

## Insights into induction of the immune response by the hepatitis B vaccine

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### Abstract

After more than four decades of hepatitis B virus (HBV) vaccine implementation, its safety and efficacy in preventing HBV infection have been proven and several milestones have been achieved. Most countries have included HBV immunization schedules in their health policies and progress has been made regarding universalization of the first HBV vaccine dose at birth. All of these actions have significantly contributed to reducing both the incidence of HBV infection and its related complications. However, there are still many drawbacks to overcome. The main concerns are the deficient coverage rate of the dose at birth and the large adult population that has not been reached timely by universal immunization. Additionally, the current most widely used second-generation vaccines do not induce protective immunity in 5% to 10% of the population, particularly in people over 40-years-old, obese (body mass index > 25 kg/m<sup>2</sup>), heavy smokers, and patients undergoing dialysis or infection with human immunodeficiency virus. Recently developed and approved novel vaccine formulations using more potent adjuvants or multiple antigens have shown better performance, particularly in difficult settings. These advances re-launch the expectations of achieving the World Health Organization's objective of completing hepatitis control by 2030.

**Key Words:** Hepatitis B virus; Vaccine; Immune response; Antibodies; Neutralizing

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**Core Tip:** Second-generation vaccines induce the production of anti-hepatitis B surface antibodies (anti-HBs). Anti-HBs levels  $\geq 10$  mIU/mL prevent against infection. More than 90% of immunized persons achieve protective anti-HBs levels 1 mo after completing the three-dose vaccination schedule. Although antibody titers significantly drop during the 1<sup>st</sup> years after vaccination, memory immunity is sufficient to prevent infection regardless of the antibody levels. In some specific settings showing lower immune response rates, schemes with larger or additional doses and novel vaccine formulations are recommended.

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## INTRODUCTION

Hepatitis B infection has been a major public health concern for a long time. Identification of the hepatitis B virus (HBV) in the 1960s and the subsequent development of a safe and effective vaccine were the kickoff to begin to retrace the path and achieve the desired control of this health problem.

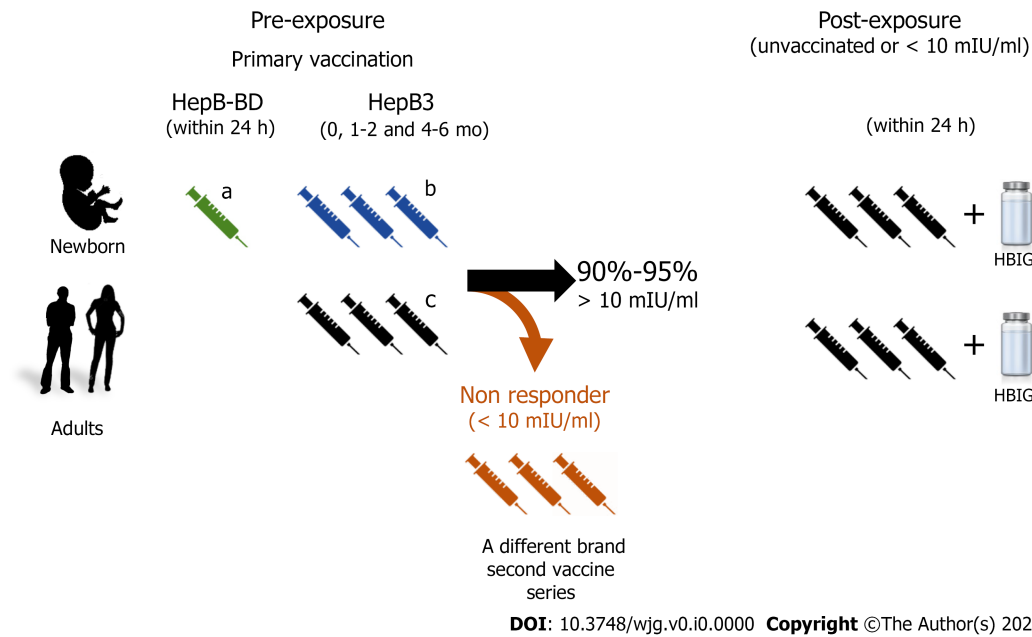
First-generation vaccines based on heat-treated plasma derived from hepatitis B surface antigen (HBsAg)-positive donors raised concerns about its safety and availability to meet the vaccine manufacturer's needs. Shortly afterwards, second-generation DNA vaccines prepared in yeast transfected with recombinant plasmids encoding small HBV surface proteins (SHBs) were developed and approved in 1986[1]. Lastly, third-generation vaccines have been produced in mammalian cells that express and secrete SHBs and middle pre-S2 proteins (MHBs) or the three HBV envelope proteins (SHBs, MHBs, and large HBs).

It is worth noting that several studies have compared the immune response to plasma-derived first-generation vaccines to the recombinant second-generation ones. Most of the studies showed that the lowering rate of anti-HBs was higher in people receiving the recombinant HBV vaccine. However, plasma-derived vaccines were replaced by the recombinant ones due to safety concerns about human blood-derived products[2-5]. In addition, it has been shown that third-generation vaccines containing the pre-S2 and pre-S1 antigens would induce a higher anti-HBs response than second-generation ones, particularly in people  $\geq 45$ -years-old[6-8]. Moreover, compared to plasma-derived vaccines, it has been observed that the HBsAg seropositive rate drops by about 71% and that the anti-HBc seropositive rate decreases by approximately 65% when recombinant HBV vaccines are used, supporting their higher effectiveness[4].

The HBV vaccine has been introduced progressively in the national vaccination calendars. Currently, second-generation HBV vaccines have been widely implemented for newborns in most countries. The pentavalent vaccine formulation protecting against diphtheria, pertussis, tetanus, hepatitis B, and *Haemophilus influenzae* type B is administered in three doses, 4 wk apart (recommended dosing at 6, 10, and 14 postnatal wk), and aims to lessen horizontal transmission. In addition, a monovalent single dose of the HBV vaccine (HepB-BD) administered within 24 h after delivery is also recommended to reduce mother-to-child transmission (Figure 1). The advised immunization schedule for the adult population includes three vaccine doses (HepB3) according to the individuals' age. Immunocompromised adults or patients on dialysis treatment require higher or additional doses of HBV vaccines. Recently, a novel vaccine (HepBisav-B) with a different adjuvant was approved for adult immunization with a recommended schedule of two doses 1 mo apart.

Since 1990, the proportion of children receiving all three doses of the HBV vaccine has increased globally from 1% to 85%. By 2020, the HBV vaccine was introduced to 190 countries with 83% of three-dose coverage rate. Few countries with very low endemicity that consider HBV infection as a limited public health problem provide the HBV vaccine to only well-defined risk groups. Likewise, a dose of HepB-BD has been introduced in the national calendar of 113 countries. Figure 2 shows the HBV worldwide three-dose infant vaccine coverage and the HBsAg seroprevalence[2,9]. However, the at birth dose coverage rate is poor (estimated at 43%) with remarkable disparities according to region and development level[10-12].

Universal vaccination is the most effective strategy to prevent and control HBV infection. In 2016, the World Health Organization (WHO) set the goal of controlling HBV by 2030. The proposed targets include the 90% global coverage of three-dose infant vaccination by 2020, birth-dose vaccination of 50%



**Figure 1 Recommended hepatitis B virus vaccination schemes.** The hepatitis B immunization schedule is flexible, but minimal intervals and ages need to be observed. The recommended dose varies (5-40 µg of hepatitis B surface antigen protein/mL) depending on the individuals' age and the vaccine brand. <sup>a</sup> Monovalent hepatitis B vaccine 0.5 mL must be used for the at birth immunization (HepB-BD). Immunocompromised adults or patients under dialysis require larger or additional doses of the hepatitis B vaccine; <sup>b</sup>Combined hepatitis B, diphtheria, tetanus, adsorbed acellular pertussis, inactivated poliovirus vaccine. This vaccine cannot be administered at birth, before 6 postnatal weeks, or at age ≥ 7 years; <sup>c</sup>HepB3: Three doses of hepatitis B vaccine; HepB-BD: Monovalent single dose of the hepatitis B virus vaccine; HBIG: Hepatitis B Immunoglobulin.

of infants by 2020, and of 90% of them by 2030[13].

## MILESTONES ACHIEVED WITH THE HBV VACCINE

One of the goals of the strategy to achieve HBV control by 2030 is to reduce HBsAg prevalence to 0.1% in 5-year-old children and many countries are already on track to that milestone[14].

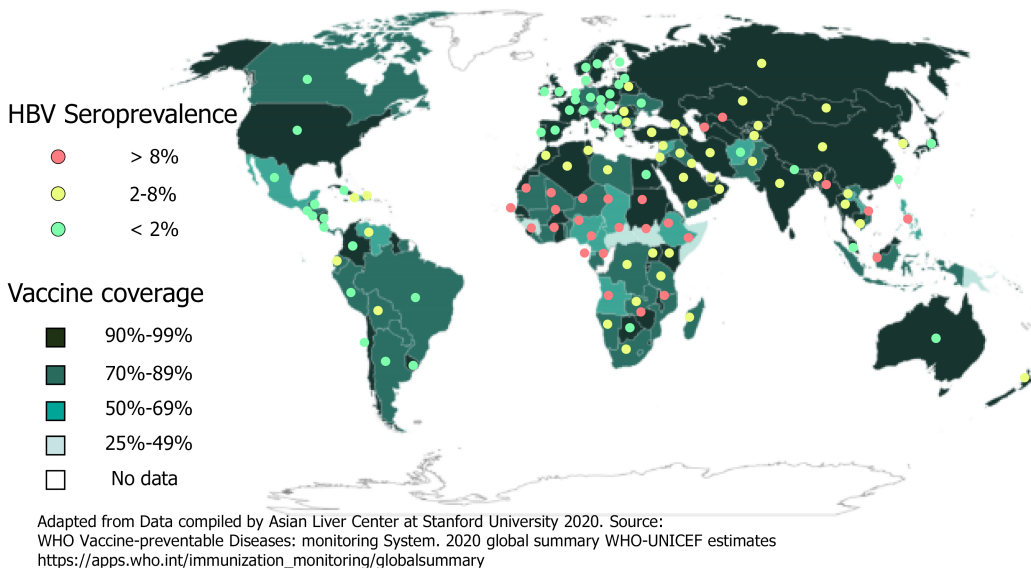
The global implementation of the HBV vaccine as part of the national health policies has contributed to directly reducing the global burden of infection, and indirectly, the HBV-related mortality. After the inclusion of HBV vaccination schedules, several surveillance studies have shown an overtime global HBsAg prevalence decrease in most countries[15], either in hyperendemic ones or in those with low or medium HBV infection prevalence[16-20].

Taiwan was the first country to implement a mass vaccination program against HBV in 1984 and it is the paradigm of its impact on the control of hepatitis. After 30 years of sustained immunization programs, the prevalence of HBsAg has decreased from 9.8% in the pre-vaccination period to 0.5% in the cohort reached by HBV vaccination protocols[21]. The main reason for Taiwan's success was its high three-dose hepatitis infant vaccine coverage rate, which increased from 88.9% in 1985[22,23] to 98.1% in 2018[21].

In the United States, since first HBV vaccine recommendations, the infection incidence has decreased by approximately 90%, from 9.6/100000 cases in 1982 to 1.0/100000 cases in 2018[24]. Similarly, in China, where the coverage of the three-dose vaccine schedule has increased from 30.0% to 93.4% and the at birth dose increased from 22.2% to 82.6%, the HBsAg prevalence decreased from 5.5% to 0.9% between 1992 and 2005[25]. In Argentina, a country with low HBV endemicity, the HBV vaccine was included in newborns' schedules in 2000 and, later in 2003, the catch-up strategy was implemented in 11-year-old adolescents. Currently, the coverage rate of protective antibodies is significantly higher in persons born after 1992 than in those born previously (Figure 3A)[26,27]. In fact, new infections generally occur in the population over 20-years-old not reached by vaccination[28]. These results emphasize the need to raise awareness among people not reached by universal HBV immunization programs and to focus vaccination campaigns on this group.

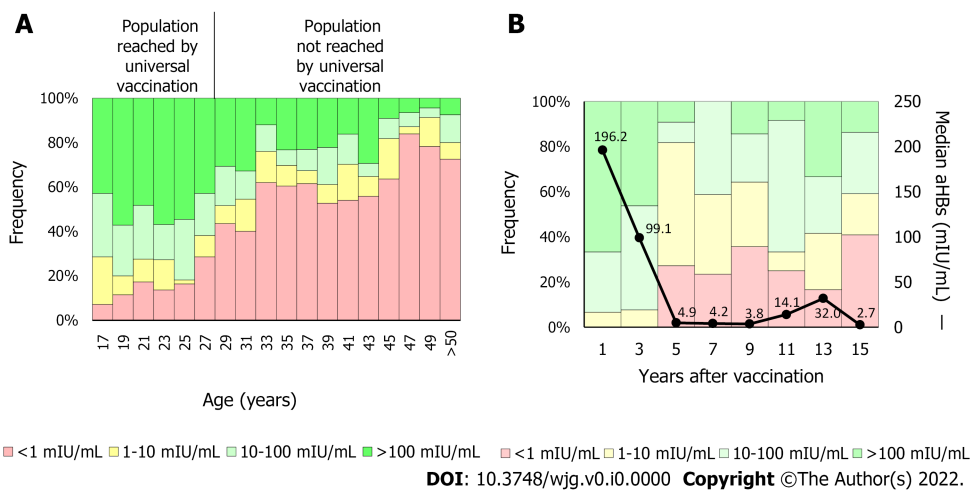
However, the most outstanding HBV preventive action impact has been detected in regions that were hyperendemic before introduction of the vaccine. In a Southern Italian area, where the vaccine was introduced in 1991, the HBsAg prevalence dropped from 13.4% in 1978 to 0.91% in 2006[29]. Likewise, in Alaska, where one of the highest HBV infection incidences has been reported, universal childhood

Hepatitis B: Infant Vaccine 3 doses Coverage and seroprevalence



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**Figure 2 Hepatitis B three doses of infant vaccine coverage and seroprevalence.** Hepatitis B virus seroprevalence data is from Polaris Observatory Collaborators: Global Prevalence, Treatment, and Prevention of Hepatitis B Virus Infection in 2016: A Modelling Study. *Lancet Gastroenterol Hepatol* 2018; **3**: 383–403. HBV: Hepatitis B virus.



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**Figure 3 Anti-hepatitis B surface antibodies titers by age.** A: The anti-hepatitis B surface antibodies (anti-HBs) titer was determined in 765 blood donors. In 2000, vaccination against hepatitis B virus was included in the Argentine newborns' National Vaccination Calendar. In 2003, the catch-up strategy for 11-year-old children was implemented. Therefore, individuals under 28-years-old are reached currently by the universal vaccine implementation. On average, protective levels of anti-HBs (> 10 mIU/mL) were detected in 75.2% of the population reached by universal vaccination (< 28-years-old) and in 32.2% of the not reached population (> 28-years-old); B: Anti-HBs kinetics. The anti-HBs titer was determined in 132 children born after 2000. In the first 2 years, the median anti-HBs titer fell from 196.2 mIU/mL to less than 10 mIU/mL (black line). Five years post-vaccination, about 20% of the population showed anti-HBs levels below 10 mIU/mL. aHBs: Anti-hepatitis B surface antibodies.

vaccination was implemented for newborns in 1993. The HBsAg prevalence dropped from 13% detected before the HBV vaccination program, to 0% HBsAg-positive children less than 10-years-old[30].

Although slowly and delayed, a significant reduction in the hepatocellular carcinoma annual average incidence has been observed concomitantly with the HBV infection incidence decline, particularly in those countries where early vaccine protocols have been introduced[31-33].

## IMMUNITY

### **HBV vaccine-induced protective immunity**

Several studies have shown that HBV vaccines induced both humoral and cellular immunity providing long-term protection[34,35]. On the one hand, neutralizing antibodies are elicited and two types of them have been identified. The first type targets the “a” determinant and neutralizes cell viral penetration by blocking the interaction with heparan sulfate[36], required by the virus at an early stage of hepatocyte entrance[37]. The second type targets the high-affinity receptor-binding site of the HBV pre-S1 domain and blocks the binding to the Na<sup>+</sup>-taurocholate cotransporting polypeptide receptor preventing the infection of hepatocytes[38,39]. On the other hand, immune memory cells are generated, which upon contact with the HBV can be activated to expand rapidly. This response has been well demonstrated in studies that administered a booster dose to previously vaccinated persons whose antibody titers had fallen below protective titers[16,40-42].

**Pre-exposure:** Efficacy and effectiveness studies carried out in animal models first and then in human beings have shown that the HBV vaccine induces the production of neutralizing antibodies against HBV surface antigen (anti-HBs)[43]. Two main questions raised suddenly once the HBV vaccine was developed: What are the levels of antibodies that protect against infection and how long does immunity last? Soon after the release of the vaccine, several studies have shown that anti-HBs levels  $\geq 10$  mIU/mL, determined 1 to 3 mo after the complete three-dose vaccination scheme administration, were a surrogate marker for vaccine-induced protective immunity[44-46].

The overall response rate to the HBV vaccine, defined as individuals achieving anti-HBs levels  $> 10$  mIU/mL, is 90% to 95% of immunized persons. Different factors such as host genetics, age, body weight, smoking, and concomitant disease have been shown to affect the response rate to the vaccine [47]. These variations probably rely on the strength of the cellular immune response. Velu *et al*[48] have characterized the cellular immune response and the cytokine profile of vaccine responders and non-responders to investigate the immunization outcome underlying mechanisms. The authors reported that HBsAg-specific interferon gamma, interleukin 10, and tumor necrosis factor alpha secretion correlated with the HBV vaccine-induced humoral immune response. Likewise, non-responders had lower levels of T helper type 1 (Th1) and Th2 cytokines. In addition, Körber *et al*[49] observed a higher frequency of regulatory B cells in HBV vaccine non-responders. Regulatory B cells suppress immunopathology by skewing T-cell differentiation. Overall, these results suggest that impaired lymphocyte activation is associated with a weak or no response to HBV vaccination.

Notably, although the HBV vaccine induces protective immunity against infection it would not be sterilizing. Consequently, vaccinated people can become infected although episodes are usually asymptomatic and self-limited[50-52]. These benign infection results are possibly due to long-lasting HBV cellular immunity induced by the vaccine despite antibody loss against HBV surface antigens[53].

**Post-exposure:** Immunization with HBV vaccines combined with different injection sites of HBV immunoglobulin administration, within 12 h after birth, showed a greater than 85% efficacy in preventing infection in infants born to HBsAg-positive mothers[54]. In adult persons, post-exposure prophylaxis is also recommended depending on the individual's vaccination and anti-HBs status. In unvaccinated subjects or with non-protective levels of anti-HBs, the HBV vaccine has shown high efficacy in preventing infection when administered within 24 h after percutaneous or mucosal exposure to HBV-positive blood. Additional post-exposure immunoprophylaxis is not suggested in individuals who achieved anti-HBs protective levels after vaccination.

Although, as previously mentioned, the massive implementation of the HBV vaccine substantially reduced the incidence and prevalence of the infection, few works have addressed the effectiveness of the vaccine and most of them have been carried out in high endemic countries. In general, a 70% to 94% effectiveness range has been reported, depending mainly on the follow-up time, the exposure risk rate (HBsAg prevalence of the population), and the studied cohort age[18,23,55]. A recent study showed an approximately 58% effectiveness in a birth cohort (mean age, 12 years) and 85% in participants at least 20-years-old[56]. The lower efficacy observed in the birth cohort could be a consequence of a lower level of exposure.

## HOW LONG DO THE ANTIBODIES LAST?

Protective antibodies levels tend to decrease over time, especially during the 1<sup>st</sup> years after vaccination [57]. In a study carried out by our group, including 132 children born after infants' vaccine implementation, we observed that anti-HBs titers were significantly higher 1 year post-vaccination compared to the 2 years and 3 years earliest vaccinated population (Figure 3B). In addition, approximately 20% of the 5-year post-vaccination cohort showed anti-HBs levels lower than 10 mIU/mL[27]. These results are in line with a study conducted in Germany, where anti-HBs levels were determined in 106 teenagers, mean age 13.7-years-old, after primary vaccination. Forty percent of cases had anti-HBs levels  $< 10$  mIU/mL. However, almost all (97%) teenagers who received a booster vaccine achieved anti-



HBs levels  $\geq 100$  mIU/mL regardless of their pre-booster levels[58]. Besides time elapsed since primary vaccination, a systematic meta-analysis including 46 studies analyzed the anti-HBs levels from 5 years to 20 years after the primary vaccination and identified the vaccination dose and the less than 6-mo interval between the last dose and the previous one as the main factors associated with anti-HBs titer loss[59]. On the other hand, the duration of antibody levels is directly correlated with the titers reached when completing the vaccination scheme[60].

Another interesting issue regarding antibodies duration refers to the subjects' age at the time of vaccination. Numerous studies have shown that vaccination in adolescence generates higher and long-lasting titers compared to children vaccinated at birth[61-64], being the age at the time of vaccination an independent variable associated with an anti-HBs titer  $< 10$  mIU/mL. However, childhood HBV vaccination, together with other vaccines, guarantees a higher coverage rate.

Overall, it is widely accepted that a large proportion of vaccinated individuals, particularly those immunized during childhood, rapidly lose their anti-HBs titers below protective levels[40]. However, it has also been extensively described that individuals who achieved anti-HBs protective titers at the time of vaccination, show a rapid anamnestic response when boosted[41,42], suggesting that memory immunity plays a decisive role in the protection against clinical disease and the development of a carrier state regardless of anti-HBs antibody levels[35]. In this regard, it has been observed that even in the lack of anti-HBs, a significant amount of HBsAg-specific memory T and B cells are detected in vaccine responders. For this reason, although it remains a controversial issue, vaccine booster doses are not recommended currently for children and adults with normal immune status, despite the overtime drop of anti-HBs antibody titers[35,65]. Nonetheless, the anti-HBs titer decline could represent a problem for high-risk groups.

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## MANAGEMENT OF SPECIAL POPULATIONS

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Adult persons with increased risk factors for infection are one of the WHO identified obstacles to HBV elimination as a public health problem[66,67]. These groups mainly include health care providers, illicit injected drug users, sexually active individuals (more than 1 partner in the past 6 mo), persons with diabetes, dialysis patients, and people living with human immunodeficiency virus (HIV). The last two groups, in addition to showing a higher risk of HBV infection compared to the general population[68-70] due to the frequent use of percutaneous materials and the common route of HBV and HIV transmission, have shown suboptimal responses to HBV immunization[71,72]. Patients on dialysis have also shown a diminished response to the HBV vaccine probably due to a uremic-associated suppression of the immune system that leads to a significant progressive reduction of the percentage and count of lymphocytes CD3+, CD4+, and CD8+ and a disturbance of antigen-presenting cells that results in an inability to sustain a satisfactory antibody titer over time[73-76]. In fact, in this population subset, the rate of seroprotection level ranges from 33.3% to 86%[77].

It has been reported that patients living with HIV present a poor initial HBV immunization response, lower seroconversion rates, and difficulty in maintaining immunity over time, mainly due to B-cell dysfunction[67,71,78,79]. For this group, the efficacy of the standard vaccine scheme in the era of the highly active antiretroviral therapy ranges from 17.5% to 71%[80-83].

Consequently, for patients on dialysis and/or living with HIV, other approaches are recommended to enhance the HBV vaccine immune response. For patients undergoing dialysis therapy, alternative strategies include the use of adjuvants, additional vaccination cycles, different vaccine formulations, greater number and concentration of doses, greater frequency of doses, dual vaccination, alternative administration routes, and/or use of booster vaccines[67,72,84-86]. On the other hand, for HIV-infected individuals with negative or  $< 10$  mIU/mL anti-HBs levels after a primary vaccine series, a second HBV vaccine series using larger or additional doses is recommended[71,87]. Furthermore, revaccination should be attempted after HIV viral load suppression and CD4 cell count improvement[83].

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## RATE OF RESPONSE TO HBV VACCINE

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As mentioned above, the average response rate to the HBV vaccine is greater than 90% with 5% to 10% vaccinated persons failing to mount a protective immunity level once the vaccination schedule is completed. The response to the vaccine ultimately relies on the individual immune system; however, different factors impairing the response rate have been identified. Response rates can drop drastically when more than one of these factors are present.

### *Host genetics*

Several studies have addressed, through different experimental approaches, the role of genetic polymorphisms in the response to the HBV vaccine. Single nucleotide polymorphisms in HLA loci[88-92], ILs (with a key role in the cellular and humoral response interplay)[93,94], or even other genes have

been associated with the response rate to HBV vaccination[90,95,96]. However, these findings have not been widely validated in different cohorts and should be considered with caution.

### Age

One of the most recognized consequences of aging is the declination of the immune function and the concomitant vaccination response reduction. The HBV vaccine response rate decreases in people 40-years-old and even more in people older than 60 years[97,98]. This highlights the need to vaccinate the population not covered by health policies before they reach 40-years-old, which will result in important cost-benefit profits.

### Body weight

Overweight and obesity are a growing public health problem worldwide that affects all age groups[99]. They are caused by the deposition of lipids into the adipose tissue and are defined as a body mass index  $\geq 25$  kg/m.

Shortly after the HBV vaccine was developed and implemented, obesity was found to be a factor impairing the strength of the immune response[100]. This finding has been widely validated in subsequent studies[101,102]. This drawback is not only attributed to the HBV vaccine but has also been described for other vaccines[103,104]. Adipose tissue has a role in modulating the immune system through different pathways, inducing a chronic pro-inflammatory state[105,106], which in the end is associated with immune system dysfunction. This includes the chronic activation of cells of the innate immune system and consequent local and systemic inflammation[107]. In addition, Frasca *et al*[108] described a percentage decrease of switched memory and transitional B cells and an increase of late/exhausted memory B cells with the consequent impaired response to the vaccine.

### Smoking

As described for obesity, the link between tobacco smoking and impaired vaccine response has been proposed to be mediated by inflammation[109]. However, data from different studies are less robust. Some studies have reported lower responses to vaccination while others showed no association[110]. This controversy could be based on the level of daily cigarette intake. A recent study reported that subjects in the non-responder group were almost exclusively 'heavy smokers' defined as consumers of  $\geq 10$  cigarettes per day[111]. The development of new vaccine formulations including either additional antigens or more potent adjuvants could represent a solution to improve the response rate of individuals affected by these factors as well as for dialyzed or immunosuppressed patients.

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## NEW FORMULATIONS

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As previously mentioned, one of the main drawbacks of the second-generation vaccines is the poor induction of immune response in 5% to 10% of the general population and individuals presenting detrimental factors that impair vaccine response. Therefore, efforts have been made to find more effective formulations to overcome this limitation. Two advances have been reported in recent years. One of them is the development and evaluation of new and more powerful adjuvants to enhance immunogenicity[112,113].

HepB-CpG (HepB-CpG), a single-antigen vaccine with a novel immunostimulatory adjuvant, has been approved for its use in people at least 18-years-old. This vaccine is administered in two doses, 1 mo apart[114]. The new adjuvant is a small synthetic cytidine-phosphate-guanosine oligodeoxynucleotide containing non-methylated CpG patterns, similar to those present in microbial DNA. This structure acts as an agonist of the toll-like receptor 9 that enhances the immune response. Several studies have shown higher response rates to other second-generation vaccines both in general population[115-117] and in persons with detrimental factors for vaccination response[118-120]. In addition, the two doses-1 mo apart-simplified schedule could help increase patient compliance and raise the coverage rate.

Alternatively, third-generation vaccines derived from mammalian cells, containing the medium and large HBV envelope proteins have been developed. The advantage of this approach is that antigens display the same *in vivo* post-translational modifications and protein folding.

In 2021, Sci-B-Vac was licensed, and phase III trials showed faster seroprotection and higher response rates than the second-generation vaccines[8,121]. These data making turn Sci-B-Vac of particular interest for its use in people with poor or no response. Particularly, Sci-B-Vac has shown greater efficacy in HIV-infected individuals' immunization and in the prevention of vertical infection transmission[122,123]. Furthermore, the multiple antigen display of the third-generation vaccines would protect against HBV vaccine breakthrough infections caused by the HBV S gene mutants widely described[124-126]. The results obtained through novel vaccine formulation approaches suppose a contribution to the prophylaxis of HBV infection and represent a promising future.

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## CURRENT CHALLENGE

Beyond significant advances in the prevention of HBV infection, several pitfalls have been identified that need to be overcome in order to eliminate HBV as a health problem[127]. Particularly, in developing countries, sustainable financial mechanisms are required to scale up screening interventions and ensure access to vaccines.

Regarding the at birth dose, out-of-hospital deliveries, shortage of monovalent vaccine formulation in some regions, insufficient training of health care providers, weak monitoring and reporting systems, and low government commitment impair its implementation. On the other hand, in the adult population not covered by universal vaccination, promoting information, raising consciousness about risk, and finally focusing and promoting vaccination campaigns should improve immunization strategies for this group.

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## CONCLUSION

The worldwide application of HBV vaccines has led to a significant decrease in HBV infection incidence and its related death rates. As a general strategy, surveys are necessary to identify local constraints (in regions or countries) in order to achieve the implementation of WHO guidelines, both at the prophylaxis and diagnostic levels. Increasing efforts to improve vaccination coverage and raise awareness among populations not reached by universal vaccination will contribute significantly to achieving the WHO goals by 2030. Although HBV vaccines induce protective immunity in more than 90% of immunized people, there are particular settings where the efficacy is lower. In recent years, new formulations containing new adjuvants or other HBV antigens in addition to HBs, that could overcome the limitations of current presentations.

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## FOOTNOTES

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