Molecular Insights into the Development and Efficacy of Hepatitis Virus Vaccines

Ridwanullah O. Abdullateef[1,2,3], Abdulmujeeb Opatola[4], Daniel O Esanju[1], Saviour G. Usin[5,6]
[1]*Faculty of Clinical Sciences, College of Medicine, University of Ibadan, Ibadan, Nigeria.*
[2]*College Research and Innovation Hub (CRIH), College of Medicine, University of Ibadan, Ibadan, Nigeria.*
[3]*Consortium of Genomics Students and Young Researchers in Africa (CoGSAYR Africa), Lagos, Nigeria.*
[4]*Faculty of Basic Medical Sciences, College of Medicine, University of Ibadan, Ibadan, Nigeria.*
[5]*Cancer Research and Molecular Biology Laboratories, Department of Biochemistry, Faculty of Basic Medical Sciences, College of Medicine, University of Ibadan, Ibadan, Nigeria.*
[6]*Department of Medical Biochemistry, Faculty of Basic Medical Sciences, University of Cross River State, Calabar, Nigeria.*

Corresponding Author
Ridwanullah O. Abdullateef
ridwanullahabdullateef2@gmail.com

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Viral hepatitis remains a major public health challenge globally, especially hepatitis B and C. This puts millions of people at risk of various forms of chronic liver diseases, such as liver cirrhosis, hepatocellular carcinoma, liver failure, etc. Vaccines have been confirmed to be effective in reducing the burden of certain infectious agents, including many of the hepatitis viruses. This article evaluates the molecular mechanisms involved in the design of the available hepatitis viruses, their efficacy, and how to improve them. HAV vaccines are designed around the formalin-inactivated virus or genetically attenuated live viruses, and their molecular design emphasizes robust immunogenicity and safety. Current HBV vaccines are primarily recombinant subunit vaccines using the HBV surface antigen (HBsAg) and are produced by expressing HBsAg in yeast or mammalian cell systems, eliciting strong immune responses. HCV lacks an approved vaccine despite significant research efforts. Its high genetic variability and immune evasion mechanisms make it complex in the development of vaccines. However, most HCV vaccine candidates focus on conserved epitopes within the viral envelope glycoproteins E1 and E2, which are critical for viral entry. Currently, there are no standalone vaccines for Hepatitis D, although the infection can be prevented by hepatitis B immunization. Moreover, efforts to develop HDV-specific vaccines focus on the large HDV antigen (HDAg), which is essential for viral assembly. The first licensed HEV vaccine, Hecolin®, is a recombinant subunit vaccine based on the ORF2 protein of HEV genotype 1 and is produced in Escherichia coli, where the ORF2 protein self-assembles into VLPs, mimicking the native virus's immunogenicity. DNA recombinant technology, protein engineering, structural biology applications, the use of virus-like particles, mRNA and nanoparticle-based platforms, etc, have all increased the efficacy of the available vaccines.

1.0. INTRODUCTION

Viral hepatitis is the inflammation of the liver following an infection by any of the major hepatitis viruses A, B, C, D, and E. Other viruses implicated include cytomegalo virus, Herpes simplex virus, Epstein Barr virus, Rubella virus, Adenovirus, Mumps virus, Yellow fever virus, etc. When the inflammation does not resolve in six months, the name changes from acute to chronic hepatitis. Some of the common risk factors for viral hepatitis include intravenous drug use, unprotected sexual intercourse, food and water contamination, blood transfusion, being a healthcare worker, being born to a hepatitis B or C-infected mother, etc.

For instance, the Hepatitis B virus (HBV) is a major public health challenge globally, with more than 30% of the global population having serological evidence of ongoing or previous infection. Chronic HBV accounts significantly for the global mortality rate, with almost a billion individuals dying annually from HBV-related hepatic diseases [1].

Vaccines are effective means of preventing and controlling many communicable diseases. The World Health Organization (WHO)'s Immunization Agenda 2030 (IA2030) emphasizes the need for global strategies to ensure everyone gets vaccinated [2]. The IA2030 highlights the ongoing challenges of infectious diseases and focuses on approaches to promote vaccine development, manufacturing, and uptake, to ensure global coverage, through the efforts of researchers, healthcare providers, manufacturers, policymakers, and governmental and non-governmental organizations [2]. Research has shown that vaccines are effective in significantly reducing worldwide HBV infection prevalence, primarily via childhood HBV vaccination which reduced the prevalence from 4.9% in the prevaccination period to 0.9% in 2019 [1]. This review explores the molecular mechanisms involved in the design of hepatitis virus vaccines, evaluating their efficacy and potential areas of improvement. The overall goal is to contribute to the understanding of the design of more effective vaccines to reduce the burden of hepatitis globally .

2.0.Molecular Basis of Hepatitis Virus Infection and Pathogenesis

Hepatitis virus invades the host through diverse molecular interactions which are peculiar to each type of virus due to their unique molecular makeup. In Hepatitis A infection, transmission is by by fecal-oral route [2]. The HAV genome (7.5 kb) codes for only one polyprotein, which is usually cleaved into structural proteins (VP4, VP2, VP3, and VP1pX capsid antigens) and non-structural proteins, such as 2B, 2C, 3A, 3B (the genome-linked protein, VPg), 3Cpro (a cysteine protease), and 3Dpol (RNA-dependent RNA polymerase). These proteins are integral to viral replication and assembly [3]. Through this means, HAV causes acute inflammation of the liver that generally resolves without leading to chronic conditions, followed by life-long immunity, which is unlike other hepatotropic viruses [4].

Hepatitis B virus transmission occurs through contact with contaminated blood or body fluids, as well as vertical transmission after birth [5] [6]. The viral genome has a partially double-stranded relaxed circular DNA (rcDNA), that replicates via an RNA intermediate [7]. It codes for key proteins including the viral DNA polymerase (reverse transcriptase), hepatitis B core antigen (HBcAg), HBsAg, hepatitis B e antigen (HBeAg), and the hepatitis B x protein (HBxAg). The survival of HBV is facilitated by the integration of viral DNA into the host genome as covalently closed circular DNA (cccDNA) during chronic infection, which also raises the risk of serious liver disorders such as cirrhosis, liver failure, and HCC [6] [8]. HBsAg envelops circulating HBV virions, sometimes referred to as "Dane particles," which are made up of three virus-coded surface proteins: large (L), middle (M), and small (S). Despite its poor affinity, the HBV virion attaches itself to the surface of hepatocytes by interacting with heparan sulfate proteoglycans (HSPGs). This is followed by interaction with the sodium taurocholate co-transporting polypeptide (NTCP) receptor, which has a high affinity for the pre-S1 domain of L-HBsAg. This contact could cause HBV to internalize into hepatic cells by endocytosis [6].

As a satellite virus, the Hepatitis D virus requires co-infection (simultaneous infection with HBV and HDV) or superinfection (HDV infection in a person with chronic HBV) for its propagation within humans, leading to the most severe form of viral hepatitis. The virus mediates its de novo entrance into hepatocytes and facilitates the release of its progeny by using HBsAg. Much like HBV, it is predominantly transmitted through parenteral exposure to contaminated body fluids, intravenous drug use, and, less commonly, through vertical transmission [9]. The HDV RNA genome is very heterogeneous, with eight different genotypes that differ in how the disease progresses and responds to therapy [10].

In hepatitis C infection, the viral lifecycle includes viral entrance, uncoating, and release of the genome into the cytoplasm, which is followed by RNA translation and replication, particle assembly, and egress [11]. Human

hepatocytes are the primary target cell of HCV infection in vivo, and the virus may effectively infect human hepatoma cell lines in vitro [12]. The attachment and internalization of HCV require four essential cellular components: occludin (OCLN), claudin-1 (CLDN), scavenger receptor class B type I (SR-BI), and CD81. Of these, the primary target for antibody-mediated neutralization is the interaction between E2 and CD81 [13]. Overall, Several host cell factors are required for virus translation, replication, and production. These include liver-specific microRNA-122 (miR-122) [14], autophagy proteins (i.e. Beclin-1, Atg4B, Atg5 and Atg12) [15], cyclophilin A (CypA) [16], lipid droplets (LDs), and the VLDL (very low-density lipoprotein) export pathway, utilizing apolipoprotein B and E (ApoB and ApoE) as cofactors [17] amongst others .

Hepatitis E Virus is the final major Hepatitis virus. Our knowledge of HEV's reproduction cycle, host cell contacts, and entrance pathways into hepatic cells has only recently improved, despite evidence that suggests outbreaks have occurred since ancient times. Unlike traditional enclosed viruses, the eHEV are infectious but do not have virus-encoded proteins on their surface [18]. Findings support the idea that the biogenesis of eHEV viral particles includes the highly selective sorting of viral capsids into multivesicular endosomes (MVEs) in a process that is dependent on endosomal sorting complexes required for transport (ESCRT), which is similar to how exosomes are produced [19]. HEV virions most likely are involved in non-specific interactions with clathrin during their initial attachment and endocytosis. Like nHEV, they are trafficked to endolysosomes by the GTPase Ras-related protein Rab-5A (RAB5A) and RAB7A [20].

Cellular enzymes in lysosomes mediate the breakdown of eHEV membrane lipids [21]. The compartment and mechanism of eHEV capsid uncoating are still unclear. The endolysosome may serve just as a transitory space when the virus sheds its quasi-envelope. It is known that the endoplasmic reticulum-associated degradation pathway allows overexpressed ORF2 proteins to go into the cytoplasm [22 .[

3.0. Current Hepatitis Virus Vaccines: Molecular Design and Properties

Hepatitis virus vaccines utilize advanced molecular designs to prevent infections effectively. Hepatitis A vaccines are usually inactivated virus formulations inducing strong, long-lasting immunity [23], while hepatitis B vaccines are recombinant protein vaccines using the hepatitis B surface antigen (HBsAg) produced in yeast or mammalian cells, ensuring robust immunogenicity [24]. Furthermore, hepatitis C lacks an approved vaccine due to its genetic diversity, though novel candidates, like recombinant protein and mRNA-based vaccines [25] [26] [27]. Hepatitis D prevention relies on the hepatitis B vaccine, as HDV requires HBV for replication. Hepatitis E vaccines, such as the recombinant HEV239, target the viral capsid protein, providing protection primarily in endemic regions [28]. An overview of the hepatitis virus vaccine, its molecular design, and other properties are depicted in Table 1 below.

Table 1: Table highlighting the molecular designs and properties of the hepatitis virus vaccines.

S/N	Vaccine	Molecular Design	Other Properties	References
1.	Hepatitis A Virus Vaccine	- Primarily based on inactivated viral particles or live attenuated strains, with the molecular	- Stable under standard refrigeration conditions and often adjuvanted with aluminum hydroxide to enhance immune response. - Induces protective	[23] [29]

		design emphasizing robust immunogenicity and safety. - Designed around the formalin-inactivated virus or genetically attenuated live viruses.	antibodies (anti-HAV IgG) in over 95% of vaccinated individuals after two doses	
2.	Hepatitis B Virus Vaccine	- Primarily recombinant subunit vaccines using the HBV surface antigen (HBsAg) - Produced by expressing HBsAg in yeast or mammalian cell systems	- Elicits a robust immune response, with seroprotection rates exceeding 90% in healthy individuals after the standard three-dose regimen - Adjuvants such as aluminum hydroxide enhance the immune response.	[30] [31]
3.	Hepatitis C Virus Vaccine	- Lacks an approved vaccine, but most candidates focus on conserved epitopes within the viral envelope glycoproteins E1 and E2, which are critical for viral entry. - Other strategies include recombinant VLPs, adenoviral vectors, and mRNA vaccines encoding	- The variability of HCV strains remains a barrier to universal vaccine efficacy.	[27] [32]

		HCV antigens.		
4.	Hepatitis D Virus Vaccine	- There are no standalone vaccines for Hepatitis D, but it can be prevented by HBV immunization.		
5.	Hepatitis E Virus Vaccine	- **A recombinant subunit vaccine based on the ORF2 protein of HEV genotype 1** - **Produced in *Escherichia coli*, where the ORF2 protein self-assembles into VLPs, mimicking the native virus's immunogenicity.**	- **Safe, stable, and induces long-lasting immunity.**	**[33]**

4.0. Technological Advances in Hepatitis Vaccine Development

4.41. **Role of DNA Recombinant Technology**

The advent of recombinant DNA technology marked a transformative era in hepatitis vaccine development, enabling the creation of safer, more effective, and scalable solutions. Early breakthroughs in this field laid the groundwork for addressing the global burden of hepatitis B and E through innovative genetic engineering techniques. In the 1980s, recombinant DNA technology revolutionized hepatitis B vaccine production by enabling the synthesis of hepatitis B surface antigens (HBsAg) in yeast cells or other expression systems [34]. These vaccines offered significant advantages over traditional plasma-derived options, demonstrating superior immunogenicity, enhanced safety, and scalability, which were crucial for widespread immunization efforts [34] [35]. Building on these early successes, researchers harnessed recombinant DNA technology to refine and optimize vaccine design. By constructing synthetic vaccines that predict viral epitopes, they improved the precision of immune responses, enhancing the vaccines' ability to target the virus effectively [36].

Similarly, the application of recombinant DNA technology to hepatitis E vaccine development has been instrumental in producing virus-like particles (VLPs). These VLPs mimic the virus's structure without carrying its genetic material, ensuring safety while achieving high efficacy [37]. More recently, DNA-based vaccines have

emerged as a promising platform. These vaccines introduce genetic material encoding viral antigens into host cells, eliciting robust immune responses. With advancements in vector design and delivery mechanisms, DNA vaccines are poised for further innovation, particularly in preclinical evaluations [38] [39]. The global rollout of recombinant hepatitis B vaccines has led to a dramatic reduction in the prevalence of hepatitis B, particularly among children under five [40] [41]. Compared to emerging platforms like mRNA vaccines, recombinant approaches remain highly profitable and manufacturing-friendly, particularly in addressing diseases like hepatitis [42]. Innovations in peptide-based vaccines further illustrate the utility of this technology. By deleting infection-causing components, peptide vaccines act as antigens to stimulate effective immune responses, enhancing both vaccine stability and specificity. The integration of nucleic acid-based platforms with recombinant DNA methodologies has opened new avenues for addressing viral infections. These combined approaches enhance vaccine efficacy, delivery, and adaptability, making them valuable tools for hepatitis management [43].

4.2. **Role of Protein Engineering**

A pivotal application of protein engineering is the development of recombinant hepatitis B vaccines, which incorporate engineered surface antigens to enhance immunogenicity. These antigens can then be precisely folded and modified, resulting in vaccines with improved efficacy and safety [44]. Key innovations include modifications to the pre-S region of the hepatitis B virus envelope protein, which significantly enhance its immunogenic potential. These engineered vaccines have shown superiority over traditional formulations in both preventing hepatitis B infection and treating chronic hepatitis B [45]. Furthermore, incorporating hepatitis C virus epitopes into engineered chimeric proteins has demonstrated promise for developing multivalent vaccines targeting both hepatitis B and C [46.[

Advances in expression systems such as Pichia pastoris yeast have further bolstered vaccine development. This system has been used to produce glycosylated recombinant proteins like CoreE1E2, which induce neutralizing antibodies against the hepatitis C virus, highlighting the role of protein engineering in optimizing antigen production for stronger immune responses [47]. Additionally, computational tools and immunoinformatics have been integrated into protein engineering to design multiepitope peptide vaccines. Techniques such as protein docking and molecular dynamics simulations allow for the identification and optimization of antigenic regions, expanding the scope of engineered proteins in vaccine design [48].

Innovative approaches such as engineering fusion proteins that combine immunogenic components from different hepatitis viruses further expand the potential for broader immune coverage. This strategy holds promise for the development of universal hepatitis vaccines [49]. Protein engineering and recombinant DNA technology are intricately linked. Recombinant DNA technology provides the foundational tools for protein engineering by enabling the cloning, expression, and genetic modification of genes encoding specific viral proteins. The synergy between these technologies is particularly evident in the engineering of pre-S regions of HBsAg, which have been modified using recombinant DNA technology to enhance their ability to elicit neutralizing antibodies [45]. Similarly, recombinant DNA techniques facilitate the production of fusion proteins that combine epitopes from multiple viruses, such as hepatitis B and C. These fusion proteins, optimized through protein engineering, offer a novel approach to creating multivalent vaccines [49]. In addition, recombinant DNA technology enables the synthesis of multi-epitope genes that serve as templates for protein engineering [48]. Their complementary roles enable the creation of safe, effective, and cutting-edge vaccines. This integration continues to expand the possibilities for combating hepatitis and other infectious diseases through advanced vaccine technology.

4.3. **Use of Virus-like Particles (VLPs) in Hepatitis Vaccine Design**

Virus-like particles (VLPs) are highly promising platforms in hepatitis vaccine design due to their ability to mimic the structural properties of natural viruses while remaining non-infectious. VLPs are self-assembled from viral structural proteins, enabling the preservation of native antigenic conformations, which is crucial for eliciting strong immune responses [50]. Their

non-replicating nature ensures a high safety profile, making them ideal candidates for developing vaccines against hepatitis B, C, and E viruses [51]. In hepatitis B vaccine development, VLPs derived from the hepatitis B surface antigen (HBsAg) have become the cornerstone of preventive strategies. These VLPs not only elicit robust antibody responses but also maintain a high degree of purity and immunogenicity through advanced expression systems such as CHO cells [52 .[

For hepatitis C, VLPs incorporating oligomeric forms of envelope protein E2 (sE2) have shown potential in eliciting broadly neutralizing antibodies. These VLPs, produced using self-assembling platforms, represent a significant step toward effective HCV vaccine development, overcoming challenges associated with traditional subunit vaccines [53]. Hepatitis E vaccines have also leveraged VLP technology, utilizing ORF2-derived particles that mimic the natural virus structure while ensuring safety by eliminating viral replication. These VLPs have demonstrated high immunogenicity, marking progress in addressing the public health burden of hepatitis E [51]. VLPs are further enhanced by their ability to incorporate multiple antigens or be chemically modified for improved stability and immune targeting. This versatility extends their application beyond hepatitis vaccines to other infectious diseases, underscoring their transformative potential in vaccine design [54].

4.4.**Role of Structural Biology**

The structural characterization of hepatitis B surface antigens (HBsAg) has also played a key role in developing vaccines with high purity and safety. Structural biology, combined with recombinant DNA technology, has enabled precise biochemical characterization and enhanced antigen folding. This synergy has led to the development of synthetic polypeptide vaccines with improved stability and efficacy. For example, mammalian expression systems have been utilized to produce structurally faithful hepatitis B surface antigens, critical for effective vaccine formulations [44] [55]. Recent breakthroughs in structural biology include the glyco-engineered production of HBV antigens to enhance immunogenicity. By leveraging N-glycosylation, researchers have improved antigen folding and immune recognition, contributing to more effective vaccine designs [56]. Additionally, computational tools such as immunoinformatics have enabled the identification of immunogenic epitopes on HCV proteins, facilitating the design of multi-epitope vaccines with enhanced immune responses [48.[

Advancements in 3D cell culture models have provided valuable platforms for studying hepatitis pathology and antigen behavior in environments that mimic in vivo conditions. These models have been pivotal in exploring antigen-antibody interactions and improving vaccine efficacy [57]. Structural analyses of HCV-neutralizing antibodies have further revealed vulnerabilities in the virus's envelope proteins, guiding the rational design of effective antigens [58]. Today, cryo-electron microscopy (cryo-EM) and X-ray crystallography are often integrated to maximize their complementary strengths. Cryo-EM offers detailed views of antigenic surfaces and antibody-binding sites, while crystallography confirms the atomic structures of antigen-antibody complexes. For example, this approach has been used to study HCV envelope glycoprotein E1E2, defining neutralizing epitopes critical for vaccine design [59]. Recent innovations combine cryo-EM with machine learning to map epitopes and optimize antigens, advancing structure-based vaccine development [60]. Together, these structural biology techniques continue to drive innovations in hepatitis vaccine development, offering comprehensive insights into viral antigens and immune interactions .

4.5. **Role of mRNA and nanoparticle-based platforms in next-generation vaccines**

mRNA and nanoparticle-based platforms are revolutionizing next-generation hepatitis vaccine development by combining the specificity and adaptability of mRNA technology with the protective and delivery capabilities of nanoparticles. mRNA vaccines rely on lipid nanoparticles (LNPs) to shield the mRNA from degradation and enhance its uptake by antigen-presenting cells, which not only facilitates antigen expression but also acts as an adjuvant to boost immune responses [61]. The versatility of nanoparticles extends beyond LNPs, with chitosan and gold nanoparticles offering additional avenues for targeted delivery. For example, chitosan nanoparticles have been

explored for nasal delivery of the hepatitis B surface antigen (HBsAg), effectively eliciting both mucosal and systemic immune responses [62]. Gold nanoparticles, meanwhile, serve as nano-adjuvants in hepatitis E vaccines, enhancing immune responses and stabilizing vaccine components [63].

Advancements in nucleoside-modified mRNA and LNP delivery systems have further enhanced the stability and immunogenicity of mRNA vaccines. These innovations became globally recognized during the COVID-19 pandemic, proving the platform's capability to produce highly effective vaccines rapidly [61]. This success has renewed interest in using mRNA technology to combat other infectious diseases, including hepatitis. Therapeutic mRNA vaccines for chronic hepatitis B virus (HBV) infections have shown promising preclinical results, demonstrating their ability to elicit robust memory T and B cell responses crucial for long-term immunity and virological suppression [64]. Furthermore, self-amplifying mRNA vaccines, which enhance antigen expression and immunogenicity, are being explored for hepatitis vaccine development [65].

The integration of nanoparticle-based delivery systems has significantly enhanced the efficacy of mRNA vaccines against hepatitis. LNPs protect mRNA, facilitate targeted delivery to antigen-presenting cells, and address challenges such as hepatic immune evasion [61]. Emerging innovations, including circular mRNA and non-viral delivery platforms, are being developed to overcome remaining challenges, such as the need for repeat doses and potential reactogenicity [66].

5.0. Challenges and Future Directions in Hepatitis Vaccine Development

5.1. Challenges and Limitations in Hepatitis Vaccine Development

Current vaccines for hepatitis viruses, while effective in many cases, face significant challenges and limitations that hinder their universal success. For hepatitis B virus (HBV), vaccine efficacy is notably limited in certain populations. Up to 10% of healthy individuals and as many as 50% of immunocompromised individuals, such as those undergoing hemodialysis, fail to generate protective antibody levels following vaccination [67]. Furthermore, the emergence of HBV escape mutants has compromised vaccine effectiveness in regions with high endemicity [68]. These challenges underscore the need for improved formulations, booster strategies, and alternative approaches.

Logistical barriers also affect HBV vaccine distribution. Current vaccines require a robust cold chain for stability, a challenge in rural and resource-limited settings that restrict coverage. Moreover, while current HBV vaccines effectively prevent chronic infections in many cases, they fail to eradicate the virus in chronic carriers due to its ability to integrate into the host genome and evade immune responses. This limitation makes complete viral control challenging, even with therapeutic interventions [69].

For hepatitis C virus (HCV), no effective vaccine currently exists, largely due to the virus's high genetic variability and rapid mutation rates, which enable immune evasion. The lack of optimal animal models and an incomplete understanding of protective immune responses further complicate vaccine development [70]. Additionally, the asymptomatic nature of many HCV infections and high vaccine development costs pose significant hurdles to awareness and prevention efforts [71]. While DNA-based vaccine approaches have shown promise, they often fail to elicit long-lasting immune responses, highlighting the need for further optimization [26].

HDV vaccine development, in particular, is fraught with unique challenges. The virus’s dependence on HBV for replication complicates the identification of specific vaccine targets. Prophylactic HBV vaccination indirectly prevents HDV co-infection, but it does not address existing HDV infections in chronic HBV carriers, leaving a significant gap in prevention strategies [72]. Moreover, the lack of robust animal models and optimized preclinical platforms hampers HDV vaccine research [39]. Virus-like particle (VLP) vaccines have shown potential for HDV, but their development faces hurdles in ensuring immunogenicity, scalability, and the selection of effective adjuvants [73].

5.2. Addressing the Limitations and Hurdles

Efforts to address the challenges and limitations of hepatitis vaccine development and efficacy have focused on advancing vaccine technologies, optimizing adjuvants, and improving delivery systems. Targeted strategies, such as booster vaccinations and the incorporation of potent adjuvants, have shown promise in enhancing vaccine effectiveness. For instance, lipid nanoparticle-based adjuvants significantly improve immunogenicity, addressing low response rates in specific populations, including individuals with obesity or genetic polymorphisms [74].

The emergence of mRNA-based vaccines offers a transformative approach to combating the hepatitis B virus (HBV). Preclinical studies show that mRNA vaccines, formulated with lipid nanoparticles and administered in prime/boost regimens, elicit robust immune responses and improve antigen presentation [75]. Similarly, recombinant viral vectors and virus-like particles (VLPs) are being developed as platforms to enhance immune responses and tackle the genetic variability and immune evasion tactics of hepatitis viruses [27]. Improving vaccine accessibility and coverage is another critical focus area. Addressing vaccine hesitancy through culturally sensitive communication and community engagement strategies is essential for increasing vaccination rates in underrepresented populations [76]. Additionally, expanding vaccination coverage at birth and targeting unvaccinated adults are vital steps toward meeting global hepatitis control targets [77].

To address the limitations in vaccine testing models, innovative outbred animal models, such as rodent hepacivirus systems, have been developed. These models provide valuable platforms for testing immunization strategies, particularly for hepatitis C virus (HCV) vaccines, and enhance their clinical relevance [78]. Gene-based vaccines and physiologically based pharmacokinetic models are also being employed to optimize vaccine safety and efficacy, especially in vulnerable populations such as pregnant women, while adhering to stringent regulatory and safety protocols [79].

HCV vaccine development faces significant challenges due to the virus's extensive genetic diversity, which includes seven major genotypes and numerous subtypes [80]. Structure-based vaccine design, leveraging insights into the E1E2 glycoprotein complex, aims to optimize antigens capable of eliciting broadly neutralizing antibodies [59]. Additionally, lipid-based nano vaccines have demonstrated enhanced neutralizing antibody responses, while polymer-based nanoparticles are being explored for their ability to stabilize antigens and improve immunogenicity, paving the way for more effective vaccines [81].

Hepatitis D virus (HDV) vaccine development presents unique challenges due to the virus's dependence on HBV for replication and its limited genome size, which restricts potential vaccine targets. Current strategies focus on experimental approaches, such as targeting HDV's farnesyltransferase pathway to inhibit replication [72]. Virus-like particles (VLPs) are also being investigated for their potential to elicit strong immune responses while overcoming the limited antigenic diversity of HDV [73]. Advancing preclinical models is critical to overcoming barriers in HCV and HDV vaccine research. The development of humanized mouse models and liver organoids provides more accurate simulations of human infection dynamics, improving the evaluation of vaccine efficacy and safety [78].

6.0.CONCLUSION

The spread of many infectious agents, including the hepatitis viruses, can be controlled by vaccination. However, there is a need to clearly understand the molecular perspectives of the design of these vaccines and they can be improved. While viruses like HAV, HBV, and HEV have approved vaccines already, HCV and HDV still lack approved vaccines because of the molecular complexities of the viruses. Future research should focus on further understanding these complexities and how they can be addressed. The development of universal hepatitis virus vaccines should also receive more attention among researchers. With continuous focus on not just the public approaches, but the molecular approaches as well, the goal of reducing the global burden of hepatitis will be achieved in the next few years.

Ethics Approval and Consent to Participate

- Not applicable

Consent for Publication

- Not applicable

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- The authors declare that they have no competing interests

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Authors' Contributions

- ROA conceptualized the study, drafted the manuscript, edited, proofread, and approved the final manuscript draft for submission

- AO, DOE, and SGU drafted the manuscript and approved the final draft for submission

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HIGHLIGHTS

- While viruses like HAV, HBV, and HEV have approved vaccines already, HCV and HDV still lack approved vaccines because of the molecular complexities of the viruses.
- The development of universal hepatitis virus vaccines should also receive more attention among researchers.
- With continuous focus on not just the public approaches, but the molecular approaches as well, the goal of reducing the global burden of hepatitis will be achieved in the next few years.

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