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Nasvac: A Novel Warrior in a Strategic Battle for the Global South

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ABSTRACT

Chronic hepatitis B virus (HBV) infection remains one of the most significant global health challenges, with approximately 1 million deaths annually due to complications such as cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Despite advances in the field of therapies, achieving a functional cure-defined as sustained loss of hepatitis B surface antigen (HBsAg) and undetectable HBV DNA-remains elusive. Current treatments, including nucleos(t)ide analogs (NUCs) and pegylated interferon (PegIFN), have limitations in efficacy, safety, and effectiveness, particularly in low- and middle-income countries where the burden of HBV is highest. In this context, therapeutic vaccination emerges as a promising strategy, leveraging the immune system to mount a coordinated and sustained attack against HBV. Nasvac, a novel therapeutic vaccine that will enter in real-life studies after a successful registration and post-marketing phase IV studies, represents a paradigm shift in the fight against CHB, offering a multi-pronged approach that activates both innate and adaptive immunity. This article revisit the current situation in the Global South in respect of Chronic Hepatitis B and explores the rationale and mechanisms of Nasvac, compares it to current therapies, and draws parallels to military strategy, ultimately calling for a global focus on the "war against the pathogen".

Keywords: Nasvac, chronic hepatitis B, immunetherapy.

INTRODUCTION

Chronic Hepatitis B in the Global South

The Global South-comprising regions such as sub-Saharan Africa, Asia (excluding high-income countries like Japan and South Korea), Latin America and the Caribbean, and Oceania (excluding Australia and New Zealand)-bears the overwhelming majority of the global chronic hepatitis B virus (HBV) burden. Chronic HBV infection remains a significant public health challenge in these regions, driven by high prevalence rates, large populations, and varying levels of access to healthcare and vaccination programs. According to the World Health Organization [**1**], the Global South accounts for approximately 80-90% of the global chronic HBV burden, highlighting the urgent need for targeted interventions in these areas.

In sub-Saharan Africa, chronic HBV prevalence is among the highest in the world, ranging from 5-10% in many countries. This region alone contributes approximately 25-30% of the global burden, with countries like Nigeria, the Democratic Republic of Congo, Ethiopia, and South Africa being particularly affected [**1, 2**]. Limited access to vaccination programs and healthcare infrastructure, coupled with high rates of mother-to-child transmission, has perpetuated the high prevalence of HBV in this region.

Asia, excluding high-income countries, is another major contributor to the global HBV burden. Chronic HBV prevalence in this region varies widely, from 2-10%, depending on the country [**1**]. Asia accounts for the largest share of the global burden, approximately 50-60%, driven primarily by China and India, which together host more than one hundred million of chronic carriers [**1, 2**]. Other countries like Indonesia, Pakistan, and the Philippines also contribute significantly to the region's HBV burden.

In contrast, Latin America and the Caribbean have a lower overall prevalence of chronic HBV, typically ranging from 0.5-2%, though certain regions like the Amazon Basin report higher rates [**1, 2**]. This region accounts for approximately 5-10% of the global burden, with countries like Brazil, Mexico, and Peru being the most affected [**1, 2**]. While vaccination programs have made progress in some areas, challenges remain in reaching remote and underserved populations.

The Pacific Island nations of Oceania (excluding Australia and New Zealand) have some of the highest HBV prevalence rates in the world, ranging from 5-20%. Despite their smaller populations, these countries contribute approximately 1-2% of the global burden, with Papua New Guinea, the Solomon Islands, and Fiji being particularly affected. The high prevalence in this region is attributed to limited healthcare access and delayed implementation of vaccination programs.

In comparison, the Global North-comprising high-income countries in North America, Europe, and parts of Asia and Oceania—has a much lower chronic HBV burden, contributing only 10-20% of the global total [**1, 2**]. This is largely due to universal HBV vaccination programs, better healthcare infrastructure, and lower prevalence rates, typically below 1% of national burden in most high-income countries [**1**].

Addressing the chronic HBV burden in the Global South is critical to achieving the World Health Organization's global elimination targets. Expanding vaccination programs, improving access to healthcare, and increasing public awareness are essential steps in reducing the prevalence of HBV in these regions. Without concerted efforts, the disproportionate burden faced by the Global South will continue to hinder global progress in combating this preventable disease.

The Battlefield: Innate and Adaptive Immunity

The immune system is akin to a well-organized military force, with innate immunity serving as the first line of defense and adaptive immunity providing specialized, long-term protection. In the context of CHB, the immune system is often compromised, leading to persistent viral replication and liver damage. Current therapies, such as NUCs, act as "suppressive forces," inhibiting viral replication but failing to restore immune control if the antiviral treatment stops.

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PegIFN, on the other hand, acts as a "stimulant," boosting immune responses but often causing significant side effects and requiring prolonged treatment [**3**, **4**].

Nasvac, however, operates like a "strategic commander," coordinating a comprehensive immune response. The vaccine combines hepatitis B surface antigen (HBsAg) and core antigen (HBcAg), stimulating both humoral and cellular immunity. This dual-antigen approach ensures that the immune system targets not only free viral particles (the "airborne threat") but also infected hepatocytes (the "ground forces"). By activating both systemic and mucosal immunity, Nasvac covers all fronts of the battlefield, ensuring a more robust and sustained defense against HBV [**5, 6**].

Training the Troops: The Role of Trained Immunity

One of the most innovative aspects of Nasvac is its ability to induce trained immunity, a concept akin to preparing soldiers for future battles through rigorous training. The vaccine's regimen of ten immunizations over 20 weeks enhances the immune system's memory and responsiveness, ensuring that even after the initial battle, the immune cells remain vigilant, developing a sustained immune response that suppress the virus and increase the functional and partial responses over time [**6**]. This is a significant advantage over NUCs, which merely suppress viral replication without restoring immune control, and PegIFN, which has limited efficacy and significant side effects **[7]**.

The Arsenal of Nasvac: Action Mechanisms

Nasvac's success on the battlefield against HBV lies in its unique action mechanisms, which are rooted in its ability to stimulate both innate and adaptive immunity. The vaccine's antigens, HBsAg and HBcAg, act as "commanders" that mobilize the immune system's "troops" to mount a coordinated attack against the virus. Table 1 offers a summary of the key mechanisms, supported by preclinical and clinical studies.

Table 1: Summary of the key mechanisms, supported by preclinical and clinical studies.

Study	Mechanisms of Action	Pharmacological Results
Dendritic Cell Activation	Nasvac activates dendritic cells (DCs), which are crucial for initiating immune responses.	High levels of anti-HBs, HBsAg-specific, and HBcAg-specific T-cells were detected in the spleen and liver of HBV-transgenic mice immunized with Nasvac [**8**].
B- and T-Cell Activation	The vaccine stimulates both B- and T-cells, enhancing adaptive immunity.	B-cell activation markers increased in CHB patients after in vitro stimulation with Nasvac, and CD4+ and CD8+ T-cells showed increased expression of activation markers [**9**].
Cytokine Secretion	Nasvac induces the secretion of pro-inflammatory cytokines, which are essential for antiviral defense.	PBMCs from vaccinated CHB patients produced significantly higher levels of cytokines (IL-1β, IL-6, IL-8, IL-12, and TNF-α) compared to unvaccinated [**10**].
Nasal Route Advantage	The intranasal (i.n.) route of administration enhances immune responses, particularly in the liver.	The i.n. route was the most effective at inducing CD4+ T-cell responses in the liver, with high frequencies of multifunctional CD4+ T-cells secreting IFN-γ, IL-2, and TNF-α [**11**].

Multi-TLR Agonist Effect	HBcAg acts as a multi-Toll-like receptor (TLR) agonist, stimulating innate immunity.	HBcAg activates TLR2, TLR3, TLR7, TLR8, and TLR9, leading to increased expression of HLA class I/II and co-stimulatory molecules, as well as type I interferons and cytokines [**12**].

This table highlights the multifaceted action mechanisms of Nasvac, which enable it to effectively "train" the immune system innate and adaptive forces, to recognize and eliminate HBV-infected cells. By stimulating both arms of immunity, Nasvac ensures a sustained and robust defense against the virus, reducing the risk of liver damage, immune mediated damage when undisciplined forces attack the liver, leading to disease progression [**13**].

Strategic Advantages over Conventional Therapies: A Comparative Analysis

To better understand the strategic advantages of Nasvac, it is essential to compare it with the current state-of-the-art therapies for CHB, including nucleos(t)ide analogs (NUCs) like tenofovir and entecavir, and pegylated interferon (PegIFN). The table below provides a comprehensive comparison across key aspects, highlighting why Nasvac stands out as a superior option in the fight against HBV.

Table 2: Comparison of Nasvac vs the state-of-the-art treatments for CHB.

Aspect	NUCs	PegIFN	Nasvac
Mechanism of Action	Suppresses HBV replication by inhibiting viral polymerase.	Stimulates innate immunity but with significant side effects.	Stimulates both innate and adaptive immunity, targeting multiple HBV antigens.
Treatment Duration	Lifelong or long-term treatment required.	Finite (48 weeks) but with high reactogenicity.	Finite (10 doses over 20 weeks), reducing long-term healthcare costs.
Safety and Tolerability	Long-term complications: nephrotoxicity, bone density loss, resistance.	High reactogenicity: flu-like symptoms, depression, hematologic issues.	Favorable safety profile with mild side effects (e.g., transient ALT flares).
Antiviral Efficacy	Strong HBV DNA suppression but limited HBsAg loss (2.5% after 10 years).	Moderate HBV DNA and HBsAg reduction (3-12% HBsAg loss).	Sustained HBV DNA suppression and significant HBsAg reduction (16% loss) **[14].**
Liver Protection	Reduces inflammation but residual HCC risk remains high.	Reduces HCC risk but limited by side effects.	Prevents liver cirrhosis and HCC, with long-term follow-up showing no progression.
Cost-Effectiveness	High cost due to lifelong treatment.	High cost and reacto-genicity limit use in low-income settings.	Suitable for large-scale use in resource-limited settings.

This table underscores the strategic advantages of Nasvac, particularly in terms of its finite treatment schedule, favorable safety profile, and sustained antiviral effects. Unlike NUCs, which require lifelong adherence and carry long-term risks, or PegIFN, which is limited by its high reactogenicity, Nasvac offers a balanced approach that is both effective and accessible, especially in low-income settings [**15**].

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While NUCs have been the cornerstone of CHB treatment for decades, their limitations are becoming increasingly apparent. NUCs act as "suppressive forces," effectively lowering HBV DNA levels but failing to eliminate the virus or restore immune control. This leaves patients vulnerable to viral rebound and long-term complications such as liver cirrhosis and HCC [**16**]. Moreover, NUCs are associated with significant risks, including nephrotoxicity, bone density loss, and the emergence of drug-resistant HBV strains [**17**]. These weaknesses highlight the need for a more effective and sustainable treatment strategy.

Nasvac, on the other hand, offers a finite treatment schedule and stimulates both innate and adaptive immunity, providing a more comprehensive defense against HBV. By targeting multiple aspects of the immune response, Nasvac not only suppresses viral replication but also reduces the risk of long-term complications, making it a superior alternative to NUCs [**18**].

Immunotherapy for Low-Income Countries: A Call to Arms

In low-income countries, where the burden of HBV is highest and healthcare resources are limited, Nasvac represents a beacon of hope. Unlike NUCs, which require lifelong treatment and constant monitoring, Nasvac offers a finite, cost-effective solution that can be implemented on a large scale. This is particularly important in regions where access to healthcare is limited, and the cost of lifelong antiviral therapy is prohibitive.

Moreover, Nasvac's ability to stimulate both innate and adaptive immunity makes it a powerful tool in the fight against HBV in these regions. By training the immune system to recognize and eliminate the virus, Nasvac not only reduces the burden of disease but also empowers the body to defend itself against future attacks. This is especially critical in low-income countries, where the prevalence of HBV is often compounded by other infectious diseases and poor healthcare infrastructure.

A CALL TO ACTION

Despite the proven potential of therapeutic vaccines like Nasvac, global investment in HBV research pales in comparison to funding for military defense. This disparity is striking, given that HBV claims nearly 1 million lives annually-a death toll comparable to many armed conflicts. It is imperative that the scientific community and policymakers recognize the urgency of this "war" and allocate resources to develop and deploy innovative strategies like Nasvac.

The world is witnessing unnecessary human conflicts while devastating battles, often fought silently, remain largely without attention. Every casualty is a war lost to a pathogen. While nations invest trillions in weapons and warfare, pathogens like HBV continue to claim lives and the expected impact is still a chimera. The scientific community has the tools and knowledge to win this war, but it requires a shift in priorities—a commitment to saving lives rather than taking them.

Nasvac represents a new frontier in the fight against chronic hepatitis B, offering a comprehensive, immune-based strategy that parallels the precision and coordination of military operations. By harnessing the full potential of the immune system, this vaccine provides a path toward functional or partial cure, and a long-term control of HBV arise from its long-lasting effect. However, the battle is far from over. A platform including the vaccine, cost effective diagnostics and informatics / AI tools are required to optimize the deployment of the

forces towards viral hepatitis elimination. The global community must recognize the urgency of this fight and invest in therapeutic vaccines and other innovative strategies to end the silent epidemic of hepatitis B.

The war against pathogens is one we can win, but only if we choose to prioritize it. Let us redirect our resources, our creativity, and our collective will toward saving lives, rather than destroying them. The time has come to declare peace on human conflicts and focus on the true enemy: disease.

FIVE YEARS FOLLOW-UP

Nasvac has been developed by a team of researchers with multiple limitations, most of the limitations created by economic sanctions and limitations of resources, however, vaccine safety, immunogenicity and efficacy has been demonstrated in 14 clinical trials including a phase III clinical trial, several long-term follow-ups and more recently in a recently completed phase IV study **[6, 7]**. Alternative developments of Nasvac have been carried out in Japanese patients and healthy volunteers further supporting the achieved results. A program to treat all chronic hepatitis B carriers will start in 2025 in Cuba, plunged in multiple rounds of sanctions to generate economic limitations. BRICS, as leaders of the Global South, should cooperate with Cuba and Bangladesh, the country's leading this sanitary battle.

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