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Comparative Review of Hepatitis B Virus Genotypes, Epidemiological Distribution, and Oncogenic Risks in India and Nigeria

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ABSTRACT

Hepatitis B virus (HBV) is the leading cause of chronic liver diseases, including hepatocellular carcinoma and cirrhosis, and it remains a serious global health threat. The virus exhibits a wide range of genetic diversity, with ten genotypes (A-J) and many subgenotypes showing distinct geographical distribution patterns and clinical implications. This comparative review highlights HBV genotypic variability and distribution in India and Nigeria, two highly endemic countries with different epidemiological molecular profiles. Recent and relevant literature from reputable scientific databases such as Scopus, Web of Science, PubMed, Google Scholar, and DOAJ was carefully and critically reviewed to explore genotype prevalence, routes of transmission, and clinical outcomes. Globally, genotypes A, B, C, D, and E contribute to nearly 96% of chronic HBV infections.

In India, D genotype predominates in most areas within the country, followed by the A genotype as a secondary type. Genotypes B and C are also found in some areas, showing a lot of regional variation. Nigeria, on the other hand, indicates a very similar dominance of the E genotype with low evidence of the A genotype, supporting phylogenetic evidence that the E genotype evolved in West Africa. These mutations have an impact on treatment response, disease progression, viral replication, and the risk of hepatocarcinogenesis. The review also highlights the significance of genotype-specific management plans by emphasizing the effect of genotype on antiviral resistance and immune response. Understanding these epidemiological molecular patterns is essential to developing successful immunization, surveillance, and treatment programs. Future research should focus on studies of antiviral resistance mechanisms and molecular profiling by using next-generation sequencing techniques to achieve HBV elimination goals by 2030 in Asia and Africa.

Keywords: *Hepatitis B virus, Hepatocellular carcinoma, Genotypes, Open reading frames, Carcinogenesis, India, Nigeria*

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1. INTRODUCTION

Hepatitis B virus (HBV) is a DNA virus that causes hepatitis and primarily targets liver cells. HBV is the smallest human DNA virus, containing around 3200 bp of partly double-stranded circular DNA (Fig. 1). This virus is a member of the Hepadnaviridae family, specifically the genus Orthohepadnavirus [1]. HBV replicates via the reverse transcriptase enzyme, which produces a reverse-transcribed RNA (ribonucleic acid) intermediate. This enzyme lacks proofreading capabilities, resulting in nucleotide synthesis that is very error-prone. As a result of the considerable genetic variation, ten HBV genotypes (A-J) and forty sub-genotypes have arisen [2]. HBV is a major public health concern around the world because it can cause chronic infections that progress to severe liver disorders such as hepatocellular carcinoma (HCC) and cirrhosis. HCC and cirrhosis are severe liver disorders caused by persistent infections, making them a major worldwide health

concern [3]. Developing successful diagnostic, treatment, and prevention measures for HBV requires an understanding of its virology and genetic traits. HBV can cause hepatocellular damage by inducing immunological responses to the infected hepatocytes, even though it is typically not regarded as a cytopathic pathogen in and of itself [4]. Furthermore, HBV DNA can become integrated inside the genome of the host, which can lead to carcinogenic potential and genomic instability [5]. While there is a 1% chance of acute liver failure, an acute infection in otherwise healthy individuals normally resolves on its own. In children under five, however, the infection typically lasts longer than six months [6]. The primary reason for high endemicity is MTCT (mother-to-child transmission), as chronicity is the norm for newborn infections (>90% of cases) [7]. There are at least ten unique genotypes of HBV (A–J), each of which is distinguished by greater than 8% nucleotide variations in the genome sequence and is found in various parts of the world. Because of the correlation between genotype and treatment response and clinical outcome, HBV genotyping is clinically relevant [8].

As estimated by the World Health Organization (WHO), there are about 257 million people worldwide who have chronic hepatitis B (CHB), which causes 887,000 deaths every year. Infections with CHB and chronic hepatitis C (CHC) account for almost 90% of the deaths and illnesses caused by viral hepatitis [9]. HBV is recognized as a critical public problem, especially in areas with insufficient healthcare infrastructure and vaccinations. WHO set a goal in 2016 to eradicate hepatitis as a public health concern by 2030. According to the baseline year of 2015, the specific objectives for HBV were to decrease mortality by 65% and incidence of infection by 95%. 10 Besides these relative targets, the eradication criteria had been broadened in 2021 to cover the exact goal as well: a prevalence of less than 0.1% in children aged below five years and an annual mortality rate of less than 4 per 100,000 population [11]. A modeling analysis shows that achieving several programmatic goals is required to achieve HBV elimination, including 90% or higher coverage of newborn vaccination with swift birth dose, 90% detection of persons with HBV infection, and around 80% testing and treatment of eligible patients [12]. However, progress has been slow, and according to 2020 Polaris Observatory statistics, no country is on track to reach all of its goals by 2030. If efforts to reduce underdiagnosis and undertreatment continue, preliminary data show that world HBV-related mortality is expected to rise by 39%, from 850,300 deaths in 2015 to 1,109,500 in 2030 [13].

In this review, we compare the distributions of different genotypes and their clinical relevance in two endemic countries, India and Nigeria, by highlighting their differences that are crucial for developing targeted treatments and improving HBV infection management. This review also identifies important research gaps that require further investigation.

1.1 Global burden and Prevalence of HBV

The prevalence of HBV is a serious global health challenge, and results from vaccinations, treatment response, and disease progression are all significantly influenced by genotype variability [14]. In 2019, WHO predicted that almost 296 million people had chronic HBV infection (CHB) and 1.5 million new infections, with 820,000 deaths caused by HBV every year. HBV is the primary cause of hepatocellular carcinoma (HCC) worldwide, accounting for 42% of cases of cirrhosis [15, 16]. Age-standardized HBsAg seroprevalence in the general population (Table 1) The prevalence is greatest in the African Region (7.5%), with the Western Pacific at 5.9% [17]. About 6.4 million children less than five years of age are infected with HBsAg, which has a 1% global prevalence [17, 18]. Except for the African region (2.5%), the prevalence of HBsAg in children under the age of five is less than 1% in all WHO regions (Table 2) [17]. Based on data from the Global Burden of Disease (GBD) in 2019, the prevalence of HBsAg in infants under the age of five has declined dramatically (77% since 1990).

Nevertheless, Western and Asian countries experienced the majority of this decline [18]. HepB-BD vaccination coverage is linked to global HBsAg prevalence in children under the age of five, according to WHO regions. According to data from the 2016 Polaris Observatory, 1.8 million children are infected each year, suggesting that MTCT or early childhood are the primary ways HBV is caught around the world [13, 17] Sixteen countries accounted for 80% of new infections, with India, Nigeria, Indonesia, and the Democratic Republic of the Congo contributing nearly 57% [13]. In addition to geographic variations, the burden of CHB varies greatly across communities. Although the prevalence of HBsAg in pregnant women is typically similar to that in the general population in the same geographical area [19], other vulnerable groups are more likely to contract HBV, including sex workers, drug injectors [20, 21], homeless people [22], people with HIV, hemodialysis patients, and prisoners [23]. As a result, more than two-thirds of CHB patients reside in low- and middle-income countries (LMICs) [24]. Furthermore, in countries with a low Socio-Demographic Index (SDI), the burden of CHB is spatially distributed. Compared to countries with high SDI, low SDI countries had significantly higher death rates and HBsAg seroprevalence in children under the age of five [18].

TABLE 1: HBsAg prevalence in the general population as reported by GBD, WHO and Polaris.

Region	2019 (GBD)	2020 (WHO)	2022 (Polaris)
Global	4.1%	3.8%	3.2%
Africa	6.5%	7.5%	5.4%

America	1.2%	0.5%	0.6%
South-East Asia	3.1%	3.0%	3.8%
Europe	1.1%	1.5%	1.8%
Eastern Mediterranean	3.1%	2.5%	2.9%
Western Pacific	7.1%	5.9%	7.1%

Footnotes:
[1] GBD: Global Burden of Disease, [2] WHO: World Health Organization

TABLE 2: Prevalence of HBsAg among children below 5 years reported by GBD, WHO and Polaris.

Region	2019 (GBD)	2020 (WHO)	2022 (Polaris)
Global	1.0%	0.9%	0.7%
Africa	2.7%	2.5%	1.7%
America	<0.1%	<0.1%	<0.1%
South-East Asia	0.5%	0.4%	0.6%
Europe	0.1%	0.3%	<0.1%
Eastern Mediterranean	0.8%	0.8%	0.4%
Western Pacific	0.5%	0.3%	0.3%

Footnotes:
[1] GBD: Global Burden of Disease, [2] WHO: World Health Organization

1.2 Importance of Genotypic Variability

Understanding the natural history and epidemiology of HBV requires an understanding of its genotype. There are several genotypes of HBV named A to J, each with unique geographic distributions and clinical implications. Variations in genotype influence disease development, treatment outcomes, and the possibility of complications such as hepatocellular carcinoma [25]. Treatment responses and clinical consequences vary according to genetics. In contrast to genotype C, people with genotype B have a higher risk of HCC and respond poorly to interferon therapy. In contrast, genotype A is typically associated with a better response to antiviral medication. 3 By finding these genotype-specific features, physicians can anticipate the prognosis of their patients' ailments and select the most effective treatment [3]. Furthermore, Variations in the HBV genome impact antigenicity, susceptibility to antiviral treatments, and viral replication, making management even more challenging. Genotype and mutation analysis is therefore essential for tailoring individual treatment plans and improving patient outcomes [26]. Therefore, it is crucial that new strains be carefully classified based on their genotype and subgenotype and that nomenclature be used in a consistent and scientifically accepted way. The genetic variability of HBV and its genotypes and subgenotypes is also important in epidemiology and transmission studies, tracking human migrations, and predicting the likelihood of developing serious liver disease and how well antiviral drugs will be effective. Furthermore, understanding the genotype and sub genotype is essential in implementing preventative strategies [26].

1.3 Rationale for comparing India and Nigeria

India and Nigeria represent different epidemiological environments with differing prevalent genotypes and high disease loads, making a comparison of their HBV genotypic variability crucial. While Nigeria and parts of West Africa have historically been dominated by genotype E, with pockets of genotype A and other kinds described more recently, India exhibits significant genotype diversity, with genotypes A and D being commonly recorded and genotype D being extensively spread throughout several locations [3, 27]. Given these disparate gene landscapes, a head-to-head comparison would be instructive for regional clinical practice and policy because genotype-specific hazards, natural histories, and public health implications are expected to vary between the two nations. Serologic marker dynamics, response to specific medications, risk of hepatocellular carcinoma, and disease progression are among the clinically significant outcomes that are influenced by HBV genotypes [28]. Though the evidence differs by population, several recent reviews have highlighted the impact of genotype and subgenotype on viral load trajectories, the probability of HBeAg/HBsAg loss, and interferon response [3, 28]. Therefore, a comparative study that combines genotype data from Nigeria and India can shed light on whether genotype-associated risks seen in one area are present in the other and whether treatments and surveillance protocols tailored to a particular nation should take genotype into account. Comparing these two contexts is also significant from a research and public health standpoint. Recent research has revised the picture of circulating genotypes and mutation patterns in several Nigerian states [29, 30].

Nigeria is still considered hyperendemic, with high population prevalence estimates and notable gaps in surveillance and molecular epidemiology. In contrast, India has a high level of intranational heterogeneity, with numerous genotyping studies carried out among different patient groups and geographical areas [31]. Identifying gaps in sampling and diagnostic coverage, spotting potential genotype shifts or the emergence of mixed/recombinant infections, and informing targeted

interventions like screening strategies for high-risk groups, genotype-specific clinical guidance, and birth-dose vaccination prioritization are all made easier by comparing datasets from the two nations. In order to enhance regional policy relevance and identify objectives for future genetic and clinical research, the two-country evidence base can be combined by systematic review and meta-analysis [27, 28].

2. GENOMIC STRUCTURE OF HBV

The hepatitis B viral genome (Fig. 1) is a tiny, partly double-stranded DNA molecule that is arranged in a relaxed circular form. It has an asymmetric structure with a whole negative (minus) strand and a shorter positive (plus) strand that terminate at separate 3′ ends. The 5' end of the minus strand is attached covalently to the terminal protein that is also linked to the viral DNA polymerase via a tyrosyl-DNA phosphodiester linkage. The short-capped RNA segment can also be detected at the 5' end of the plus strand. Complementary base pairing between these two strands maintains the genome's circular structure [29]. The RNA portion at the 5' end of the plus strand acts as a primer for the synthesis of the plus strand, while on the other side, the terminal protein functions as a primer for minus strand synthesis. After replication is completed, both primers, that is, the terminal protein as well as the RNA fragment, remain connected to their respective DNA strands [29].

2.1 Open Reading Frames of HBV

The viral genome of HBV has four different overlapping open reading frames (ORFs): P, S, C, and X. These ORFs are all regulated by two enhancer regions, EN1 and EN2, four promoters, as well as a single polyadenylation site (Fig. 1). Each ORF encodes a specific protein. The P gene produces DNA polymerase, the S gene encodes surface antigens, the C gene generates precore and core proteins, and the X gene produces the regulatory HBx protein. Infected hepatocytes produce four RNA transcripts (3.5 kb, 2.4 kb, 2.1 kb, and 0.7 kb) with a shared 3′end. The 3.5-kb pregenomic RNA (pgRNA) serves as both the mRNA for core and polymerase proteins and the replication template, whereas the precore RNA (pcRNA) encodes the precursor of HBeAg, which is detected in infected sera [30].

The C gene has two in-frame start codons that generate precore (p25) and core (p21) proteins. The P gene, which covers the majority of the genome, encodes the 90-kDa DNA polymerase with terminal protein, reverse transcriptase, spacer, and RNase H domains. The S gene encodes big, medium, and tiny surface proteins that are essential for receptor binding and virion assembly. The X gene produces the multifunctional HBx protein, which regulates transcription, enhances viral replication, and contributes to HBV-related liver disease and oncogenesis [30,31].

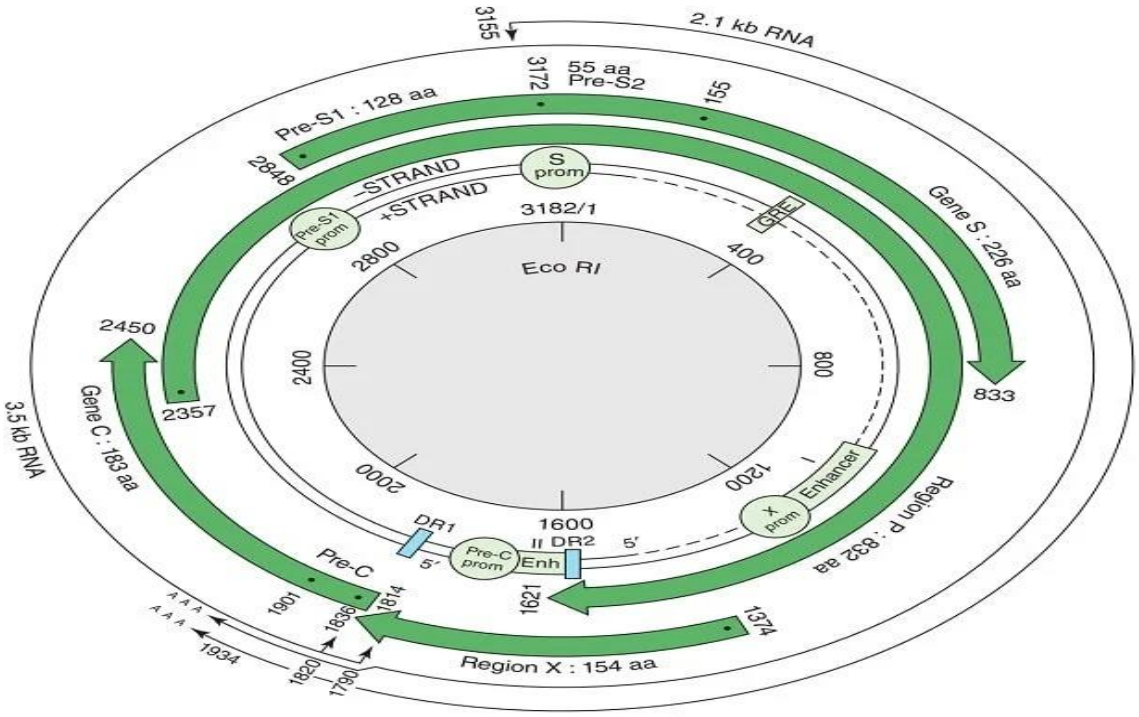

Figure 1: Circular representation of the complete HBV genome (~3.2 kb), showing the natural relaxed circular DNA (rcDNA) structure with the four major overlapping open reading frames (P, S, C, and X), PreS1/PreS2 regions, the key regulatory elements such as Enhancer (ENH I and ENH II), Direct repeat regions (DR1 and DR2), and the polyadenylation site (PolyA). The diagram reflects functional and structural complexity of the HBV genome.

Footnotes:
Reproduced from: Aryal S., 2022. [Ref. 32].

2.2 HBV Transmission

HBV is mostly spread via direct contact with infected blood and other body fluids like semen and saliva. The main course of HBV infection includes mother-to-child transmission during childbirth, sexual contact with an infected individual, and parenteral exposure resulting from practices such as sharing contaminated needles, unsafe medical procedures, or transfusions involving infected blood. Perinatal and early childhood infections add significantly to the pool of chronic HBV cases in highly endemic countries, as infections acquired during these stages are more likely to proceed to chronic hepatitis [33, 34]. Because HBV is highly infectious and present in high concentrations in the blood, percutaneous exposures are particularly effective in spreading the virus. Other routes of HBV transmission include, among others, occupational exposure among healthcare workers and domestic contact, such as sharing personal belongings like toothbrushes and razors with infected persons. Another common method of getting chronic hepatitis B viral infection is transmission via mother to child (MTCT). The presence of hepatitis B e antigen (HBeAg) and a high maternal viral load both significantly increase the probability of perinatal infection and viral transmission during birth [35].

2.3 HBV Pathogenesis

HBV is the leading cause of hepatocellular carcinoma (HCC). More than 80% of newly diagnosed HCC cases in HBV endemic regions, particularly in Asia as well as in the Pacific, are directly linked to chronic HBV infection [36]. In individuals with chronic HBV infection, the development of liver cirrhosis significantly increases the likelihood of progressing to hepatocellular carcinoma (HCC). Some other risk factors include serum alanine aminotransferase (ALT), age, gender, HBV DNA viral load levels, and HBeAg positivity. Even in the absence of advanced cirrhosis, indicators such as HBV DNA levels lower than 10,000copies/mL, elevated ALT, and positive HBeAg status are all regarded as strong predictors of HCC progression. Moreover, a persistently high viral load alone may signal an increased likelihood of HCC recurrence following surgical intervention. Epidemiologically, the male-to-female ratio for HCC ranges from 5:1 to 7:1, demonstrating a clear gender disparity among HBV carriers. This difference has been observed in HBV transgenic mouse models as well. Research suggests that the androgen receptor (AR) plays a key role in this gender-based difference through its positive feedback interaction with HBV. Studies using HBV transgenic mice have confirmed AR's involvement in HBV-induced hepatocarcinogenesis. The HBx protein can directly bind to AR and enhance its activity, or it can indirectly activate AR via the (Src and GSK3β) signaling pathways [30]. Once activated, AR promotes HBV gene expression by interacting with androgen-responsive elements (AREs) in the viral genome, leading to increased viral replication and carcinogenesis [37]. Liver-specific deletion of AR has been shown to reduce both HBV gene expression and HCC incidence [38]. Additionally, sex-related differences in chronic liver inflammation further contribute to the observed disparity in HBV induced liver cancer.1Integration of HBV DNA into the host genome is found in over 80% of HBV-associated HCC cases. Within the viral genome, the HBx coding region harbors the highest number of integration sites, leading to the production of C-terminally truncated HBx proteins and chimeric RNA transcripts containing both host and viral sequences. Initially, HBV integration was believed to occur randomly within host chromosomes. However, whole-genome sequencing has identified several recurrent integration hotspots, including protein tyrosine phosphatase receptor type D (PTPRD), telomerase reverse transcriptase (TERT), tumor protein 53 (TP53), catenin beta 1 (CTNNB1) genes and retinoic acid receptor beta (RARB) [30, 39]. The integration of HBV DNA can induce chromosomal instability, disrupt gene expression, and promote angiogenesis, metastasis, and tumor formation by either activating oncogenes or inactivating tumor suppressor genes. Further insights into these mechanisms are discussed in recent reviews [39, 40].

2.4 HBV Genotype Distribution

Global Distribution

Hepatitis B virus (HBV) exhibits marked genotypic diversity across different geographical regions, with each genotype associated with unique clinical outcomes and epidemiological patterns (Table 3). In Europe and Africa, genotype A is predominant, while in East Asia, genotypes B and C are more frequently encountered [41, 42]. Genotype D is widespread in the Mediterranean region and parts of the Middle East, whereas genotype E is largely confined to West Africa. In contrast, genotypes F and H are primarily found in Central and South America. And genotype G remains relatively rare, being sporadically detected in the United States and France. This global distribution pattern points out the complex epidemiology of HBV, influenced by socioeconomic factors, historical human migration, and regional healthcare practices. Among the nine recognized genotypes, five of them A, B, C, D, and E account for more than 96% of chronic HBV infections worldwide. Genotype C, representing approximately26% of global infections, it is the most common in East Asia. Genotype D is prevalent across the Middle East, India, and the Mediterranean basin, accounting for about 22% of cases. Genotype E, which constitutes roughly 18% of global infections, is largely restricted to sub-Saharan Africa. Meanwhile, genotype A predominates in North America, Europe, and Africa, representing about 17% of global cases, whereas genotype B accounts for 14%, mainly in Southeast Asia. Understanding the global distribution of HBV genotypes is important for effective public health planning and disease control strategies. Tailoring vaccination programs and therapeutic approaches to target the predominant genotypes in specific areas can significantly enhance their efficacy.

Moreover, genotype based epidemiological surveillance enables the identification of high-risk populations, facilitates early diagnosis, and supports the development of region-specific intervention strategies, ultimately contributing to a global reduction in HBV related morbidity and mortality [42].

TABLE: 3 Global Distribution and Prevalence of Hepatitis B Virus (HBV) Genotypes

Genotype	Geographical Distribution	Prevalence of CHBV Infections
A	Europe, Africa, North America	17%
B	Southeast Asia, East Asia	14%
C	East Asia (most common in region)	26%
D	Middle East, India, Mediterranean region	22%
E	Sub-Saharan Africa, West Africa	18%
F	Central and South America	Rare
G	Sporadic in United States and France	Rare
H	Central and South America	Rare

Footnotes:
[1] CHBV: Chronic Hepatitis B virus

Genotype Distribution in India
HBV genotype distribution within India exhibits distinct regional heterogeneity. Studies from New Delhi have shown that both genotypes A and D are present in North India, with genotype A making up roughly 16% of cases and genotype D being dominant (84%). There have been reports of genotypes D, A, and C in South India; the most common genotype is D (57.3%), followed by A (18%) and C (11.5%). There have only been reports of genotypes D and A in the western region, with genotype D accounting for 91.93% of cases and genotype A being

found in roughly 8% of cases. A study from Chandigarh identified genotypes D, A, B, and C, with genotype D again being the main type, while genotype B was only detected in mixed infections. In a different pattern, genotype B was found to be the most prevalent genotype in Meerut, Uttar Pradesh (North India), with a prevalence of 68.8%, followed by genotype A (31.25%) [43]. Overall, genotype D is still the most common in India, although genotype A is constantly found as a secondary type. Regional variation in the distribution of HBV genotypes
throughout the country is highlighted by the fact that genotype B has been widely recorded in Meerut, whereas genotype C is primarily found in the southern and northern regions [43].

Genotype Distribution in Nigeria
In Nigeria, the HBV genotype landscape is comparatively less diverse, with genotype E being overwhelmingly predominant across most regions. It is highly prevalent in Plateau State (North Central), the Niger Delta, Southwest Nigeria, and Enugu (Southeast Nigeria). Phylogenetic and phylogeographic studies indicate that genotype E likely originated in Nigeria, suggesting a long-standing endemic circulation pattern [44]. Although genotype A has been reported in some areas, such as Nasarawa State, it occurs much less frequently than genotype E [44]. Information on the clinical and virological characteristics of genotype E remains limited, yet evidence shows that this genotype is associated with higher chronicity rates, elevated viral loads, and a greater proportion of HBeAg positive individuals compared to other HBV genotypes [45,46]. Additionally, it has been proposed that genotype E may have entered the human population through cross-species transmission and spread throughout West Africa within the last two centuries [47].

Comparative Distribution of HBV Genotypes in India and Nigeria
The distribution patterns of HBV genotypes in India and Nigeria reveal marked regional and evolutionary differences, reflecting different epidemiological and genetic dynamics (Table 4). In India, genotype D is the most prevalent nationwide, dominating in New Delhi (84%), Western India (91.93%), and Southern regions (57.3%), while genotypes A and C occur at lower frequencies. Unique local variations also exist, such as the high prevalence of genotype B (68.8%) in Meerut, Uttar Pradesh, which underscores the country's complex and heterogeneous genotype structure. Conversely, the population of HBV in Nigeria is largely genetically homogeneous, with genotype E dominating nearly all regions. It is significantly more prevalent than genotype A found in Nasarawa State and remains the major strain across Plateau State, Enugu, the Niger Delta, and Southwestern Nigeria [44]. The strong predominance of genotype E has been linked to higher viral loads, chronic infection rates, and HBeAg positivity further distinguishes the Nigerian HBV genotype profile from that of India. Overall, India exhibits a diverse genotype distribution, with multiple genotypes (D, A, B, and C) coexisting and varying by geography, while Nigeria shows a near-uniform dominance of genotype E. This contrast highlights fundamental geographical, evolutionary, and epidemiological distinctions in HBV transmission and persistence between the two countries.

TABLE :4 Comparative Distribution of Hepatitis B Virus Genotypes in India and Nigeria

Country	Genotype(s)	Region / State	Prevalence Rate (%)
India	D, A	North India (New Delhi)	D (84%), A (16%)
	D, A, C	South India	D (57.3%), A (18%), C (11.5%)
	D, A	West India	D (91.93%), A (8%)
	D, A, B, C	Chandigarh	D (major), A, C; B only in mixed infections
	B, A	Meerut (Uttar Pradesh)	B (68.8%), A (31.25%)
Nigeria	E	Plateau State, Enugu, Niger Delta, Southwest Nigeria	E (dominant, no specific % reported)
	E, A	Nasarawa State	E > A (exact % not reported)

2.5 Geographical Distribution of HBV Subgenotypes

HBV Subgenotypes A1, A2, and A3 up to A8 are mostly found in South Africa, Brazil, and Northern and North western Europe, where the A genotype is distributed. Subgenotypes B1-B10 are mainly distributed in Asia and the Arctic Circle. Genotype C and its subgenotypes C1-C17, on the other hand, are spread throughout the Pacific Islands, and subgenotypes D1-D12 are widely distributed in India, Russia, and the Mediterranean Sea [48]. Genotype E is found in West Africa, particularly Nigeria and Central Africa; genotype F is also distributed in African regions, including subgenotypes F1-F6. Genotype G is found in Africa, America, Asia, and Europe. Genotype H is only found in America; genotype I and subgenotypes I1, I2, and I3 are widely spread in Asia, eastern India, Laos, southwestern China, and Vietnam; and genotype J is distributed in Japan [48].

2.6 Effect of Genotype on the course of Disease and response to treatment

The pathogenicity and antiviral treatment response of different HBV genotypes vary. These genotypes are not only geographically distinct, but they have also been demonstrated to have a clinical impact on the course of the disease and the response to therapy. Research has shown that specific HBV genotypes, sub-genotypes, and mutations in certain regions of the viral genome influence several key aspects of infection. These include the rate of HBeAg and HBcAg seroconversion, levels of viremia, immune evasion, the development of viral mutants, the progression of liver disease, as well as the response and resistance to antiviral therapy and the effectiveness of vaccination against the virus [44].

Viral replication dynamics and medication resistance profiles are two other ways that genotype-specific mutations can impact the outcomes of treatment. Drug-resistant mutations, for instance, are more likely to emerge in people with genotype C, making treatment plans more difficult. Genotype B, on the other hand, is associated with a higher risk of liver inflammation and fibrosis but a lower incidence of medication resistance. It is essential to comprehend these genotype-specific variations in order to improve patient care and optimize therapeutic approaches [3].

According to research, some genotypes like genotype C are more likely to experience chronicity and liver damage, which can result in more severe clinical outcomes. On the other hand, patients with genotype A frequently respond better to pegylated interferon therapy, which makes them good candidates for this treatment strategy. The significance of genotype testing in clinical practice is shown by these discoveries regarding the connections between genotype

and disease. Healthcare professionals can improve the quality of care for HBV-infected patients by using genotype analysis in regular diagnostics to better monitor disease progression, make more informed treatment decisions, and more [3].

2.7 Genotype Specific Mechanisms of HBV-Induced Hepatocarcinogenesis

Genotype-specific viral characteristics strongly influence the development of HCC in chronic HBV infection. Genotypes B and C, which predominate in East and Southeast Asia, show distinct oncogenic behaviours, while genotype C particularly subgenotype C2 is associated with persistent infection, higher viral loads, delayed HBeAg seroconversion, and significantly increased HCC risk, especially in cirrhotic individuals. In contrast, genotype B2 is linked to early-onset HCC in non-cirrhotic young patients and higher recurrence rates after treatment [49]. HBV-induced carcinogenesis is further driven by genotype-dependent mutations, particularly in the Enhancer II/basal core promoter (BCP), precore, and preS regions. Key mutations such as A1762T/G1764A, C1653T, and T1753V enhance viral replication, disrupt regulatory pathways, alter transcription factor binding, and produce truncated or dysfunctional viral proteins including mutated HBx which can dysregulate host oncogenes. PreS deletions, more common in genotype C, promote endoplasmic reticulum stress, oxidative damage, and malignant transformation. These viral factors accumulate during chronic infection and serve as strong predictors of HCC, highlighting genotype as a critical determinant of HBV-related hepatocarcinogenesis [49].

The incorporation of HBV DNA into the host genome is another important process in the development of HCC, with the rate and pattern of integration changing by genotype. These integration events frequently damage tumor suppressor genes

like TP53 and RARB, or activate oncogenes like TERT and CTNNB1, resulting in genomic instability and uncontrolled hepatocyte proliferation [38,46]. Notably, genotype E, the main strain in Nigeria, is associated with greater viral loads and persistent HBeAg positive, both of which promote DNA integration and chronic liver damage, raising the risk of HCC [44]. In contrast, genotype D, which is common in India, is associated with pre-core mutations that limit HBeAg synthesis, resulting in long-term immune-mediated liver damage. These recurring cycles of necroinflammation and regeneration aid in the accumulation of genetic modifications that promote carcinogenesis [43].

In addition to viral factors, host genetics and hormonal variations shape genotype-specific HCC risks. The androgen receptor (AR), for example, promotes HBV transcription by directly binding to HBx or activating downstream signalling cascades, an action that is especially evident in genotypes C and D, which may explain the increased incidence of HBV-related HCC in men [38]. Persistent inflammation, oxidative stress, and the emergence of truncated HBx or pre-S2 deletion mutants further amplify oncogenic signalling and promote tumor development [38,39]. These molecular findings highlight the importance of incorporating genotype-based monitoring into HBV management methods in highly endemic countries such as India and Nigeria. Understanding the way different HBV genotypes promote liver carcinogenesis is critical for improving early detection, guiding medical interventions, and promoting HCC prevention efforts.

2.8 Future Directions

The future research should focus on developing novel therapeutic strategies and enhancing diagnostic tools. In order to detect mutations in HBV-specific genotypes, emerging technologies such as next-generation sequencing (NGS) will assist in identifying drug-resistant variants early and guide tailored treatment decisions. Understanding the molecular mechanisms responsible for HBV genotype-specific pathogenesis and treatment responses should be another part of future research. Achieving global HBV control and eradication goals requires addressing the challenges posed by HBV escape mutants through the use of novel antiviral treatments and vaccination.

2.8 Conclusion

This review focuses on the variations in HBV genotype distributions between Nigeria and India, highlighting the prevalence of genotype E in Nigeria and the diversity of genotypes in India. These disparities have significant clinical and public health ramifications, including immunization plans, treatment outcomes, and the course of the disease. To increase the precision of diagnosis, customize treatment plans, and strengthen preventative initiatives, a better grasp of genotype-specific patterns in both nations is crucial. The advancement of HBV
control and elimination objectives in Asia and Africa will depend heavily on ongoing study concentrating on molecular epidemiology, genotype-associated clinical consequences, and resistance mechanisms.

Declarations

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