified after 2000 as intermediate endemic<sup>[18,26]</sup>. Alaska is a world and happy case study for HBV vaccination and a real life history of success: all the consequences of HBV has been reduced: acute hepatitis B, chronic carriers, and HCC in children under 20 years of age.

In Africa, in the 1980s, HBsAg carriage in Gambia was 10% in children and 15% in adults. The annual incidence of HCC was 23/100000 population. The HBV vaccination was introduced gradually between 1986 and 1990. Studies conducted in 2008 have shown a vaccination coverage rate of 92%. The prevalence of HBsAg has been reduced to 1%<sup>[18]</sup>.

In Europe, in 1980, in Catalonia, it is estimated that 1% of the population was chronic HBsAg carriers. Vaccination of newborns of HBsAg positive mothers and other risk populations was started in 1984. In 2002, universal HBV vaccination of children was included in the program. Between 1992 and 2010, vaccine coverage has been around 80%-90%. The reported incidence of acute HBV has fallen by 61% between 1991 and 2001<sup>[18]</sup>.

The success of HBV vaccination has been clearly demonstrated. The Global Alliance for Vaccines and Immunisation recognizes that the effect of HBV vaccination in reducing the incidence of liver cancer result in an impact on public health worldwide<sup>[18]</sup>. Countries that have adopted the recommendation had a marked reduction in carrier rates as well as complications from HBV including HCC<sup>[27,28]</sup>. This has been most evident in regions with a high prevalence of chronic HBV infection. At present, global HBV vaccine coverage is estimated at 75% and has reached 91% in the Western Pacific and 89% in the American, the largest decline in incidence was seen in children<sup>[14]</sup>.

## TYPES OF VACCINES

The first vaccines were plasma-derived, which contained purified HBsAg obtained from the plasma of people with chronic HBV infection<sup>[4]</sup>. Derivation from plasma has left some worries regarding the potential to transmit blood infections<sup>[29]</sup>. In the following years, yeast-derived recombinant HepB vaccines have been developed by cloning the HBV S gene in yeast cells<sup>[4,30]</sup>.

Currently, a mammalian cell-derived recombinant vaccine was developed. We can distinguish three vaccines of this class. One of these contain, in addition to the S antigen, antigen from the pre-S2 region while the other two contain antigens from the pre-S1 and pre-S2 regions. A controlled trial shown that this class of vaccine was associated with a better immunologic response<sup>[4]</sup>. Although this advantage, vaccines with pre-S antigens are not widely available.

Currently recombinant DNA HBV vaccines are being used for universal HBV immunization programs. Bearing in mind that more than 1 billion doses of vaccine have been used since 1982, the safety record is noteworthy<sup>[12]</sup>.

HBV vaccines are not only available in monovalent formulations that protect only against hepatitis B, but also in combination formulations that protect against HBV and several other disease: diphtheria, polio, tetanus, pertussis, and *Haemophilus influenzae* type B. The immunogenicity of these multivalent vaccines is similar to that of the univalent vaccines. The multivalent vaccines are commonly used in childhood immunization programs and have greatly facilitated compliance and reduced the cost<sup>[12]</sup>. But ideally, the first dose of vaccine should be given as soon as possible after birth (< 24 h) in order to avoid early intrafamilial transmission which is around 95%. When immunizing against HBV at birth, only monovalent vaccine should be used.

Currently, WHO is evaluating the possibility to use HBV vaccines "out of the cold chain" to minimize the risk of freezing in order to improve vaccination efficacy and reduce the costs<sup>[12]</sup>.

## EFFICACY

### Impact in complications

Hepatitis B is self-limited in most adult patients with acute infection. Meanwhile 1%-2% of patients progress to fulminant hepatic failure, and < 10% progresses to chronic infection. Chronic HBV infection can lead to liver cirrhosis, hepatic decompensation (ascites, variceal bleeding, hepatic encephalopathy, and spontaneous bacterial peritonitis), HCC, and premature death. The rate of progression from acute to chronic HBV infection is reported to be 90% in newborns and 5%-10% in adults. The progression of acute hepatitis B to chronic hepatitis is greater in Western countries. The different rates of chronicity are supposed to be attributable to the different distribution of HBV genotypes<sup>[31]</sup>.

As many as 25% of HBV-infected patients will

**Table 1 The proved benefits of hepatitis B vaccination**

Reduction of incidence/prevalence
Acute hepatitis B
Fulminant hepatic failure
Chronic carrier
Chronic hepatitis B
Liver cirrhosis
Hepatocellular carcinoma
Comorbidities (vasculitis, neuropathy, cutaneous, personal stigma, social discrimination)

develop HCC, which is the fourth most common solid tumor worldwide. Between 500000 and 700000 people die each year from chronic infection related cirrhosis, HCC or from acute hepatitis B<sup>[12]</sup>. Reduction in the morbidity and mortality of HBV related HCC can be achieved as a result of HBV vaccination, intensive screening programs, and antiviral treatment<sup>[32-34]</sup>. The benefits of vaccination are summarized in Table 1. HBV vaccination has proven to be a safe and effective way of protecting populations from developing clinical acute or chronic HBV. The universal immunization led to a huge reduction of the prevalence of HBV and the HBV-related morbidity and mortality<sup>[6,35]</sup>. In fact HBV vaccine has been the first vaccine with a triple target: to double viral and one cancer prevention, *i.e.*, HBV, hepatitis delta and hepatocellular carcinoma. HBV is an oncogenic one, according WHO.

**Response to the vaccine**

A positive immune response to the vaccine is defined as the development of HBV anti-HBs at a titer of > 10 mIU/mL, after a complete and adequate immunization schedule measured preferably 1 to 3 mo after the last vaccine administration<sup>[18,36]</sup>.

Long-term follow-up studies of newborn vaccination showed that antibodies become negative in 15%-50% among the vaccine responders within 5 to 10 years<sup>[4]</sup>. The decline of HBV antibody titer seemed mainly to be proportional to the antibody titer initially acquired<sup>[4]</sup>. A natural booster effect with activation of memory B cells, due to environmental exposure to HBV, can contribute to persistence of anti-HBs antibodies, particularly in areas of high endemicity. The clinical significance of the disappearance of specific antibodies in immunocompetent responders to previous vaccination remains controversial<sup>[4,18]</sup>. Long-term protection is present despite a decrease in anti-HBs antibodies over time. The exact mechanism of long-term protection, however, is not yet fully understood but it is probably due to the priming of memory cells, which are capable of producing anamnestic response when challenged. This means that the immunological memory for HBsAg can outlast antibody detection<sup>[4,36]</sup>.

Protection has been estimated to persist at least for 25 years after the primary vaccination schedule<sup>[24,36-39]</sup>. Currently, decisions to offer a booster dose, based on anti-HBs antibody titre < 10 mIU/mL, is controversial

and not recommended by WHO, center for disease control or prevention or viral hepatitis prevention board. When estimating how long protection is needed, it is important to consider the periods with a high risk of exposure to HBV and increased chances for chronic evolution of an acute infection. The neonatal period and childhood constitute the high risk period, because it more likely evolves towards chronicity than infections later in life. The next high risk periods of exposure are adolescence, in which the onset of sexual activity is rising the risk of transmission.

Based on the current scientific evidence, there is consensus that there is no need to administer booster doses of vaccine to ensure long-term protection in immunocompetent subjects. A booster dose can be provided to non-responders and exceptionally to some high-risk individuals (*e.g.*, healthcare workers, couples of chronic carriers). However, more longterm data regarding the actual risk of acquiring HBV infection among individuals who completed a course of vaccination are needed before recommendations on booster dose administration can be formulated.

While most recipients of three doses of currently available HBV vaccines produce a strong, protective and long-lasting anti-HBs response, 5%-10% of healthy adults do not produce protective levels of anti-HBs, and can be considered non-responders. Several factors, such as inappropriate vaccine storage conditions, administration not following the recommendations, age, body mass index, chronic alcoholism, cirrhosis or chronic renal failure, immune-suppression, organ transplant recipients, chronic hemodialysis, type I diabetes, celiac disease and smoking, drug abuse or infections at the time of vaccination, have been found to be associated with a lower rate of response. Genome-wide association study (GWAS) has been developed to systematically investigate the associations between polymorphisms and polygenic inheritance disorders. It has been demonstrated a possible genetic predisposition to vaccine non-responsiveness likely due to the presence of specific human leukocyte antigen (HLA) haplotypes and specific single nucleotide polymorphism (rs497916, rs3922, rs676925 and rs355687) in genes of cytokine/ cytokine receptors and toll like receptors. GWAS reported that genetic variants in HLA-DP, HLA-DQ, HLA-DR influence response to vaccination<sup>[40,41]</sup>.

The problem of unresponsiveness could represent - depending on the size of the problem - a global health issue, because the group of non-responders could be considered as a reservoir of HBV-susceptibility<sup>[42]</sup>. Luckily, with universal programs starting at birth or infancy, the rate of non-response very low.

Persons unresponsive to a first series of three doses of vaccine are recommended to complete a second course of vaccine. Non-responders to the second course should be evaluated for underlying chronic HBV infection. Another approach, to improve the effectiveness of vaccination, it is to administer the vaccine intradermally<sup>[41]</sup>.

Vaccine escape mutants are another problem that

affects the response to the vaccine. Several mutations in the S protein have been identified, and these mutations may evade neutralizing anti-HBs and infect vaccinated people. The most widely reported escape mutants was associated with a point substitution of glycine by arginine residue at position 145 (G145R). The vaccine-escape mutants are more common in countries with high rates of endemic infection. Third generation of vaccines may also be effective in preventing infection with HBV containing a S-mutation. Nonetheless, the prevalence of these mutants appears to be low and reductions in the efficacy of HBV vaccine have not been yet observed<sup>[41,43]</sup>.

## CONCLUSION

For three decades HBV vaccination has effectively reduced the infection and chronicity rates and related complications. Vaccination represents the cornerstone of public health measures to control or eradicate HBV, but, other public health measures, including health education and infection control measures, remain important. The elimination of HBV is technically feasible through universal vaccination. However, we must bear in mind the hundreds of millions of already chronically infected subjects, and the 5% to 10% of individuals that do not respond to currently available vaccines<sup>[12]</sup>.

Many communities have lost - in the absence of disease - the awareness of its natural consequences; the misconception emerge that vaccination is no longer required. Besides introducing universal HBV immunization programs, there is fundamental to insure that existing programs are sustained<sup>[12]</sup>. There are a few European countries, even with a substantial number of immigrants from high endemic countries, who still have not approved the inclusion of the HBV vaccine into their universal immunization programs. Healthcare workers are at risk of incidents like needle stick, sharp injuries. Occupational exposures are responsible for about 40% of HBV infection in healthcare workers. The risk of acquiring HVB infection among this special population is about 10 times higher than other group. Serologic HBV testing of at-risk health care workers remains also necessary. About 13% to 60% of individuals who have received first HBV vaccine may lose immunity<sup>[44,45]</sup>. A booster HBV vaccine could be useful for those health care workers that recognized as hyporesponders, having a titer of anti-HBs less than 100 IU/mL. In addition, health education for both health care workers and patients is still needed<sup>[10]</sup>.

Vaccination and treatment strategies should take into account the risk of mutant formation. Studies on viral mutants and influence of genotype and phenotype are required<sup>[18]</sup>. Otherwise the real impact if this issue of mutants in terms of health public seems to be minimal, if any.

In conclusion, the huge benefits of HBV vaccination achieved in the last three decades, clearly superposes the other aspects. Nevertheless, much work remains to

achieve the goal of global eradication of HBV infection.

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