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Review Article

Hepatitis B eradication: vaccine as a key player

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Abstract: Objective: Despite the availability of a highly effective and safe vaccine against hepatitis B virus (HBV) infection for 40 years, still almost 300 million persons are estimated to be chronically infected by this virus worldwide. The World Health Organization (WHO) has proposed a plan for hepatitis elimination by 2030. However, several factors, such as the reduction and limitation in vaccination campaigns or vaccine hesitancy (VH) in some regions of the World, might have played a role in limiting the worldwide coverage of hepatitis B prophylaxis. This review aims to describe which factors, such as VH, may be hampering the WHO 2030 goal for hepatitis B eradication. Methods: The review describes the development and characteristics of the HBV vaccine, from the first plasma-derived to the recombinant one. Eventual limitations in its effectiveness and particularly VH were reviewed. Results: The apparent pitfalls of the HBV vaccine, such as long-term effectiveness, vaccine-escape mutants, and adverse effects, were proven not to be a concern for this vaccine. However, VH persists and was even intensified by the COVID-19 pandemic. Conclusions: Many barriers still exist, such as vaccine availability, lack of awareness of the benefits of HBV vaccination, and VH. HBV VH seems to be eventually overcome in many settings with active education campaigns and information, stressing the importance of developing these strategies to achieve the 2030 goal of the WHO.

Keywords: Hepatitis B virus, vaccine hesitancy, adverse effects, vaccine coverage, eradication

Hepatitis B infection: A health problem

Almost 300 million persons are estimated to be chronically infected with hepatitis B virus (HBV) worldwide [1]. HBV chronic infection causes cirrhosis and hepatocellular carcinoma (HCC), and is responsible for at least 800,000 deaths each year [1]. HBV infection is highly endemic in Sub-Saharan Africa, Asia, and indigenous populations from America and Oceania [2, 3].

With the availability of a highly effective vaccine for prophylaxis against HBV infection and highly active antivirals against the hepatitis C virus (HCV), the World Health Organization (WHO) has proposed a plan for hepatitis elimination by 2030 [4]. In the case of HBV, this goal implies 90% infant vaccine coverage [4]. However, several factors may be considered to make this plan feasible. Of particular concern, in light of the COVID-19 pandemic, some factors, such as the reduction in vaccination campaigns or vaccine hesitancy (VH) in some regions of the world, might have played a role in reducing the worldwide coverage of hepatitis B prophylaxis. The aim of this review is to evaluate which factors, such as VH, may be hampering the WHO 2030 goal for hepatitis B eradication.

Hepatitis B vaccine development

HBV is a partially double stranded DNA virus of around 3,200 bp and belongs to the *Hepadnaviridae* family. The members of this family share a unique peculiarity: the circulation of naturally-occurring viral-like particles, composed exclusively of the HBV surface antigen (HBsAg) inserted in a non-infectious envelope (**Figure 1**) [5]. The concentration of these HBsAg particles can reach up to 10^4 times the concentration of the infectious virions, allowing the easy detection of this antigen. Since 1982 it

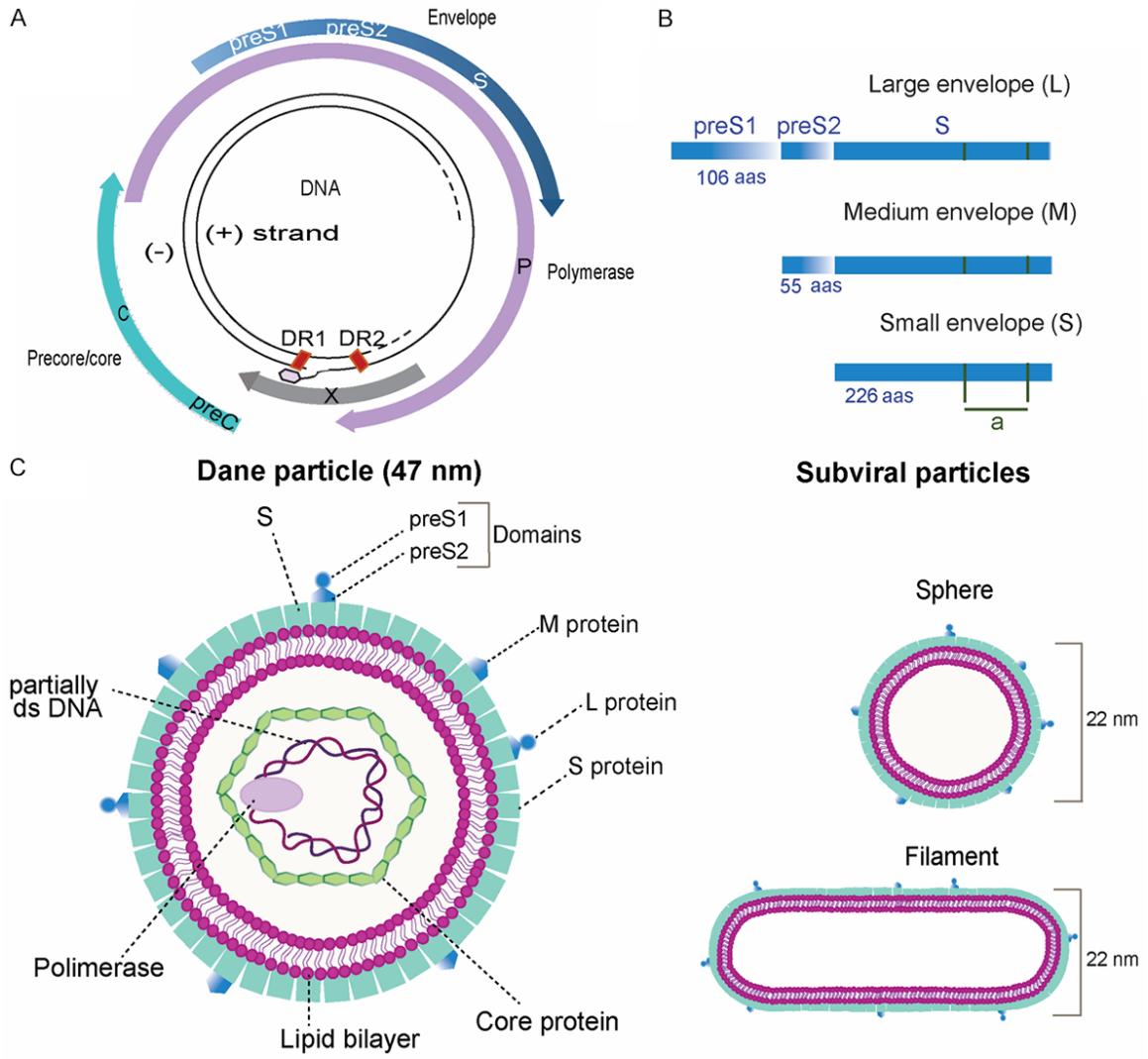

Figure 1. Genome proteins and viral structures of Hepatitis B virus (HBV). A. HBV is a partially double-stranded DNA genome of around 3200 nt. Despite bearing one of the smallest animal virus genomes, it encodes 7 different proteins, by using several starting codons and overlapping open reading frames (ORF). B. The virus is enveloped and the three surface antigens coded by the Envelope gene (small, medium and large) are inserted in the membrane envelope. The "a" determinant of the HBV surface antigen (HBsAg) is indicated. Most of the neutralizing antibody response induced by the vaccine is directed against it. C. The viral and subviral particles (spheres or filaments, containing only the envelope) are also shown: they contain less Medium protein (M) and Large protein (L), and more Small protein (S), compared to the virions [5].

has also led to the production of a plasma-derived vaccine, the first version of the HBV vaccine, by taking advantage of this excess HBsAg, which has proven to induce neutralizing antibodies [5-7].

The plasma-derived vaccine was rapidly replaced by a recombinant version, because of the complexity in the manufacturing of the plasma-derived one, but also because of unfounded concerns about the possibility of being infected by an infectious agent, notably human Immunodeficiency virus (HIV), which was not adequately inactivated during the elaboration of the vaccine [8]. The recombinant HBV vaccine was indeed the first recombinant vaccine produced [9].

Hepatitis B vaccine: effectiveness

After more than 30 years of profuse HBV vaccination in several regions of the world, the high effectiveness of this vaccine has been proven, both for the prevention of viral infection, but

Table 1. Examples of the effectiveness of the hepatitis B vaccine after more than 30 years of application

Country	Outcome	Ref
Alaska	Elimination of HCC and acute hepatitis B in children.	[61]
China	Incidence rate of liver cancer significantly lower after vaccination in a randomized control trial.	[62]
China	Reduction of the risk of HBV infection in blood donors.	[63]
Cuba	Reduction in the annual incidence of acute HBV infection cases.	[64]
Italy	Modeling shows a significant reduction in HBV-related diseases (infections, chronic disease, and HCC), and related costs.	[65]
Senegal	Absence of HBsAg positivity in children below 4 years of age.	[66]
Taiwan	Decline in HBsAg positivity rate, from 9.7% in university students born before June 1974 to <1.0% in those born after 1992.	[67]
Taiwan	Steady decline in HCC incidence in children from 1981 to 1994.	[68]
Global burden	31.3% decline in chronic HBV infection between 1990 and 2019, 76.8% in children younger than 5 years.	[2]

HCC: hepatocellular carcinoma. HBV: Hepatitis B virus. HBsAg: HBV surface antigen.

also for the reduction of HCC incidence (**Table 1**).

In addition to the more classical outcome described in **Table 1**, it has been demonstrated that the HBV vaccine produced benefits against other sequelae of HBV chronic infection, such as fulminant hepatic failure, liver cirrhosis and many comorbidities [10].

'Apparent' pitfalls of HBV vaccination

Decline in the protective antibody levels

Despite the high effectiveness of HBV vaccination at birth, some concerns were raised about the eventual need for booster doses during life. A concentration superior to 10 IU/L of the antibody to HBsAg (anti-HBs) is considered protective [11]. Growing evidence suggests a rapid decline of the anti-HBs levels after the first year of initial vaccination. The relatively rapid anti-HBs decline had raised the question of the need for a booster vaccination [10, 12]. However, it is generally accepted that long-term protection persists even with anti-HBs levels below 10 IU/L, probably mediated by a T memory cell response [10, 12]. The only exceptions could be some immunocompromised or high-risk populations, for whom a booster dose might be advisable [10].

Vaccine escape mutants

The occurrence of vaccine-escape mutants also warranted to explore the need for modifying/improving the existing HBV vaccine formulation. At the end of the 90s, a mutation in the loop of the "a" determinant of HBsAg, the main epitope of this antigen, was detected in children born from HBsAg positive mothers, albeit passive and active immunization [13, 14]. The mutation G415R in the HBsAg leads to a conformational change in the "a determinant", affecting its immune recognitions. Because of the extensive overlap in the HBV coding frames, this mutation was shown later to appear during antiviral treatment. A mutation in the Polymerase gene, associated with resistance to lamivudine, for example, induces the emergence of G415R in the HBsAg gene, because of the overlap of the two genes. Since then, several other mutations in the enzyme gene have been described, that result in structural changes in the HBsAg protein [15].

The risk of reducing the HBV vaccine effectiveness through the emergence of vaccine-escape mutants prompted the investigation of the development of immunogens comprising the preS region of the HBsAg. Despite this concern, the great effectiveness of vaccination over these last 30 years showed that breakthrough infections caused by vaccine-escape mutants have not proven to be very frequent, and did not seem to pose a problem. However, the increasing appearance of drugs resistant mutants also leads to an altered "a" determinant of the S protein (**Figure 1**) [15-17], which might revive the concern of hepatitis B transmission despite vaccination. In Africa, for example, a systematic review showed a high incidence of vaccine-escape mutations associated with a high rate of drug-induced antiviral resistance in HIV-infected patients, also associated with low vaccination coverage in some settings [16]. The implication of vaccine-escape mutants' circulation deserves further studies. It has been shown, however, that the HBV vaccine

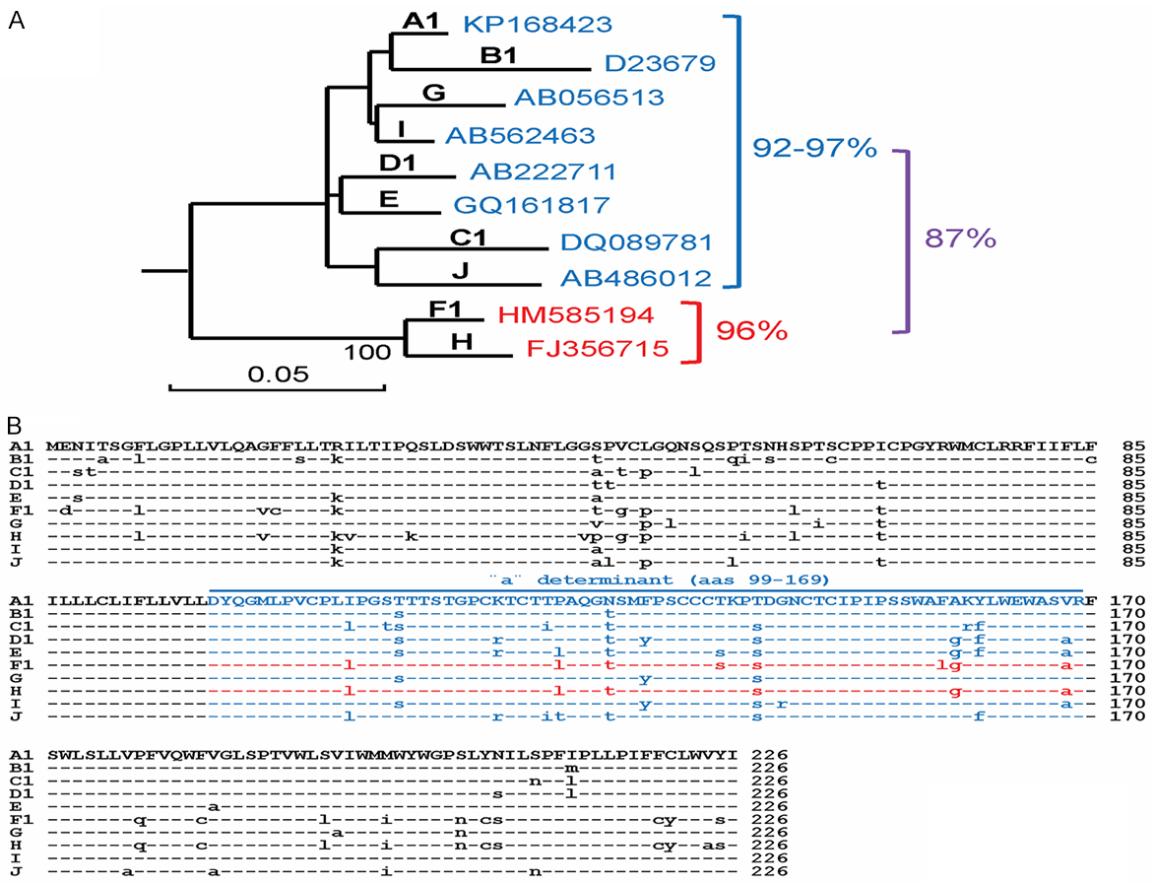

Figure 2. A. Phylogenetic tree (protein, Poisson corrected, 1000 bootstrap replicas) of the hepatitis B virus surface antigen (HBsAg) (226 aas). One isolate for each hepatitis B virus (HBV) genotype was selected for this analysis. Homology between the American genotypes (in red) and the other genotypes (in blue) is compared with the homology between the two groups (in lilac). Bootstrap values over 90 are shown in black. B. Amino acid alignment of HBsAg sequence, with a sequence for each genotype. The "a" determinant is shown in color (in red the American genotypes).

protects chimpanzees against the most common vaccine-escape mutant [18].

Genotypic variability and vaccine effectiveness

Up to 10 genotypes and numerous subgenotypes have been described for HBV [19]. The American genotypes F and H are the most divergent [20]. They exhibit up to 13% amino acid sequence divergence in the HBsAg from the other genotypes, as shown in **Figure 2A**. This divergence raised the concern of an eventual reduced effectiveness for these genotypes, of a vaccine based on an HBV genotype A2 genome. However, an experts review study showed that the HBV vaccine has been effective worldwide, including in the regions where the American HBV genotypes prevail [21]. Indeed, the "a" determinant of the American genotypes does not harbor many particular mutations, not shared with some of the other genotypes (**Figure 2B**).

Vaccine for non-responders

The preS-containing HBV vaccines could also be useful for the 5-10% of the population that do not respond to the vaccine, in an attempt to overcome this non-responsiveness [22]. In addition, improved vaccine formulations have also been developed to try to break the immune tolerance or exhaustion present in chronic HBV carriers [23]. Recently, a vaccine containing the preS1 and preS2 regions of the S antigen has been licensed, exhibiting superior immunogenicity, a more durable protection and reducing non-responder rates [24].

Several therapeutic vaccine candidates have and are being assayed against chronic HBV infection [25]. An immunotherapeutic vaccine for chronic HBV infection should address the following issues: to restore dysfunctional HBV-specific immune response, particularly at the

Table 2. Hesitancy to hepatitis B vaccine. Africa, Asia, Europe and Oceania

Country	Year	Comment	Ref
Australia	2017	HBV VH of the birth dose because of perception of low risk for their infants and instead risk of administration of a vaccine at birth.	[69, 70]
China	2014	In 2013, two media reported infant deaths after the administration of the HBV vaccine. Questionnaires on the impact of this information led to 30% VH at the peak of the event.	[71]
	2013-2016	In 2016, a second event was linked to illegal vaccines private sale. Up to 79.2% VH on a private sale, just after the event.	[72]
France	2013	Although most of the surveyed population recognized and were aware of the risk of HBV infection, more than half of them expressed fears about vaccine's adverse effect.	[73]
	2014	General practitioners were less prone to recommend HBV vaccination to their patients than to vaccinate their children.	[74-76]
	2016	VH for several viral vaccines was over 40%, while the effective refusal of a vaccine was lower than 30%. In general, VH for the hepatitis B vaccine was higher than for other viral vaccines.	[77]
	2017	High VH in France, with up to 30% VH for the HBV vaccine.	[78]
	2017-2018	Low self-vaccination acceptance for most recommended vaccines, and high VH among the general population, particularly hepatitis B.	[79]
Israel	2013-2017	High HBV VH for children [40% during the whole period]. No correlation with social media traffic as for other vaccines.	[80]
	2014-2016	One of the reasons for HBV VH was the perception of a lack of risk of infection for newborns.	[81]
Turkey	2011-2020	HBV VH increased with the COVID-19 pandemic, because of fears of adverse effects.	[82]
Uganda	2020	High HBV VH among pregnant women, is related to lower education level and knowledge of infection risks.	[83]
Vietnam	2017	Almost 40% of HCWs expressed non confidence in the safety of the HBV vaccine.	[84]

HBV: Hepatitis B virus. VH: Vaccine hesitancy. HCWs: Health Care Workers.

CD8+ T-cell level, and to induce novel HBV-specific immune responses, targeting viral antigens other than HBsAg [25]. However, a functional cure has not been yet obtained with neither of these strategies. Probably a combination of strategies, including immunomodulators, viral inhibitors, and therapeutic vaccines, would probably be necessary to achieve this goal [26].

Multiple sclerosis after hepatitis B vaccination

In 1991, two cases of multiple sclerosis (MS) were reported after HBV vaccination [27]. This occurrence prompted the French sanitary authorities to temporarily suspend HBV vaccination, attending to the cautionary principle. Several studies confirmed later the absence of a relationship between HBV vaccination and multiple sclerosis (revised by [28]). Indeed, the hepatitis B vaccine has been widely administrated at birth, and during pregnancy, with a highly satisfactory safety profile [29-31].

Vaccine hesitancy and limitations

As shown in the previous section, the concern on the association of hepatitis B vaccination with multiple sclerosis was thoroughly addressed: multiple studies showed a lack of association between the two events (revised by [30]). Indeed, multiple sclerosis concerns seem to have diminished among the public. However, a more recent study reports a case of multiple sclerosis, again presumably associated with hepatitis B vaccination [32]. Thus, the concern of neurological adverse effects of hepatitis B seems to be an issue periodically revisited, although does not seem to affect the willingness to get vaccinated. Most of the associations between vaccines and nervous system autoimmune syndromes are not found in well-conducted epidemiological studies [33].

Several studies on VH have been performed on the acceptance of the hepatitis B vaccine (**Tables 2** and **3**). Many of them have been performed in France, one of the countries displaying the highest level of VH worldwide, particularly for the hepatitis B vaccine [34]. The main reasons for the VH in France were fears of adverse effects, although the precise nature of these presumed adverse effects was generally unknown (**Table 2**). Vaccination for hepatitis B became mandatory in France in 2018. This law, together with an effective communication campaign, lead to a significant increase in hepatitis B vaccination coverage for children at birth [35]. The fears of MS after HBV vaccination persists in France and neighboring countries, such as Belgium [36].

In Brazil, systematic vaccination against HBV was incorporated for children younger than one

Table 3. Hesitancy to hepatitis B vaccine. America

Country	Year	Comment	Ref
Brazil	2003	Lower vaccination coverage among older dentists is associated with reduced information on the benefits of the vaccine, and with a lower frequency of gloves use. Dental assistants exhibited significantly lower levels of vaccination.	[85, 86]
	2008-2009	Almost 30% of adolescents non vaccinated in Sao Paulo: the main reasons were the lack of orientation and not considering the vaccine necessary.	[87]
	2009	Non-vaccination among Health care workers [HCW] in Minas Gerais was associated with not having a partner, lower education level, less exposure to disease because of the type of work, and not using personal protection equipment.	[88]
	2010	In contrast to physicians, the majority of family health nurses did not indicate the hepatitis B vaccine for pregnant women.	[89]
	2010	Despite the availability of the HBV vaccine for pregnant women since 2009 in Brazil, low vaccination coverage because not frequently offered by physicians.	[90]
	2019	Only 58% of HCWs exhibited complete vaccination against HBV. More VH was found among HCWs with lower instruction. HCW of Italian origin manifested frequent VH because of fear of MS and assumed Alzheimer's disease associated with aluminum adjuvants.	[91]
	2020	Increased HCW HBV vaccination rates in medical students during the 6 years of course [53 to 93%], associated perhaps with an increase in awareness of vaccine benefit and the risk of disease.	[92]
Paraguay	2020	Almost 40% of medical students were not vaccinated against HBV, mainly because of a lack of interest.	[93]
Canada and USA	2012-2014	Analysis of media content arose higher negative perceptions [concerns of adverse effects] of the HBV vaccine, compared to other vaccines.	[94]
USA	2008-2013	Missing the HBV birth dose was strongly associated with the non-completion of vaccination.	[95, 96]
	2018-2019	Low VH for birth dose hepatitis B vaccination, compared to other vaccines.	[97]
	2018-2020	Rates of birth dose vaccination increased over the 3-year period. Racial differences in HBV birth dose vaccination rates were observed: Asian Americans had the highest rate of newborn vaccination, and high VH for African American infants.	[98]

HBV: Hepatitis B virus. VH: Vaccine hesitancy. HCWs: Health Care Workers. MS: Multiple sclerosis.

year, and the coverage expanded for those until 20 years old since 2001. A systematic review showed a significant reduction of HBV infection throughout the country, passing from moderate to low endemicity (less than 1% HBsAg general prevalence) during this century. However, some clusters of high endemicity persist, particularly in rural settings and among indigenous populations [37]. In addition, low HBV vaccine coverage is still reported in particular population groups, such as pregnant women (88% non-vaccinated in 2011-2013 in Bel Horizonte, Brazil) [38], hemodialysis patients (59% with complete doses in 2012-2014 in Sao Carlos, Brazil) [39], and people living with HIV (only 56.7% were vaccinated against HBV in 2015-2016 in Espirito Santo, Brazil) [40]. Even more recently, a significant remnant of VH can be appreciated in some population groups, particularly for young children vaccination [41] (**Table 3**).

In the USA, although the levels of hepatitis B VH have been lower than the ones found in France, ethnic disparities were found in some studies, African American exhibiting more VH than Asian Americans, for example. The importance of not delaying the HBV birth dose vaccine for achieving the completion of vaccination was also observed (**Table 3**).

A good example of the influence of social media on VH is the two reported adverse effects associated with HBV vaccination that occurred in China (**Table 2**). In contrast, social media do not seem to be a factor associated with VH in Israel (**Table 2**). Another factor associated with HBV VH is the age of vaccine administration. The parents do not perceive the risk of chronic infection during childhood and in contrast manifest fears of eventual harm from a vaccine administered at birth, as shown in Australia (**Table 2**).

Another factor that seems to influence the coverage of HBV vaccination at birth is the place of delivery. In Nigeria, the delivery either at home or in a private clinic (after adjusting for other factors), was associated with a significant reduction in the odds of the infant getting the vaccine [42]. A similar observation was reported in Peru [43]. In both cases, the availability of the HBV vaccine in private institutions may be an important limitation.

Little information is still available on the potential influence of the intense anti-COVID-19 vac-

cination campaigns developed in several countries on HBV VH. A first example was reported in Turkey, where VH was shown to increase after COVID-19 (**Table 2**). Moreover, in a study covering 55 countries, the confidence that vaccines are important for children was reduced in 52 of them, in some of them up to 44% [44]. More time is needed to evaluate the extent of this eventual deleterious association. In any case, both because of increasing VH and/or because of vaccination campaigns reductions, the COVID-19 pandemic affected the HBV vaccination coverage, as well the coverage for other vaccines.

The COVID-19 pandemic has also caused important reductions in routine immunizations. As inferred by modelling, a reduction of 20% vaccination coverage in 2020 would lead to more than 500,000 additional chronic HBV infections and 67,000 deaths in Africa and similar numbers in the Western Pacific Region [45]. Another modelling study in Amsterdam addressed the effect of the pandemic on the incidence of HBV infection among men who have sex with men (MSM). The first lockdown might have led to a significant decrease in the number of sex partners for MSM. A 15-25% decrease in sex partners during the first lockdown and 5% during the second lockdown, was associated with a decline of 6.6% in HBV incidence in 2020, even with more than 70% reduction in HBV testing and vaccination during the first lockdown. However, since the number of sex partners rebound in 2021, the fact that HBV testing and vaccination were still not optimal in 2021, lead to an increase of 1.4% in incidence in 2021 and 3.1% in 2022. To bring the HBV incidence in 2023 back to that expected in the absence of the pandemic, an increase of at least 60% would have been needed in HBV vaccinations in 2022 [46]. A continued decline in vaccination coverage during 2020-2021 was observed for most vaccines, including HBV [47].

Real world vaccine coverage

From 1990 to 2019, a 32% reduction in HBsAg prevalence was observed globally. As can be seen in **Figure 3**, a higher percentage reduction can be observed in the regions exhibiting higher HBsAg prevalence, reaching up to a 36% reduction in Africa, for example, compared to only 29% in the Americas (**Figure 3**). In 2019, 68 of 194 countries already had achieved the 2030 target proposed in the WHO Interim Guidance of an all-age HBV-related death rate of four per 100,000 [2]. Most countries in the Americas adopted universal HBV vaccination at birth more than 20 years ago [48]. However, several countries did not reach the expected 90% vaccination coverage, particularly in Africa (**Figure 3**). Even if the HBV vaccination coverage is higher in other regions, a recurrent observation is the low birth dose coverage almost in all the regions of the world, except for the West Pacific Region (**Figure 3**).

There are huge global disparities in HBV epidemiology that poses several concerns to achieving the 2030 goal of the WHO. The prevalence of HBsAg in low-income countries can be up to 6 times higher than the one found in high income countries. Fewer infants are vaccinated at birth in these countries, and fewer people get access to diagnosis [49]. Additional resources are needed to attain birth vaccination coverage in the countries exhibiting the highest prevalence worldwide [50, 51]. Birth dose HBV vaccine is important for many reasons. Acquisition of the disease at birth increases dramatically the odds of chronicity, up to 80-90%, compared to 10-15% evolution of chronicity in adults [52]. Even in a region such as Africa, where mother to infant transmission is far less common than in Asia, a significant number of infants are infected at birth, leading to the increased risk of development of HCC [53], stressing the importance of not delaying the vaccination of infants.

Importance of education campaigns

Several reports have shown that VH or delays in vaccination can be easily overcome with appropriate education campaigns. In Sierra Leone, exposure to vaccination information from faith leaders and health facilities was associated with an increased likelihood of vaccination uptake [54]. Among HCV positive homeless persons in San Francisco, CA, USA, 35% were eligible for HBV vaccination. After education, 72% of them agreed to be vaccinated [55]. A study of hepatitis B knowledge among Asian individuals from Cleveland, OH, USA, showed that there are still deficits regarding the viral mode of transmission, and vaccination. The authors propose education efforts

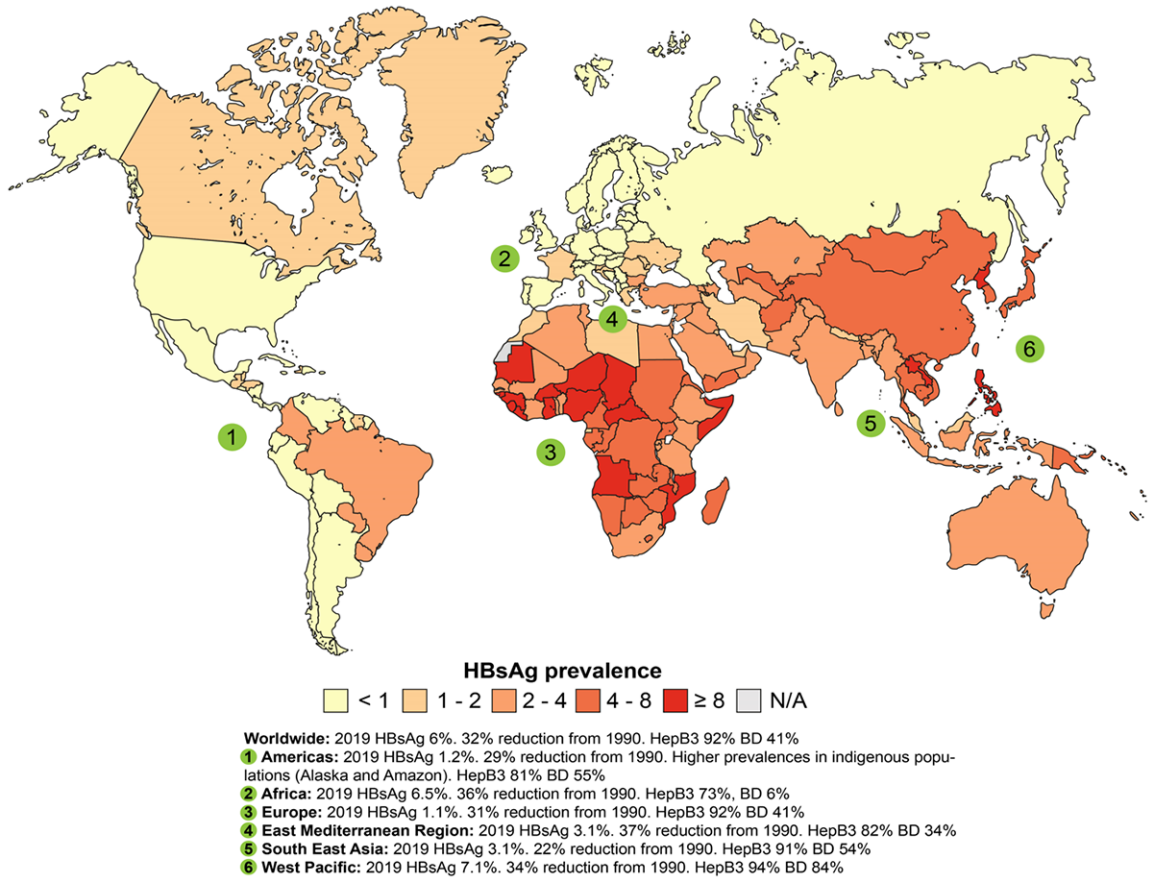

Figure 3. Prevalence of hepatitis B virus surface antigen (HBsAg) worldwide and vaccine coverage in each region. HepB3: 3 doses of hepatitis B virus (HBV) vaccine coverage. BD: Birth dose coverage. N/A: not available. HBsAg prevalence was obtained from [2]. Data on vaccination coverage was obtained from Asian Liver Center at Stanford University 2020 (https://med.stanford.edu/liver/research/global-vaccination-coverage-2.html, accessed on April 19, 2023), using for source https://apps.who.int/immunization_monitoring/globalsummary and https://ourworldindata.org/world-region.map-definitions.

to improve the knowledge about HBV, using culturally sensitive Internet and social media platforms [56]. As stated in this study, it is important to address the cultural barriers that may be hampering vaccine acceptance. A study of prisoners in Italy took into account the multiethnic origins of the detainee population: for example, they received an HBV brochure in various languages. A high rate of adherence was obtained [57]. A study in Uganda showed the frequent absence of knowledge on HBV disease: an example of this is the lack of specific words to describe it in the local language, implying again the importance of providing appropriate and accessible information to the populations for vaccine acceptance [58].

On the other hand, mandatory vaccination seems to be still needed to increase vaccine coverage. In a study in Pakistan, job entry requirement was the primary reason for complete vaccination in Health Care Workers (HCWs) [59]. Public health institutions have to choose between enforcing promotion or mandatory policies to achieve complete vaccination coverage [60].

Conclusions

There is still no effective cure for HBV, but the vaccine has largely proven its effectiveness. In contrast to COVID-19, there is no biological barrier that reduces the effectiveness of the HBV vaccine. However, many barriers still exist to the effective eradication of this harmful disease, such as vaccine availability, and lack of awareness of the beneficial relationship between the risk of acquiring HBV and the benefits of getting vaccinated, and remaining VH. HBV VH seems to be easily overcome in many

settings with active education campaigns and information, stressing the importance of developing these strategies to achieve the 2030 goal of the WHO.

Disclosure of conflict of interest

None.

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