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REVIEW ARTICLE

A critical review of the prospects and challenges of Hepatitis B therapeutic vaccines

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ABSTRACT

Hepatitis B therapeutic vaccines hold great promise in the treatment of chronic Hepatitis B virus (HBV) infection. However, like any medical intervention, they also face certain prospects and challenges which forms the aim of this critical review. Therapeutic vaccines offer a targeted approach to manage chronic Hepatitis B infections, aiming to stimulate the immune system to recognise and eliminate infected cells. The potential to halt disease progression holds promise for preventing severe liver diseases associated with chronic Hepatitis B, such as cirrhosis and hepatocellular carcinoma. Therapeutic vaccines, if effective, could contribute to a more equitable distribution of treatment options globally, especially in resource-limited settings. Hepatitis B therapeutic vaccines may play a crucial role in preventing vertical transmission, reducing the global incidence of perinatal HBV infections and improving maternal-child health outcomes. Diverse vaccine platforms and combination strategies, including immunomodulation and checkpoint inhibitors, are advancing, optimising immunogenicity, and eliciting strong immune responses. Tailoring therapeutic vaccines to individual patients based on genetic considerations may enhance efficacy, recognizing the genetic diversity of Hepatitis B. Therapeutic vaccines need to align with global health goals related to infectious disease elimination, contributing to broader efforts to reduce the burden of Hepatitis B worldwide. While Hepatitis B therapeutic vaccines hold significant promise in transforming the management of chronic infections, addressing challenges related to access, viral variability, and long-term monitoring is crucial for their successful integration into global healthcare strategies.

Keywords: clinical trial; Hepatitis B; hepatocellular; therapeutics; vaccine

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1. Introduction

Hepatitis B viral infection (HBV) is a global health challenge with significant implications for public health. The prevalence and burden of HBV on a global scale, highlighting key regions, risk factors, prevention efforts, and existing challenges[1]. HBV exhibits a geographically diverse distribution, with certain regions bearing a higher burden of infection. Sub-Saharan Africa and parts of Asia, particularly China and Southeast Asia, are considered high-endemic areas, hosting a substantial proportion of the world's chronic HBV cases[2]. Intermediate-endemic regions include parts of Eastern Europe and the Middle East, while North America, Western Europe, and

Australia generally experience lower prevalence rates[3]. Chronic HBV infection constitutes a major global health concern, affecting over 250 million individuals worldwide[4]. The chronic nature of the infection makes it a leading cause of severe liver diseases, including cirrhosis and hepatocellular carcinoma (HCC)[5]. Mortality associated with HBV-related complications is a significant contributor to global death rates, emphasizing the urgency of addressing this public health issue[6].

Efforts to combat the global burden of HBV infection have been multifaceted. Key strategies include widespread vaccination programs, particularly in regions with high endemicity[7,8]. The integration of hepatitis B vaccination into routine childhood immunization schedules has been a pivotal step in preventing new infections. Screening programs identify individuals with chronic infection, enabling timely intervention and treatment to prevent disease progression. Public health campaigns and educational initiatives aim to raise awareness about the modes of transmission, the importance of vaccination, and the availability of screening and treatment[9]. Disparities in access to vaccination, screening, and treatment contribute to the persistence of HBV in certain regions, particularly in low-resource settings. The stigma associated with hepatitis B can lead to discrimination and hinder individuals from seeking testing and treatment[10]. Lack of awareness about the risks, modes of transmission, and preventive measures remains a challenge, particularly in areas with high prevalence. Global health inequalities exacerbate disparities in the burden of HBV infection, with vulnerable populations facing a higher risk of transmission and poorer outcomes[11].

Hepatitis B therapeutic vaccines represent a promising frontier in the battle against chronic HBV infection[12]. As researchers and pharmaceutical companies continue to advance in vaccine development, the potential for improved patient outcomes and a reduced global burden of hepatitis B-related diseases becomes increasingly tangible. The ongoing commitment to addressing the challenges and refining therapeutic vaccine strategies is essential to realizing the full potential of these innovative interventions and bringing about a transformative impact on global public health. Therapeutic vaccines for HBV were an area of active research, and several candidates were in different stages of development[12]. It's important to note that the landscape of medical research is dynamic, and new developments may have occurred since then. Hence the need to review the latest scientific literature, clinical trial databases, or official regulatory updates for the most recent information on hepatitis B therapeutic vaccines as the field continues to evolve.

2. Results

2.1. Hepatitis B therapeutic vaccine development strategies

The development of an effective therapeutic vaccine for Hepatitis B is crucial in addressing the global burden of this disease. Unlike preventive vaccines administered before exposure, therapeutic vaccines aim to stimulate the immune system in individuals already infected to control or eliminate the virus. Hepatitis B therapeutic vaccines employ various mechanisms to induce a robust and targeted immune response. Many focus on stimulating cytotoxic T lymphocytes (CTLs) to recognize and eliminate infected hepatocytes. Some vaccines target the viral capsid, disrupting its assembly and hindering the virus's ability to replicate. Others employ immunomodulatory agents to overcome the immunotolerance often observed in chronic HBV infection. The various strategies used in the development of the hepatitis B therapeutic vaccine are discussed below:

2.1.1. T-cell stimulation

As preventative vaccines have been successful in reducing new infections, therapeutic vaccines designed to stimulate T-cell responses hold promise in managing chronic Hepatitis B infections[13]. T-cells play a central role in the immune system's ability to recognize and eliminate infected cells[14]. In the context of Hepatitis B, CD8+ cytotoxic T-cells are particularly important, as they can recognize and destroy hepatocytes harboring the virus[15]. However, chronic HBV infection often results in T-cell exhaustion and dysfunction, limiting the effectiveness of the host immune response. Therefore, designing therapeutic vaccines that present specific viral

peptides to T-cells can stimulate a targeted immune response. Peptide vaccines can be tailored to epitopes associated with critical viral proteins, such as the HBV core and polymerase[16]. DNA vaccines deliver genetic material encoding viral antigens directly into host cells, promoting the expression of antigenic proteins and subsequent T-cell activation[17]. This approach can induce both CD4+ and CD8+ T-cell responses, enhancing the breadth of the immune reaction. Utilizing viral vectors, such as adenoviruses or lentiviruses, to deliver HBV antigens can effectively stimulate T-cell responses[18]. Viral vectors can efficiently infect host cells, expressing viral antigens and triggering a robust immune reaction. Incorporating immune modulators, such as cytokines or checkpoint inhibitors, can enhance T-cell responses. This approach aims to overcome T-cell exhaustion and improve the effectiveness of the immune system against chronic HBV infection. Designing vaccines that target multiple viral antigens can broaden T-cell recognition and improve the likelihood of successful immune clearance. Multivalent vaccines may include components targeting both surface antigens (HBsAg) and internal antigens (HBcAg)[19].

2.1.2. Capsid inhibition

In the pursuit of effective treatments for chronic Hepatitis B infections, researchers are exploring innovative therapeutic vaccine strategies. One promising avenue is capsid inhibition, a novel approach that targets the viral capsid, a protein shell encapsulating the viral genome. The HBV capsid, composed of the HBcAg, plays a crucial role in the viral life cycle[20]. It protects the viral genome and facilitates its transport into the host cell nucleus, where replication occurs. By targeting the capsid, researchers aim to disrupt viral replication and prevent the production of new infectious particles. Capsid inhibition represents an exciting and innovative approach to the development of therapeutic vaccines for Hepatitis B[13,21]. By targeting the viral capsid, researchers aim to disrupt the viral life cycle and reduce the burden of chronic infection. While challenges such as resistance and immune response modulation must be addressed, the potential of capsid inhibition to revolutionize Hepatitis B treatment underscores its importance in the ongoing efforts to combat this global health challenge. As research progresses, the development of capsid-inhibiting therapeutic vaccines holds promise for a future where Hepatitis B is more effectively managed and treated.

2.1.3. Immunomodulation

While preventive vaccines have been successful in reducing new infections, therapeutic vaccines designed to stimulate the immune system hold promise in managing chronic Hepatitis B infections. In chronic HBV infection, the virus can evade the host immune response, leading to persistence and potential progression to severe liver diseases[22,23]. Immunomodulation involves manipulating the immune system to enhance its ability to recognize and eliminate infected cells, a critical aspect in the development of therapeutic vaccines for Hepatitis B[24]. Immunomodulation stands as a pivotal strategy in the development of Hepatitis B therapeutic vaccines by manipulating the immune system's responses, these vaccines aim to overcome the challenges of chronic infection and improve the clearance of HBV-infected cells with Nasvac therapeutic vaccine being administered intranasal[25,26]. As research progresses, the integration of immunomodulation into therapeutic vaccine approaches holds great promise for transforming the landscape of Hepatitis B treatment, offering hope for more effective and personalized solutions in the fight against this persistent global health challenge.

2.1.4. Targeting Hepatitis B surface antigen

The Hepatitis B Surface Antigen (HBsAg) is a critical component of the HBV envelope and is essential for viral entry into host cells. Targeting this surface antigen presents a promising approach to developing therapeutic vaccines capable of inducing robust immune responses against infected hepatocytes. The development of Hepatitis B therapeutic vaccines targeting the Hepatitis B surface antigen represents a promising avenue in the fight against chronic HBV infections. Advancements in protein subunit vaccines, DNA-based vaccines, and nanoparticle formulations have demonstrated the potential to induce robust immune

responses. As research continues, the integration of innovative technologies, combination approaches, and personalized strategies holds great promise for revolutionizing the landscape of therapeutic interventions against Hepatitis B on a global scale. Targeting HBsAg in therapeutic vaccines aims to induce the production of neutralizing antibodies[27]. These antibodies can bind to the surface antigen, preventing viral entry into host cells. In addition to antibody responses, targeting HBsAg in therapeutic vaccines aims to activate CTLs. These cytotoxic T cells recognize and eliminate infected hepatocytes, contributing to viral clearance[28,29]. Some therapeutic vaccines targeting HBsAg are designed to be multivalent, incorporating additional viral components[30,31]. This approach enhances the breadth of the immune response, providing a comprehensive strategy for tackling chronic Hepatitis B.

2.1.5. Targeting Hepatitis B core antigen

Hepatitis B Core Antigen (HBcAg) is a critical viral protein that forms the core of the HBV nucleocapsid. Targeting HBcAg in therapeutic vaccines aims to stimulate robust immune responses, particularly cytotoxic T lymphocytes (CTLs), which play a crucial role in eliminating HBV-infected cells[32,33]. The development of Hepatitis B therapeutic vaccines targeting the Hepatitis B core antigen represents a promising frontier in combatting chronic HBV infections[34]. As research progresses and clinical trials advance, the focus on targeting HBcAg offers hope for more effective therapeutic interventions, contributing to the global efforts to manage and treat chronic Hepatitis B infections. Targeting HBcAg in therapeutic vaccines aims to induce the activation of CTLs. These cytotoxic T cells specifically recognize and eliminate cells presenting HBcAg, contributing to viral clearance. Therapeutic vaccines targeting HBcAg contribute to the development of robust T-cell responses[35]. This broadens the spectrum of immune recognition, improving the vaccine's effectiveness against diverse HBV strains by eliciting strong CTL responses against HBcAg, therapeutic vaccines aim to enhance the immune system's ability to clear persistent HBV infections, preventing the progression of severe liver diseases[29]. The HBcAg produced using a recombinant technique in Cuba, known as HeberNasvac, possesses distinctive characteristics that make it a potent activator of toll-like receptors and a strong inducer of interferon production, including both type I and type II interferons. The HeberNasvac therapeutic vaccine contains both major antigens from HBV, which can activate both cellular and humoral responses to HBV. Additionally, the vaccine can stimulate innate immunity and activate ISG genes such as ISG20. ISG20 is important for clearing HBV because it can degrade both HBV RNA during replication and the persistent cccDNA of HBV[36]. HeberNasvac functions both as an immune modulator specific to HBV antigens and as a non-specific immune modulator that stimulates innate immunity. An effective innate immune response is crucial for the development of a robust adaptive immune response against specific antigens. In this context, we are referring to the two primary antigens, HBcAg and HBsAg[37]. Overcoming immunotolerance to persistent viral antigens, such as HBcAg in chronic infections, is a significant challenge and continued research seeks innovative ways to overcome immune exhaustion and stimulate effective immune responses.

2.1.6. Personalized medicine approaches

The innovative strategies employed in the development of Hepatitis B therapeutic vaccines using personalized medicine approaches, tailoring interventions to individual patient characteristics for more effective and targeted outcomes. Personalized medicine recognizes the genetic diversity of HBV among infected individuals and tailoring vaccines to specific viral variants present in a patient's infection enhances the likelihood of an effective immune response[38]. Personalized vaccines can be designed to target patient-specific viral epitopes, accounting for variations in the HBV genome[38]. This approach increases the precision of the immune response against the unique viral profile of each patient. Understanding the individual immune profiles of patients allows for the customization of immunomodulatory strategies which includes assessing the status of T-cell responses, cytokine profiles, and immune checkpoint expression[39]. Personalized medicine enables the selection of specific cytokines based on the patient's immune status, optimizing the balance between antiviral activity and potential side effects[40]. Personalized vaccines can incorporate a combination

of viral antigens tailored to the patient's viral variants which may involve targeting specific regions of the HBV genome, such as surface or core antigens[41–43]. The integration of personalized medicine approaches in the development of Hepatitis B therapeutic vaccines represents a groundbreaking paradigm in tailoring interventions to individual patient characteristics. As research progresses, addressing challenges related to manufacturing, immune exhaustion, and trial design will be crucial for translating personalized medicine strategies into effective therapeutic solutions. Personalized Hepatitis B therapeutic vaccines hold immense promise for enhancing treatment precision and effectiveness, bringing us closer to a future where individualized approaches play a pivotal role in combating chronic Hepatitis B infections.

2.1.7. Combination approaches

The development of Hepatitis B therapeutic vaccines has gained momentum, with researchers exploring combination approaches that leverage the strengths of multiple interventions. Multivalent vaccines incorporate multiple viral components, such as HBsAg and HBcAg[44,45]. This approach aims to stimulate a comprehensive immune response, targeting various aspects of the viral life cycle by addressing different viral components, multivalent vaccines enhance the breadth and potency of the immune response. This can contribute to more effective viral clearance and long-term immune memory. Integrating immunomodulation and cytokine therapy into therapeutic vaccines aims to enhance the host immune response. Cytokines such as interferons or interleukins can augment both humoral and cellular immunity[46]. The integration of combination approaches in the development of Hepatitis B therapeutic vaccines represents a strategic and multifaceted approach to combat chronic HBV infections[47]. By leveraging the strengths of various interventions, these combination strategies aim to enhance the overall efficacy, breadth, and durability of the immune response. As research progresses, addressing challenges related to resistance, adverse effects, and optimizing treatment duration will be crucial in translating these innovative combination approaches into effective therapeutic solutions for Hepatitis B.

2.2. Hepatitis B therapeutic vaccine challenges and consideration

Hepatitis B virus (HBV) poses a persistent global health challenge, necessitating innovative therapeutic solutions. The development of Hepatitis B therapeutic vaccines holds promise, yet it is accompanied by a range of challenges that require careful consideration[48]. Chronic HBV infections can persist for years, leading to a state of immune exhaustion. Developing therapeutic vaccines that effectively stimulate immune responses in the context of chronic infections is a formidable challenge. Chronic HBV infections often induce immunotolerance, where the immune system becomes less responsive to the virus[32]. Overcoming the immunotolerance induced by chronic infection, addressing the genetic diversity of HBV genotypes, and determining the optimal timing and staging for treatment are critical considerations[49]. Additionally, balancing an effective immune response without causing immune-mediated liver damage poses a delicate challenge in therapeutic vaccine development[50]. Chronic hepatitis B is associated with immunotolerance, where the immune system is less responsive to the virus. Therefore, developing vaccines that can overcome this tolerance is a significant challenge. HBV exists in various genotypes with distinct antigenic properties[51]. Designing a therapeutic vaccine that effectively targets multiple genotypes is challenging, as the vaccine must account for this genetic diversity. The optimal timing for therapeutic vaccination in the course of HBV infection and the selection of patients at different stages of the disease are critical factors. Vaccination may be more effective at certain stages of infection, as excessive immune activation can lead to immune-mediated liver damage. Striking a balance between an effective immune response and avoiding collateral damage to the liver is a delicate challenge. Developing and producing therapeutic vaccines can be expensive as such, ensuring accessibility to these vaccines, particularly in regions with high HBV prevalence and limited healthcare resources, is a substantial challenge[52]. The regulatory pathway for approving therapeutic vaccines may be complex and demonstrating safety, efficacy, and long-term benefits in clinical trials poses a challenge for vaccine developers.

2.3. Prospects of Hepatitis B therapeutic vaccine

Several therapeutic vaccine candidates have shown promise in preclinical and clinical trials like GS-4774, developed by Dynavax[53], which aims to induce strong T-cell responses against HBV. Assembly Biosciences' ABX203 targets the viral capsid assembly[54], and nanoparticle therapeutic vaccine for immune activation[55]. Therapeutic vaccines aim to stimulate the patient's immune system to attack and clear the virus. Successful vaccines can lead to a significant reduction in viral load, slowing or even halting disease progression by reducing viral replication, therapeutic vaccines may prevent or minimize liver damage caused by chronic inflammation, thereby lowering the risk of cirrhosis and hepatocellular carcinoma[56,57]. Ideally, therapeutic vaccines could induce a sustained immune response, providing long-term control of HBV infection, even after the completion of the vaccination regimen. Therapeutic vaccines can be used in combination with existing antiviral drugs to enhance treatment efficacy and this combination approach may reduce the likelihood of drug resistance and improve overall patient outcomes[57]. Effective therapeutic vaccines could have a profound impact on global public health by reducing the burden of chronic HBV infection, especially in regions where the virus is endemic[1]. The prospects of Hepatitis B therapeutic vaccines offer a beacon of hope in the battle against chronic infections as shown in **Figure 1**. The convergence of advancements in vaccine platforms, immunomodulation strategies, personalized medicine, and regulatory support paints a promising picture for the future. As research progresses and clinical trials unfold, these therapeutic vaccines have the potential to transform the landscape of Hepatitis B management, preventing disease progression, reducing the global burden of infection, and offering renewed hope for those affected by chronic Hepatitis B.

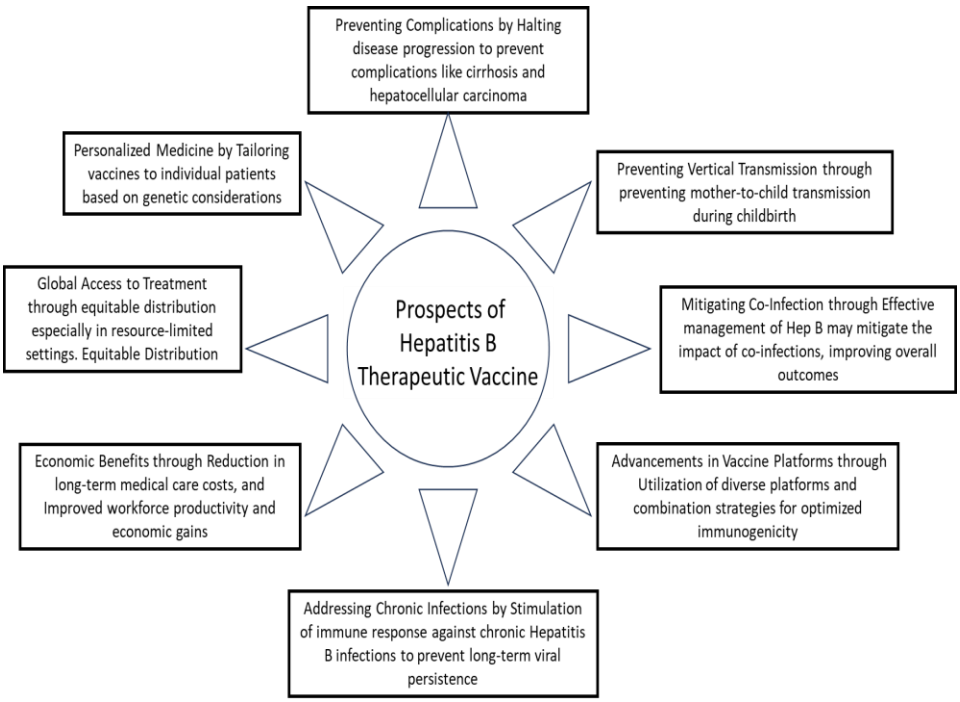

Figure 1. This structure represents a conceptual flowchart where each "Prospect" leads to a specific description of the prospect's details. You can adapt this to your preferred design tool and add visual elements to enhance the representation.

2.4. Global health implications of Hepatitis B therapeutic vaccine

The emergence of Hepatitis B therapeutic vaccines holds immense promise in transforming the landscape of global health[58]. The global health implications of Hepatitis B therapeutic vaccines, exploring the potential benefits, challenges, and their impact on public health as shown in **Table 1**. The successful development and implementation of hepatitis B therapeutic vaccines could revolutionize the management of chronic HBV infection[59]. By reducing viral load and preventing disease progression, these vaccines have the potential to mitigate the risk of cirrhosis and hepatocellular carcinoma. Moreover, combining therapeutic vaccines with

existing antiviral drugs may enhance treatment efficacy and reduce the likelihood of drug resistance. Chronic Hepatitis B infections contribute substantially to the global burden of liver diseases[60]. Therapeutic vaccines have the potential to reduce the burden of chronic infections by stimulating the immune system to recognize and eliminate HBV-infected cells, thereby preventing the progression of severe liver diseases[32,61]. The capacity of therapeutic vaccines to halt disease progression holds the promise of preventing complications such as cirrhosis and hepatocellular carcinoma, ultimately improving the quality of life for individuals with chronic Hepatitis B. The global nature of the Hepatitis B epidemic necessitates interventions that are accessible worldwide. If proven effective, therapeutic vaccines can contribute to a more equitable distribution of effective treatment options, reducing health disparities across regions. Therapeutic vaccines that are cost-effective, easily deployable, and adaptable to resource-limited settings have the potential to reach populations that might otherwise have limited access to advanced medical interventions. Mitigating the impact of Hepatitis B through therapeutic vaccination can alleviate the strain on healthcare systems, reduce hospitalization rates, and free up resources for addressing other pressing health issues[62].

Table 1. Provides a structured overview of the global health implications, with each implication linked to a brief description. Adjustments can be made based on specific data or additional details you wish to include.

Global health implications	Description	Reference
Reduction of Chronic Infections	Stimulation of the immune system to recognize and eliminate chronic Hepatitis B infections. Prevention of complications such as cirrhosis and hepatocellular carcinoma.	[63,64]
Global Access to Treatment	Equitable distribution of therapeutic vaccines globally, especially in resource-limited settings.	[65]
Prevention of Vertical Transmission	Role in preventing mother-to-child transmission during childbirth. Contributing to the elimination of perinatal HBV infections.	[66]
Mitigation of Co-Infections	Effective management of Hepatitis B may mitigate the impact of co-infections with viruses such as HIV or Hepatitis C.	[67]
Economic Benefits	Reduction in long-term medical care costs and improvement in workforce productivity decreased the economic burden on individuals and societies.	[68]
Advancements in Vaccine Platforms	Diverse platforms and combination strategies for optimized immunogenicity and integration of immunomodulation and checkpoint inhibitors.	[69]
Personalized Medicine	Tailoring vaccines based on individual genetic considerations and recognition of genetic diversity in Hepatitis B.	[70]
Challenges	Access and equity issues in distribution, adaptation to viral variability, long-term monitoring challenges, and overcoming immune exhaustion and tolerance	[71]

3. Expert opinion

Hepatitis B virus (HBV) infection poses a significant global health challenge, affecting millions of individuals and leading to chronic liver diseases. While preventive vaccines have been successful in reducing the incidence of new infections, the management of chronic cases remains a complex endeavour. In recent years, the development of hepatitis B therapeutic vaccines has emerged as a promising avenue for addressing the persistent burden of chronic HBV infection. Unlike traditional vaccines that aim to prevent infection, therapeutic vaccines for hepatitis B are designed to treat individuals already infected with the virus. Chronic HBV infection is characterized by the virus's ability to evade the immune system, leading to prolonged viral replication and liver damage. Therapeutic vaccines seek to stimulate the immune response, particularly T-cell responses, to recognize and eliminate infected cells, ultimately controlling viral replication and preventing disease progression. Ensuring equitable access to therapeutic vaccines across diverse populations and geographic regions is a challenge. Addressing issues related to vaccine cost, distribution, and healthcare infrastructure is vital to maximizing their global impact. The genetic diversity of HBV poses challenges in

designing vaccines effective against diverse viral strains. Continuous research and development efforts are needed to ensure that therapeutic vaccines remain effective against evolving viral variants. The long-term safety and efficacy of therapeutic vaccines necessitate rigorous monitoring. Establishing robust post-marketing surveillance systems is crucial to detect any unforeseen adverse effects and ensure the sustained effectiveness of the vaccines. The global health implications of Hepatitis B therapeutic vaccines are profound, offering a potential paradigm shift in the management and prevention of chronic infections. If successful, these vaccines can reduce the burden of Hepatitis B, prevent complications, and contribute to global health goals related to infectious disease elimination. However, realizing these benefits requires addressing challenges related to accessibility, viral variability, and long-term monitoring. The development and deployment of Hepatitis B therapeutic vaccines represent a beacon of hope in the pursuit of a healthier and more equitable world.

4. Conclusions

In conclusion, hepatitis B viral infection is a global health challenge with a considerable impact on morbidity and mortality. While progress has been made in prevention efforts through vaccination and awareness campaigns, the persistent challenges of access, stigma, and inequalities highlight the need for continued commitment to addressing HBV on a global scale. Therapeutic vaccines for hepatitis B hold immense potential in transforming the management of chronic HBV infection, addressing the challenges associated with their development, implementation, and accessibility is crucial for their success in improving patient outcomes on a global scale. The development and deployment of Hepatitis B therapeutic vaccines represent a beacon of hope in the pursuit of a healthier and more equitable world.

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Conflict of interest

The authors declare no conflict of interest.

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