



An Insight into the Epidemiology and Genetic Diversity of Hepatitis B Virus in Africa

Hepatit B Virusunun Afrika'daki Epidemiyolojisine ve Genetik Çeşitliliğine Bakış

Shuaibu Abdullahi HUDU¹ [ID]

¹Department of Medical Microbiology and Parasitology, Faculty of Basic Clinical Sciences, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria.

Article Info: Received; 10.01.2022. Accepted; 22.04.2022. Published; 11.05.2022.

Correspondence: Shuaibu Abdullahi Hudu; PhD, Department of Medical Microbiology and Parasitology, Faculty of Basic Clinical Sciences, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, 840232 Sokoto State, Nigeria. E-mail: hudu.shuaibu@udusok.edu.ng

Abstract

Hepatitis viruses (*hepatotropic viruses*) are classified into five kinds, denoted by the letters A, B, C, D, and E, each with its own unique genotypes, clinical implications, and geographic distribution. Viral hepatitis is a type of liver inflammation that can resolve on its own or proceed to cirrhosis or hepatocellular cancer. Hepatitis A, B, and C infections are the most common types of infectious viral hepatitis. Over the previous five decades, hepatitis B virus (HBV) infection has exhibited an intermediate or high endemicity level in low-income nations. HBV genotype variation is thought to be crucial in regulating disease development, infection outcome, antiviral therapy response, and illness prognosis. HBV is divided into ten genotypes (A-J) and roughly 40 sub-genotypes, correlated with different geographic distributions, transmission routes, and disease progression. The goal of this study was to figure out how hepatitis virus genotypes were distributed among West African countries. HBV genotypes A, D, and E have been reported the most widely prevalent genotypes in Africa so far, while there are limited reports of genotypes B and C. HBV genotype A is shown to be more prevalent in Africa than on other continents, implying that it has an African origin. Genotype D has been found across Africa, particularly in the Mediterranean and North African regions. Except in Africa, HBV genotype E infection is extremely rare, even when infection with this genotype has been recorded outside of Africa, it has virtually always been in African origin people. Within Africa, HBV genotype E is abundant and broad across the continent, reaching from Senegal's west coast to Namibia's southwestern tip and eastward to the Central African Republic. These epidemiological findings and differences have important implications for the immunization, antiviral therapy, and clinical outcomes of HBV on a national and regional level.

Keywords: Hepatitis B virus, HBV genotypes, Genetic diversity, Africa, Epidemiology.

Özet

Hepatit virüsleri (*hepatotropik virüsler*) A, B, C, D ve E harfleriyle ifade edilen beş türe ayrılır ve her birinin kendine özgü genotipleri, klinik sonuçları ve coğrafi dağılımları bulunur. Viral hepatit, tedavi edilmeksizin düzelebilen ya da siroz veya hepatosellüler kansere ilerleyebilen bir tür karaciğer inflamasyonudur. Hepatit A, B ve C enfeksiyonları enfeksiyöz viral hepatitin en yaygın tipleridir. Hepatit B virusu (HBV) enfeksiyonu son elli yıllık dönemde düşük gelirli ülkelerde orta veya yüksek endemisite düzeyi sergilemiştir. HBV genotip varyasyonunun hastalık gelişiminin düzenlenmesini, enfeksiyon sonucunu, antiviral tedavi yanıtını ve hastalık prognozunu belirlemede çok önemli olduğu düşünülmektedir. HBV coğrafi dağılımları, bulaşma yolları ve

hastalık progresyonundaki farklılıkları ile ilişkili olarak on genotipe (A-J) ve kabaca 40 alt genotipe ayrılmıştır. Bu çalışmanın amacı, Batı Afrika ülkelerindeki HBV prevalansı ve genotip dağılımının güncel durumunu ortaya koymaktır. Şimdiye kadar HBV A, D ve E genotipleri Afrika'da en yaygın raporlanan genotipler olurken, genotip B ve C'yi içeren sınırlı sayıda rapor bulunmaktadır. HBV genotip A'nın Afrika'da diğer kıtalara göre daha yaygın olduğu gösterilmiştir ve bu da bu genotipin Afrika kökenli olduğunu düşündürmektedir. Genotip D, Afrika genelinde, özellikle Akdeniz ve Kuzey Afrika bölgelerinde bulunmuştur. HBV genotip E enfeksiyonu ise Afrika dışında son derece nadirdir, öyle ki bu genotip ile enfeksiyon Afrika dışında kaydedilmiş olsa bile neredeyse her zaman Afrika kökenli insanlarda saptanmıştır. HBV genotip E Afrika'da kıta genelinde yaygındır ve Senegal'in batı kıyısından Namibya'nın güneybatı ucuna ve doğuda Orta Afrika Cumhuriyeti'ne kadar geniş bir alana yayılmıştır. Bu epidemiyolojik bulguların ve farklılıkların HBV bağışıklaması, antiviral tedavi ve ulusal ve bölgesel düzeyde klinik sonuçlar üzerinde önemli etkileri vardır.

Anahtar Kelimeler: Hepatit B virüsü, HBV genotipleri, Genetik çeşitlilik, Afrika, Epidemiyoloji.

Introduction

Hepatitis B virus (HBV) infection is a globally endemic disease which often lead to acute and chronic liver disorders. While transient infection may result in a severe illness with approximately 0.5% individuals progressing to fatal, fulminant hepatitis, chronic HBV infections may present untreatable serious sequelae with nearly 15% to 25% of infected individuals by develop cirrhosis or hepatocellular carcinoma [1,2]. The WHO (World Health Organization) estimated 296 million people are chronically infected with HBV as defined by their reaction to surface antigen for at least 6 months [3]. Among these infected individuals, nearly 820,000 persons died in 2019, more than 80% of death occurring in chronically infected persons as a result of cirrhosis and liver cancer, remains are recorded as a result of acute hepatitis B infection [3]. In addition, about 1.5 million new cases of HBV infection occur annually with a quarter developing liver disease [3]. Although the distribution of the disease is worldwide, Africa, particularly the sub-Sahara region and Asia (*western pacific region*) are the most endemic regions with about 5-10% of their adult population being chronically infected [3,4]. On the other hands, only approximately 1% of people in countries of North America and Europe are chronically infected with the virus [5]. An HBV carrier rate of less than 2% has been reported in low endemic areas like Australia, Northern Europe, United States, and South America [3]. Intermediate endemic areas such as Eastern Europe, the Mediterranean basin and the Middle East has a carrier rate ranging from 2-8% [3]. Although the burden of HBV infection majorly

occurs in poor resource African region, extended data on the genotype diversity of HBV in Africa is scanty. This information will invariably add value to the global understanding of hepatitis B infection vis-à-vis, its molecular epidemiology, evolution, and control. This study reviewed aspect of epidemiology and genetic diversity of HBV in Africa with emphasis on published research and nucleotide sequence database.

HBV genome organization and proteins

Hepatitis B infection is caused by HBV; a member of Orthohepadnavirus genus in the *Hepadnaviridae* family [6]. The genome of HBV is a 3.2 kb DNA that is partially double stranded and structured into four open reading frames (ORF) with the longest open-reading frame being the "Pol" which encodes viral polymerase. Within the Pol-ORF, the envelope ORF is located in a frame shift manner [7]. The Pol ORF partially overlaps the core (C) and X ORF, thus forming a covalently closed circular DNA template that is transcribed into four major types of RNAs of different sizes: 3.5, 2.4, 2.1 and 0.7 kb transcripts viral RNA [7]. These four differently sized RNAs transcripts expresses with the help of an enhancer-II/basal core, large surface antigen, major surface antigen as well as an enhancer I/X promoters respectively, thought to play role in progression to liver cirrhosis and hepatocellular carcinoma [8]. Hepatitis B viral proteins are derived from the four sets of mRNAs which are translated into nucleocapsid proteins (HBcAg) and secreted or soluble proteins (HBsAg), polymerase protein (Pol gene), envelope proteins (HBsAg) and X proteins (HBx) (Figure 1) [9,10].

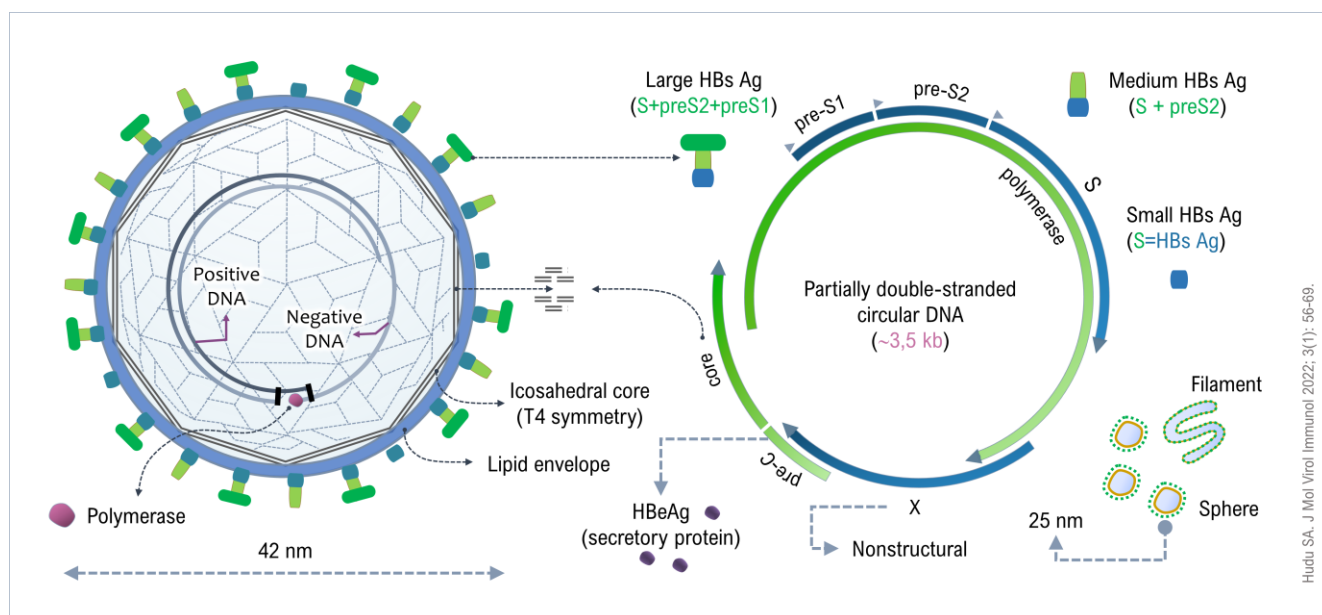


Figure 1. The structure of the hepatitis B virus (HBV) virion and schematic representation of HBV genome. The partially double stranded DNA genome, enclosed by a capsid, comprised of HBcAg and surrounded by a lipid envelope containing large (L)-HBsAg, middle (M)-HBsAg and small (S)-HBsAg. The virus also expresses two non- structural proteins; X protein and HBeAg [11].

Envelope protein

The main function of the envelope protein, also known as hepatitis B surface protein, is to form the HBV envelope [9]. Hepatitis B surface proteins are further classified as S, M, and L (small, medium, and large) proteins [9,12]. Hepatitis B surface protein, commonly known as "s antigen", is an important marker in diagnostics tests, as well as the main antigenic marker of HBV infection. The a-determinant, which is found in all hepatitis B subtypes, is found in HBsAg [13]. The HBsAg a-determining region located in the major hydrophilic region, is the primary target for post infection or vaccination neutralizing antibodies [10,14]. The introduction of a variation in this region (a determinant) may result in production of antibodies towards hepatitis B surface antigen avoiding neutralization and escaping identification by conventional diagnostic assays, posing a danger to vaccination efficacy and increasing the risk of improper blood transfusion [10,13].

Core-protein

The core gene which encodes for the viral capsid as well as the polymerase genes which like retroviruses possess an RNase H activity are essentially responsible for the replications of HBV viral genome [9]. Clinically, the presence of antibodies to hepatitis B surface (HBs) and core

(HBc) proteins signifies previous HBV infection while the presence of only HBs antibodies indicates post HBV vaccination immunity [15].

E antigen

HBeAg is the final product of precore ORF [9]. HBeAg in chronically infected patient indicates high HBV infectivity as a result of active viral replication as such, antibodies to this protein indicates seroconversion of HBeAg, thus, signifying the absence of virus replication and the transition to the inactive carrier state of infection [9]. Therefore, this can be used in monitoring treatment to determine the potential point to end treatment.

X protein

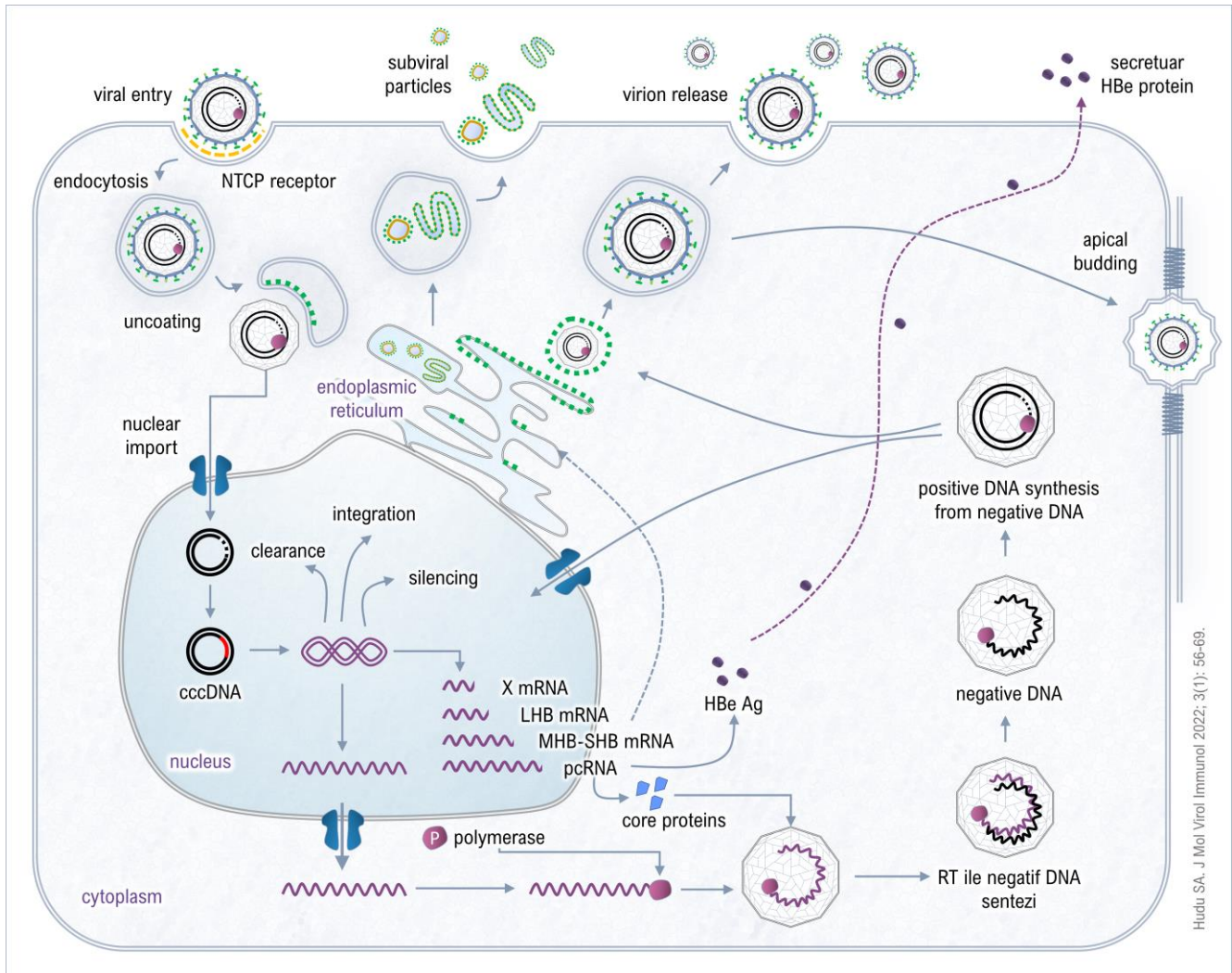
The smallest of the four major HBV proteins is the HBx protein which plays essential roles during HBV replication and mediating hepatocellular carcinogenesis by activating oncogenes that stimulate hepatocytes proliferation [9,16], thereby, inactivating growth regulators and promoting cell cycle progression. It also down regulates p53 tumour suppressor gene and other tumour suppressors as well as senescence related factors [9,16,17]. Therefore, HBx protein act as a strong epigenetic deregulating agent, epigenetic changes in this tumour suppressor gene induced hepatocellular carcinoma [18].

Polymerase protein

The largest HBV mRNA encodes polymerase protein which consists of three functional domains, namely reverse transcriptase-polymerase (RT/Pol) and RNase H (P) domains [9]. In addition this mRNA consist a variable spacer region [9].

HBV Virus Replication

HBV viral replication start with the attachment of the virus via pre-s1 protein (L-HBsAg) to the hepatocyte via sodium-taurocholate cotransporting polypeptide (NTCP) and subsequent penetration into the cytoplasm and uncoated [19].



Hudu SA. *J Mol Virol Immunol* 2022; 3(1): 56-69.

Figure 2. Replication cycle of hepatitis B virus [20]. NTCP; Sodium taurocholate cotransporting polypeptide.

HBV core particles are then transported from the cytoplasm into the nucleus and converted to covalently closed circular DNA (cccDNA) to serve as a transcriptional template for the host polymerase II enzyme which generate subgenomic and genomic RNA transcripts [21]. The cytoplasmic pregenomic RNA is translated to viral polymerase and core protein while, the subgenomic RNA is translated into envelope proteins (L, M and S) and the X protein. In the cytosol, nucleocapsids are assembled and viral polymerase as well as the genomic RNA are

incorporated into the assembled viral core. The reverse transcription of viral RNA begins as soon as the RNA is encapsulated, leading to the sequential synthesis of two viral DNA with the encapsidated RNA template been the first DNA strand after being degraded by viral polymerase RNase enzymes; the newly made first strand is used as a template for the synthesis of the second DNA strand. The core particle containing the viral genome finally enveloped with the L, M, and S protein (envelope proteins) and released from the cell whole, some of the core particle can be

reimported into the nucleus for formation of additional cccDNA (Figure 2) [22,23].

HBV transmission in Africa

HBV has been detected in body fluids, including blood, vaginal secretion, semen, tears, and saliva [24], as such viral transmission depend on the pattern of epidemiology within the geographical area affected. However, parenteral transmission and sexual intercourse are the main mode of transmission [25]. In Northwestern Europe, North America and Australia, the transmission route of HBV is usually by sexual transmission or injecting drug use among adult in which up to 10% of them progresses to chronic infection but rarely progress to liver cancer [26,27]. In South-East Asia, mother-to-child transmission predominate which often progresses to chronic and advance into liver cancer [27,28]. On the other hand, in Africa HBV infection in childhood predominate the mode of transmission with very high likelihood of becoming chronic making liver cancer in young ages very common [27]. The nosocomial transmission due to unsafe injection is one of the major transmission routes for HBV in Africa [29]. Recently, the WHO has estimated that about 24% of blood donations are not properly screen for HBV/HCV in low-income countries of Africa [30]. Similarly, most of the African countries lack capacity for efficient HBV and HCV screening such as the nucleic acid-based detection in their blood bank [30].

The major transmission route globally is via perinatal and it has been a significant factor in preserving reservoir of infection most especially in Southeast Asia, China and Africa [27,28,31]. In particular, sexual transmission occur in heterosexuals with multiple sex partners or contact with commercial sex workers as well as unvaccinated men who have sex with men [32]. However, the risk of this perinatal transmission increases in the absence of prophylaxis for infants of viremic mothers especially those with seropositive HBeAg and also in mothers with acute HBV infection in second or third of pregnancy and two months post-delivery [33,34]. HBV transmission may also be as a result of accidental inoculation of small amounts of blood or body fluids during dental, surgical or medical

procedures [35], similarly, transmission may occur via objects contaminated with HBV infected blood or body fluids such as; razor, unsterilized of poorly sterilized syringes and needles. Other harmful practices like tattooing, piercing, acupuncture, intravenous and percutaneous drug abuse may also contribute to HBV transmission [35].

Epidemiological distribution of HBV

Forty five percent of the world population lives in high endemic areas such as the middle East, Amazon Basin, Asia and Africa in where HBsAg prevalence is more than 8% with more than 60% lifetime risk of infection, while 24% of the world population lives intermediate endemic areas like South America, Russia, Central America, East and Southern Europe with 2-7% prevalence and 20-60% lifetime risk of infection [5,32,36]. On the other hand only 12% of the world population live in low endemic areas like Australia, Western Europe and United States in where HBsAg prevalence is less than 2% with less than 20% lifetime risk of infection [36]. The region with the largest number of chronic HBV carriers is Asia, followed by Africa [37], but is difficult to assess the precise burden of HBV infection in Africa, as a result of under reporting and inaccurate records. However, evidence of past HBV infection has been reported in 70-90% of adult population while seroprevalence was estimated between 6 and 20% [37].

Within the African region, the West, central and southern Africa have been identified to have the highest endemicity with markers of past exposure present in 70 to 95% of the adult population and one of the highest rate of hepatocellular carcinoma (HCC) in the world [36]. The largest continent in the world is Asia followed by Africa which occupy one-fifth of the global land area which is approximately thirty million square kilometer and constitute 16% of the world population [38]. The precise burden of HBV infection is difficult to quantify in Africa as a result of insufficient data collection and under reportage.

Nevertheless, available statistics shows that out of the 296 million people chronically infected with HBV globally 81 million live in Africa [3]. Similarly, of the 820,000 deaths due to HBV

infection worldwide, in 2019, 80 million occur in WHO African region [39]. In Africa, the west African subregion has the highest rate of endemicity (> 8%) [40]. The prevalence rate of

HBV infection in some of the West African countries as follows; Ghana 8.36% in adults, Senegal 11 to 15 in adults, Nigeria 9.5% (see Table 1) [41–43].

Table 1. Selected studies and references on the seroprevalence of HBV infection in some African countries.

Country	Prevalence (%)	Population demography	Sample size	Level of endemicity*	Year of sampling	Ref.
Angola	7.5	pregnant women	1,612	intermediate endemic		[44]
Benin	9.9	blood donors	national survey	hyperendemic	2012	[45]
Burkina Faso	9.1	population-based survey	15,377	hyperendemic	2015	[46]
Cameroon	10.1	blood donors	543	hyperendemic	2012	[47]
Chad	10.1	blood donors	30,123	hyperendemic	2010-2011	[48]
Congo (Brazzaville)	9.9	blood donors	1,363	hyperendemic	2013	[49]
Cote d' Ivoire	11.1	blood donors	91,962	hyperendemic	2010-2012	[50]
Egypt	1.4	adults, aged 15-59	15,777	low endemic	2015	[51]
Ethiopia	6	a systematic review and meta-analysis	106,125	intermediate endemic	2010-2019	[52]
Gabon	7.3	blood donors	69,862	intermediate endemic	2009-2016	[53]
Ghana	8.4	a systematic review and meta-analysis in adults	28,351 (pooled)	hyperendemic	2015-2019	[41]
Gambia	9.20	pregnant women	424	hyperendemic	2015	[54]
Guinea Bissau	6.1	blood donors	2,970	intermediate endemic	2010-2011	[48]
Kenya	1.6	blood donors	244,228	low endemic	2010-2011	[48]
Liberia	7.4	blood donors	13,472	intermediate endemic	2010-2011	[48]
Libya	2.2	cross-sectional study (all age groups)	65,761	intermediate endemic	2008	[55]
Malawi	8.1	systematic review	5,984	hyperendemic	1990-2018	[56]
Mali	14.8	blood donors	8,059	hyperendemic	2018	[57]
Mauritania	10.7	antenatal	946	hyperendemic	2008-2009	[58]
Mozambique	9.3	blood donors	1,578	hyperendemic	2004	[59]
Mozambique, Maputo	12.2	youths (18-24 age)	1,377	hyperendemic	2009-2011	[60]
Nigeria	9.5	a systematic review and meta-analysis	21,702 (pooled)	hyperendemic	2010-2019	[42]
Rwanda	3.9	cross-sectional study (> 25 years old)	327,360	intermediate endemic	2018	[61]
Senegal	11 to 15	in adults (three different studies)	3,539 (pooled)	hyperendemic	2006-2009	[43]
Sierra Leone	9.7	blood donors	16,807	hyperendemic	2016	[62]
South Africa	4	population-based survey (15-49 years old)	9,791	intermediate endemic	2014-2015	[63]
Sudan	9.1	systematic review and meta-analysis	5,848	hyperendemic	1997-2016	[64]
South Sudan	11.1	pregnant women	280	hyperendemic	2012-2013	[65]
Tanzania	7	health care workers	598	intermediate endemic	2012	[66]
Uganda	7	13 to 49-years-old	517	intermediate endemic	2013-2015	[67]
Zambia	3.7	adults	4,961	intermediate endemic	2013-2014	[68]
Zimbabwe	10.1	general population	WHO estimation	hyperendemic	2019	[69]

*The prevalence of chronic HBV infection (WHO definition): High (>8%), intermediate (2-8%), low (<2%).

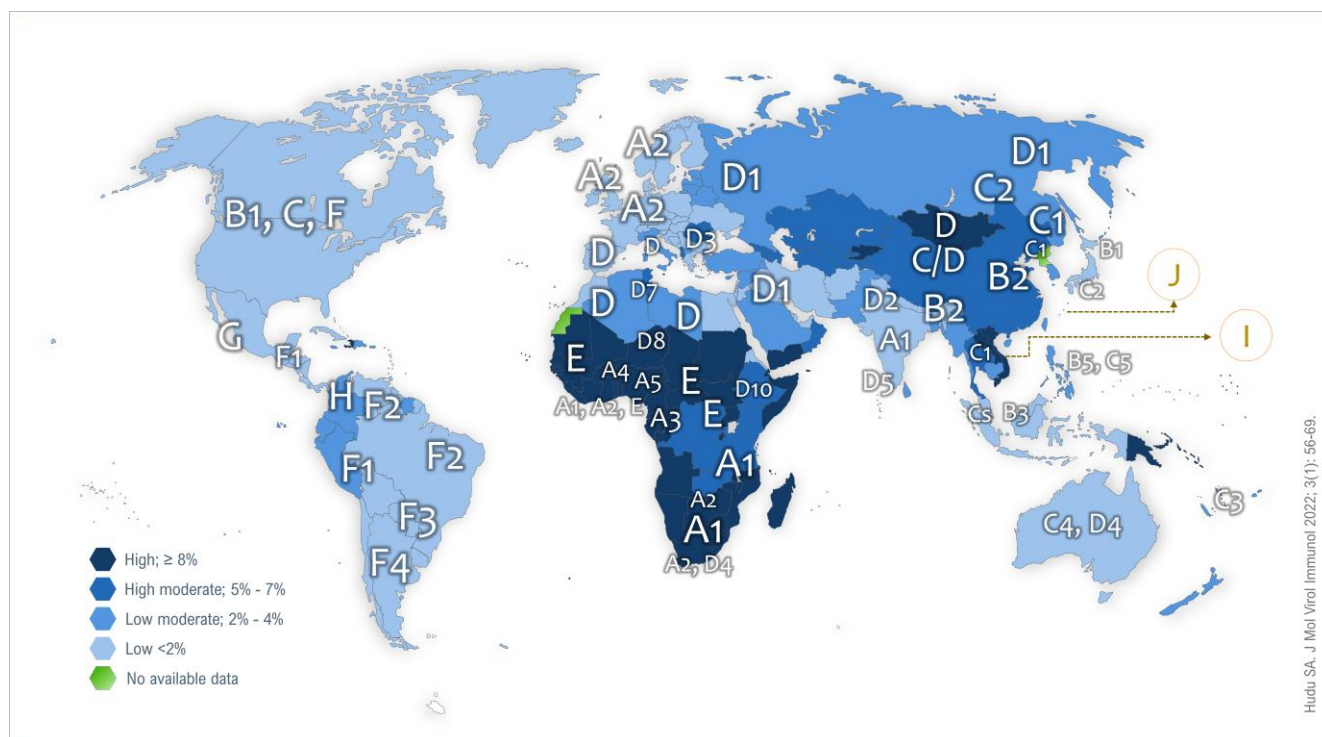


Figure 3. Global prevalence and genotype and sub-genotype distributions of Hepatitis B infection [2,36,70,71]. Note the predominance of genotype A and E in the high-risk African region.

Genetic diversity of HBV in Africa

HBV has been classified into different genotypes based on nucleotide sequence differences (>8%), in this regards, eight genotypes designated A, B, C, D, E, F, G to H have been identified [72]. Similarly, two other unresolved and probably recombinant genotypes I and J have been reported in Vietnam and Laos [73], as well as in Ryukyu Islands (Japan) [74], respectively. On the other hand, HBV sub-genotyping was based on 4-8% nucleotide sequence differences and over 30 related sub-genotypes have been so far determined and reported in different geographical regions [75]. The HBV genotype variation is considered important in determining the clinical relevance in disease progression, infection outcome, response to antiviral treatment, and disease prognosis [76]. For example, variations in clinical outcome as well as response to interferon treatment have been found to be HBV genotype dependent. HBV genotype C and D infected patients having more severe outcomes than genotype A and B infected patients [76]. Likewise, hepatocellular carcinoma and liver cirrhosis are commonly diagnosed in patients infected with HBV genotype C and D more

than those with genotype A and B infection [76]. Some studies have shown that, patient with HBV genotype A and B infection are likely to respond to interferon treatment than patient infected with genotype C and D [77].

While HBV genotype A were found to be predominant in Europe (where the main subgenotype is A2), genotype B and C are mainly in East Asia, genotype D in North Africa, genotype E in West Africa, and genotype F and H dominate the Latin America (Figure 3) [70,71].

In Africa, HBV genotypes A, D and E have been so far as predominant genotypes, although few report involving B and C have been reported (Table 2) [71,78]. In terms of genotypes, HBV A genotype is found in almost all the sub-regions with the more diverse (4.00%) in Africa than compared to other continents (2.96%), thus suggesting an African origin [79]. Previously, the HBV A genotype have been classified into seven subgenotypes namely HBV A1, HBV A2, HBV A3, HBV A4, HBV A5, HBV A6, and HBV A7, although researchers proposed re-classification that will entails the combination of A3, A4, A5 and A7 as a quasisubgenotype A3 [80–82]. Now genotype A is classified as HBV A1, HBV A2, quasi-subgenotype

A3 (QS-A3) and HBV A4 [83]. However, the old classification is still used in the literature. The search for HBV of genotype A origin resulted in the identification of HBV A3 in Cameroon [84]; HBV A4 in Mali [85]; HBV A5 in Nigeria [85]; HBV A6 in African–Belgian patients [86], and more recently, HBV A7 has been identified and reported in patient from Cameroon [87]. HBV A1 subgenotypes are prevalent in sub-Saharan Africa, and A3 in West Africa [40,80]. The molecular characteristics of the African genotype A1 determine early clearance of HBeAg at transcription and translation level [88]. A1 subgenotype is mainly found in countries like Kenya, Tanzania, Malawi, Somalia, and South Africa [80]. In a recent study conducted among HIV infected women, Matthews et al. (2015), reported that HBV genotypes A1 and A2 were the predominantly identified subgenotypes, in Botswana and South Africa [89]. HBV subgenotype A1 is more likely to predisposed patient to hepatocellular carcinoma than other A-subgenotypes as reported in some studies [90,91]. HBV A2, the most frequent subgenotype in northwest Europe and has also being identified in South Africa [83,89], and this genotype appear to be associated with a lower risk of complications of HBV [92]. The third subgenotype A3 was first isolated in Cameroon, West Africa and found to show a nucleotide divergence of 3.9% and this subgenotype was further suggested to be a recombinant of hepatitis B and E viruses whose clinical consequences is yet to be determined [84]. Forbi et al. (2013) conducted a study across Côte d’Ivoire, Ghana, Cameroon and Uganda, which represent highly endemic countries in West, Central and East African subregions [93]. The authors, observed that, a prevalence rate of 12.9% HBV A infection in Côte D’Ivoire, 33.3% Cameroon, and 100% in Uganda. Further analysis revealed three different subgenotypes in Côte D’Ivoire of which 11.1% were of HBV A1, 33.3% were of HBV A2 and 55.6% were HBV A3. On the other hand, 100% of HBV A detected in Cameroon. In Uganda, 92.6% of HBV A strains belonged to HBV A1 and 7.4% were HBV A3.

Although genotype D is more prevalent in Southern Europe, the Middle East, and India, studies have reported genotypes D in Africa

especially in the Mediterranean and North African regions [70,71]. Currently 10 different HBV D subgenotypes have been described namely D1 to D10 [94]. Genotype D1, D7 and D3 have been reported in North and South African regions respectively, and D10 circulating in Ethiopia [95–97]. In fact, it was due to more than 4% sequence divergence observed from genotype D strains detected from Tunisian blood donors as compared to other known subgenotypes, genotype D7 was proposed, although evidence of recombination between D7 and genotype E HBV was implicated in this novel subgenotype [98]. Another important subgenotype reported in Africa is the HBV D8 identified in Niger in 2010 [99]. Like in the case of HBV D7 subgenotype, HBV D8 was also thought to be a result of intergenomic recombination between HBV D/E [99]. As with it is important to note that reclassifications (RS-D4, RS-D5, RS-D6, RS-D7, RS-D8, RS-D9) have been proposed taking into account recombinations for D7 subgenotypes in order to correct the misclassifications [82,100]. The clinical relevance genotype D infection is that both mutation and chronicity occur commonly in patient with genotype D infection compared to other genotypes. Therefore, patient infected with genotype D commonly progresses to HCC as reported with the HBV genotype C infection [101].

Hepatitis B genotype E infection is extremely rare, except in Africa [102–104]. Even when reported outside Africa, infection with this genotype has been almost exclusively to black patients with African descent [105]. Within Africa, HBV genotype E is prevalent and widespread throughout the vast “African Crescent” spanning from Africa’s west coast of Senegal of its southwestern part of Namibia and extending eastward to the Central African Republic [106]. Hepatitis B genotype E was first described in 1992 from a HBsAg-positive Cameroonian blood donor [107]. Forbi et al. have recently identified HBV E genotype in 87.1% infected pregnant women in Cote d’Ivoire, 66.7% in Cameroon, and 100% in the sampled population in Ghana [93]. Despite its widespread across Africa, HBV E has been reported to exhibit a very low genetic diversity and only few sequences from Democratic Republic of the Congo, Angola and Namibia could possibly

Table 2. African HBV genotype distribution.

Country	Isolate/strain	Accession*	Genotype	Country	Isolate/strain	Accession*	Genotype
Angola	8510-91	DQ060822	E	South Africa	N005v3	KF922416	A
Angola	8504-91	DQ060823	E	South Africa	N005v4	KF922417	A
Cameroon	CAE168	AM180624	A	South Africa	N005v5	KF922418	A
Cote d'Ivoire	ABI-129	AB091255	E	South Africa	N005v6	KF922419	A
Cote d'Ivoire	ABI-212	AB091256	E	South Africa	N005v7	KF922420	A
Gabon	FE-929-MO	EU054331	A	South Africa	N005v8	KF922421	A
Gambia	ik3346	AY934763	A	South Africa	3319v1	KF922422	A
Gambia	9210699	AY934764	A	South Africa	3319v2	KF922423	A
Ghana	HBV-GA325	AB106564	E	South Africa	4070v1	KF922424	A
Ghana	HBV-G758-2	AB205129	E	South Africa	4312v1	KF922426	A
Ghana	GH2537	GQ161753	rA/E	South Africa	4312v2	KF922427	A
Ghana	GH16	GQ161754	rE/D	South Africa	4312v3	KF922428	A
Guinea	GU1694	GQ161755	E	South Africa	3274v1	KF922429	A
Guinea	GU1684	GQ161756	E	South Africa	3274v2	KF922430	A
Guinea	GU1125	GQ161837	rA/E	South Africa	3274v3	KF922431	A
Guinea	GU1127	GQ161838	rA/E	South Africa	N011	KF922432	D
Kenya	KM2109	JQ927384	D	South Africa	3658v1	KF922433	A
Madagascar	235-01	DQ060830	E	South Africa	3658v2	KF922434	A
Mali	MAL36	AM180623	A	South Africa	N060v1	KF922435	A
Namibia	0121-20	DQ060824	E	South Africa	N060v2	KF922436	A
Namibia	0262-09	DQ060825	E	South Africa	N060v3	KF922437	A
Niger	bne6	FN594748	E	South Africa	PO04v1	KF922438	E
Niger	bne8	FN594749	E	South Africa	PO04v2	KF922439	E
Niger	bne127	FN594767	rE/D	South Africa	3358v1	KJ010776	A
Niger	bne272	FN594768	rE/D	South Africa	3358v2	KJ010777	A
Nigeria	A5_24063	FJ692554	A	South Africa	3358v3	KJ010778	A
Nigeria	A5_24074	FJ692555	A	South Africa	A1_G1862T_Mutant_SA	KM519452	A
Nigeria	29137	FN545825	A	South Africa	A1_Wild_SA	KM519453	A
Nigeria	C16	HM363567	E	South Africa	D3_WT_SA	KM519455	D
Nigeria	C98	HM363568	E	South Africa	A1-SA	KP234050	A
South Africa	41	AF297619	rA/D	South Africa	7983	U87742	A
South Africa	57	AF297620	rA/D	South Africa	7782	U87746	A
South Africa	78	AF297621	A	South Africa	Wong	U87747	B
South Africa	5283	AY233284	A	Sudan	SDAC_024	KF170739	D
South Africa	179	AY233291	D	Sudan	SDAC_031	KF170740	D
South Africa	184	AY233292	D	Sudan	SDAC_047	KF170741	E
South Africa	ZADGM50	GQ184325	C	Sudan	SDAC_125	KF170742	E
South Africa	ZADGM501	GQ184326	C	Sudan	SDAC_109	KF170777	rE/D
South Africa	3791v4	KF922409	A	Sudan	SDAC_016	KF170778	rE/D
South Africa	N199v1	KF922410	A	Sudan	SDAC_058	KF170779	E
South Africa	N199v2	KF922411	A	Sudan	SDAC_059	KF170780	E
South Africa	N199v3	KF922412	A	Sudan	SDH184overt A1	KM108588	A
South Africa	N199v4	KF922413	A	Zimbabwe	67 Mutare	HM535191	A
South Africa	N005v1	KF922414	A	Zimbabwe	797 Masvingo	HM535192	A
South Africa	N005v2	KF922415	A				

*Hepatitis B Virus database (<https://hbvdb.lyon.inserm.fr/HBVdb/>) and GenBank database (<https://www.ncbi.nlm.nih.gov/genbank/>).

be classified as a geographically unique HBV E cluster [106]. There was a low mean genetic diversity of around 1.5% when the preS/S and preC/C regions were considered, however, this mean slightly increase to 1.73% in terms of the intragenotype nucleotide divergence when the whole genome is taking into consideration. Several reports also confirmed the detection of recombinant HBV/E in African countries [106]. A recombination between A/E have been reported in Cameroon and Nigeria, A/D recombinant has been reported in Nigeria, D/E recombinant from Central African Republic [106]. Effort in tracing the possible route of HBV E entry into Africa became a subject of concern after finding that HBV E was probably absent from the Americas in the 19th century during the Afro-American slave trade [106].

Control and prevention of HBV in Africa

A yeast or mammalian cells derived recombinant hepatitis B vaccine was introduced in 1986 to address safety concerns of using the plasma-derived hepatitis B vaccine [108]. This vaccine has undergone thorough purification and incorporated with alum or thiomersal adjuvants

[109]. It's a subsequent version which is intended for the vaccinating adult patients with renal insufficiency, however, uses alum and lipid A as adjuvants [110]. With the introduction of new potent vaccines, the World Health Organization (WHO) set a goal for all countries to incorporate hepatitis B vaccination into their universal childhood vaccination programs. In 2001, about 126 (66%) of 191 WHO member states had complied with the universal infant or childhood hepatitis B vaccination programs as mandated by the WHO [111]. In 2014, 179 (93%) countries have added HBV vaccination to their routine vaccination programs with great results [112].

Conclusion

The burden of Hepatitis B infection still continues to grow in most of the African countries, this is in part due to lack of effective screening of blood donors, poor vaccination coverage, absence of well-equipped laboratories as well as a limited number of trained medical personnel in Africa. Control and prevention programs may also be adversely affected by, hunger, insecurity and other socioeconomic factors that are common in many African regions.

Conflict of interest: The author declares that there is no conflict of interest. The author alone is responsible for the content and writing of the paper. **Financial disclosure:** There is no financial support to this study.

References

1. Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. *Cancer* 1988; 61(10): 1942-56. [Crossref]
2. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet* 2015; 386(10003): 1546-55. [Crossref]
3. World Health Organization (WHO), Geneva, Switzerland. Hepatitis B. Available at: <https://www.who.int/news-room/fact-sheets/detail/hepatitis-b> [Accessed July 27, 2021].
4. Spearman CW, Afihene M, Ally R, Apica B, Awuku Y, Cunha L, et al; Gastroenterology and Hepatology Association of sub-Saharan Africa (GHASSA). Hepatitis B in sub-Saharan Africa: strategies to achieve the 2030 elimination targets. *Lancet Gastroenterol Hepatol* 2017; 2(12): 900-9. [Crossref]
5. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine* 2012; 30(12): 2212-9. [Crossref]
6. International Committee on Taxonomy of Viruses, Washington, DC. *Virus Taxonomy: 2020*, October. Available at: <https://talk.ictvonline.org/taxonomy/> [Accessed September 16, 2021].
7. Chen C, Jia H, Zhang F, Qin Y, Zong L, Yuan Q, et al. Functional characterization of hepatitis B virus core promoter mutants revealed transcriptional interference among co-terminal viral mRNAs. *J Gen Virol* 2016; 97(10): 2668-76. [Crossref]
8. Hayashi S, Nagaoka K, Tanaka Y. Blood-Based Biomarkers in Hepatitis B Virus-Related Hepatocellular Carcinoma, Including the Viral Genome and Glycosylated Proteins. *Int J Mol Sci* 2021; 22(20): 11051. [Crossref]
9. Lamontagne RJ, Bagga S, Bouchard MJ. Hepatitis B virus molecular biology and pathogenesis. *Hepatoma Res* 2016; 2: 163-86. [Crossref]

10. Romani S, Hosseini SM, Mohebbi SR, Boonstra A, Hosseini Razavi A, Sharifian A. Characterization of the "a" determinant region of the hepatitis B virus genome in Iranian patients at different clinical phases of chronic infection. *Gastroenterol Hepatol Bed Bench* 2018; 11(2): 131-7. [PubMed]
11. Şahiner F. Hepatitis B virus virion structure and genome organization. In: *tibbiviroloji.com, Türkiye*. Available at: <http://tibbiviroloji.com/4/tr/virology/en.1.HBV.virion.genom.png> [Accessed April 13, 2022].
12. Thomas HC, Lemon S, Zuckerman AJ. Viral Hepatitis. In: Kann M, Gerlich WH (eds), *Structure and molecular virology* (3rd edition). 2005, Blackwell Publishing, Oxford. pp:149-180.
13. Howard CR, Allison LM. Hepatitis B surface antigen variation and protective immunity. *Intervirology* 1995; 38(1-2): 35-40. [Crossref]
14. Waters JA, O'Rourke SM, Richardson SC, Papaevangelou G, Thomas HC. Qualitative analysis of the humoral immune response to the "a" determinant of HBs antigen after inoculation with plasma-derived or recombinant vaccine. *J Med Virol* 1987; 21(2): 155-60. [Crossref]
15. Gish RG, Basit SA, Ryan J, Dawood A, Protzer U. Hepatitis B Core Antibody: Role in Clinical Practice in 2020. *Curr Hepatology Rep* 2020; 19: 254-65. [Crossref]
16. Feitelson MA, Lee J. Hepatitis B virus integration, fragile sites, and hepatocarcinogenesis. *Cancer Lett* 2007; 252(2): 157-70. [Crossref]
17. Diao J, Garces R, Richardson CD. X protein of hepatitis B virus modulates cytokine and growth factor related signal transduction pathways during the course of viral infections and hepatocarcinogenesis. *Cytokine Growth Factor Rev* 2001; 12(2-3): 189-205. [Crossref]
18. Kew MC. Hepatitis B virus x protein in the pathogenesis of hepatitis B virus-induced hepatocellular carcinoma. *J Gastroenterol Hepatol* 2011; Suppl 1: 144-52. [Crossref]
19. Tong S, Revill P. Overview of hepatitis B viral replication and genetic variability. *J Hepatol* 2016; 64(1 Suppl): S4-S16. [Crossref]
20. Şahiner F. Cellular replication cycle of hepatitis B virus. In: *tibbiviroloji.com, Türkiye*. Available at: <http://tibbiviroloji.com/4/tr/virology/en.2.HBV.replicaton.png> [Accessed April 13, 2022].
21. Xia Y, Guo H. Hepatitis B virus cccDNA: Formation, regulation and therapeutic potential. *Antiviral Res* 2020; 180: 104824. [Crossref]
22. ViralZone, Swiss Institute of Bioinformatics, Switzerland. *Hepadnaviridae*. Available at: https://viralzone.expasy.org/30?outline=all_by_species [Accessed December 18, 2021].
23. Urban S, Schulze A, Dandri M, Petersen J. The replication cycle of hepatitis B virus. *J Hepatol* 2010; 52(2): 282-4. [Crossref]
24. MacLachlan JH, Cowie BC. Hepatitis B virus epidemiology. *Cold Spring Harb Perspect Med* 2015; 5(5): a021410. [Crossref]
25. Kwon SY, Lee CH. Epidemiology and prevention of hepatitis B virus infection. *Korean J Hepatol* 2011; 17(2): 87-95. [Crossref]
26. Aspinnall EJ, Hawkins G, Fraser A, Hutchinson SJ, Goldberg D. Hepatitis B prevention, diagnosis, treatment and care: a review. *Occup Med (Lond)* 2011; 61(8): 531-40. [Crossref]
27. Michielsen PP, Francque SM, van Dongen JL. Viral hepatitis and hepatocellular carcinoma. *World J Surg Oncol* 2005; 3: 27. [Crossref]
28. World Health Organization (WHO), Geneva, Switzerland. *Global Health Sector Strategy on Viral Hepatitis 2016–2021, Towards Ending Viral Hepatitis*. Available at: <https://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf> [Accessed December 27, 2021].
29. Büchner A, Du Plessis NM, Reynders DT, Omar FE, Mayaphi SH, Haeri Mazanderani AF, et al. Nosocomial outbreak of hepatitis B virus infection in a pediatric hematology and oncology unit in South Africa: Epidemiological investigation and measures to prevent further transmission. *Pediatr Blood Cancer* 2015; 62(11): 1914-9. [Crossref]
30. Lemoine M, Eholié S, Lacombe K. Reducing the neglected burden of viral hepatitis in Africa: strategies for a global approach. *J Hepatol* 2015; 62(2): 469-76. [Crossref]
31. Nelson NP, Easterbrook PJ, McMahon BJ. Epidemiology of Hepatitis B Virus Infection and Impact of Vaccination on Disease. *Clin Liver Dis* 2016; 20(4): 607-28. [Crossref]
32. Inoue T, Tanaka Y. Hepatitis B virus and its sexually transmitted infection - an update. *Microb Cell* 2016; 3(9): 420-37 [Crossref]
33. Tran TT. Management of hepatitis B in pregnancy: weighing the options. *Cleve Clin J Med* 2009; 76 Suppl 3: S25-9. [Crossref]
34. Borgia G, Carleo MA, Gaeta GB, Gentile I. Hepatitis B in pregnancy. *World J Gastroenterol* 2012; 18(34): 4677-83. [Crossref]
35. Biset Ayalew M, Adugna Horsa B. Hepatitis B Vaccination Status among Health Care Workers in a Tertiary Hospital in Ethiopia. *Hepat Res Treat* 2017; 2017: 6470658. [Crossref]
36. Te HS, Jensen DM. Epidemiology of hepatitis B and C viruses: a global overview. *Clin Liver Dis* 2010; 14(1): 1-21, vii. [Crossref]
37. Hwang EW, Cheung R. Global epidemiology of hepatitis B virus (HBV) infection. *N Am J Med Sci* 2011; 4(1): 7-13.
38. Ige TA, Hasford S, Tabakov S, Trauernicht CJ, Rule A, Azangwe G, et al. *Medical Physics Development in Africa - Status, Education, Challenges, Future*. Medical

Physics International 2020; 8(1) Special Issue, History of Medical Physics 3: 303-16.

39. World Health Organization (WHO), Geneva, Switzerland. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Available at: <https://www.who.int/publications/i/item/9789240027077> [Accessed December 27, 2021].

40. Assih M, Ouattara AK, Diarra B, Yonli AT, Compaore TR, Obiri-Yeboah D, et al. Genetic diversity of hepatitis viruses in West-African countries from 1996 to 2018. *World J Hepatol* 2018; 10(11): 807-21. [[Crossref](#)]

41. Abesig J, Chen Y, Wang H, Sompou FM, Wu IX. Prevalence of viral hepatitis B in Ghana between 2015 and 2019: A systematic review and meta-analysis. *PLoS One* 2020; 15(6): e0234348. [[Crossref](#)]

42. Ajuwon BI, Yujuico I, Roper K, Richardson A, Sheel M, Lidbury BA. Hepatitis B virus infection in Nigeria: a systematic review and meta-analysis of data published between 2010 and 2019. *BMC Infect Dis* 2021; 21(1): 1120. [[Crossref](#)]

43. Jaquet A, Wandeler G, Tine J, Diallo MB, Manga NM, Dia NM, et al. Prevention and Care of Hepatitis B in Senegal; Awareness and Attitudes of Medical Practitioners. *Am J Trop Med Hyg* 2017; 97(2): 389-95. [[PubMed](#)]

44. Sebastião CS, Neto Z, Jandondo D, Mirandela M, Morais J, Brito M. HIV, hepatitis B virus, hepatitis C virus, and syphilis among pregnant women attending antenatal care in Luanda, Angola: Seroprevalence and risk factors. *J Med Virol* 2020 [Epub ahead of print]. [[Crossref](#)]

45. Kodjoh N. Fighting viral hepatitis B and C in Africa. Focus on Benin. *Med Sante Trop* 2015; 25(2): 141-4. [[PubMed](#)]

46. Meda N, Tuailon E, Kania D, Tiendrebeogo A, Pisoni A, Zida S, et al. Hepatitis B and C virus seroprevalence, Burkina Faso: a cross-sectional study. *Bull World Health Organ* 2018; 96(11): 750-9. [[PubMed](#)]

47. Noubiap JJ, Joko WY, Nansseu JR, Tene UG, Siaka C. Sero-epidemiology of human immunodeficiency virus, hepatitis B and C viruses, and syphilis infections among first-time blood donors in Edéa, Cameroon. *Int J Infect Dis* 2013; 17(10): e832-7. [[Crossref](#)]

48. Apata IW, Averhoff F, Pitman J, Bjork A, Yu J, Amin NA, et al; Centers for Disease Control and Prevention (CDC). Progress toward prevention of transfusion-transmitted hepatitis B and hepatitis C infection--sub-Saharan Africa, 2000-2011. *MMWR Morb Mortal Wkly Rep* 2014; 63(29): 613-9. [[PubMed](#)]

49. Atipo-Ibara BI, Itoua-Ngaporo AN, Dzila-Lepfoundzou A, Ahoui-Apendi C, Deby-Gassaye C, Bossali F, et al. Hepatitis B virus in Congo (Brazzaville): prevalence and genetic diversity among blood donors in hyper endemic areas. *J Afr Hepato Gastroenterol* 2015; 9: 127-31. [[Crossref](#)]

50. Seri B, Minga A, Gabillard D, Dembele B, Konate S, Le Carrou J, et al. Twenty-Year Evolution of Hepatitis B Virus and Human Immunodeficiency Virus Prevalence and Incidence in Voluntary Blood Donors in Côte d'Ivoire. *Open Forum Infect Dis* 2018; 5(4): ofy060. [[Crossref](#)]

51. Ismail SA, Cuadros DF, Benova L. Hepatitis B in Egypt: A cross-sectional analysis of prevalence and risk factors for active infection from a nationwide survey. *Liver Int* 2017; 37(12): 1814-22. [[Crossref](#)]

52. Yazie TD, Tebeje MG. An updated systematic review and meta-analysis of the prevalence of hepatitis B virus in Ethiopia. *BMC Infect Dis* 2019; 19(1): 917. [[Crossref](#)]

53. Eko Mba JM, Bisseye C, Ntsame Ndong JM, Mombo LE, Bengone C, Mouelet Migolet G, et al. Prevalent hepatitis B surface antigen among first-time blood donors in Gabon. *PLoS One* 2018; 13(4): e0194285. [[Crossref](#)]

54. Bittaye M, Idoko P, Ekele BA, Obed SA, Nyan O. Hepatitis B virus sero-prevalence amongst pregnant women in the Gambia. *BMC Infect Dis* 2019; 19(1): 259. [[Crossref](#)]

55. Daw MA, El-Bouzedi A; In association with Libyan Study Group of Hepatitis & HIV. Prevalence of hepatitis B and hepatitis C infection in Libya: results from a national population based survey. *BMC Infect Dis* 2014; 14: 17. [[Crossref](#)]

56. Stockdale AJ, Mitambo C, Everett D, Geretti AM, Gordon MA. Epidemiology of hepatitis B, C and D in Malawi: systematic review. *BMC Infect Dis* 2018; 18(1): 516. [[Crossref](#)]

57. Jary A, Dienta S, Leducq V, Le Hingrat Q, Cisse M, Diarra AB, et al. Seroprevalence and risk factors for HIV, HCV, HBV and syphilis among blood donors in Mali. *BMC Infect Dis* 2019; 19(1): 1064. [[Crossref](#)]

58. Mansour W, Malick FZ, Sidiya A, Ishagh E, Chekaraou MA, Veillon P, et al. Prevalence, risk factors, and molecular epidemiology of hepatitis B and hepatitis delta virus in pregnant women and in patients in Mauritania. *J Med Virol* 2012; 84(8): 1186-98. [[Crossref](#)]

59. Cunha L, Plouzeau C, Ingrand P, Gudo JP, Ingrand I, Mondlane J, et al. Use of replacement blood donors to study the epidemiology of major blood-borne viruses in the general population of Maputo, Mozambique. *J Med Virol* 2007; 79(12): 1832-40. [[Crossref](#)]

60. Viegas EO, Tembe N, Macovela E, Gonçalves E, Augusto O, Ismael N, et al. Incidence of HIV and the prevalence of HIV, hepatitis B and syphilis among youths in Maputo, Mozambique: a cohort study. *PLoS One* 2015; 10(3): e0121452. [[Crossref](#)]

61. Makuza JD, Rwema JOT, Ntihakose CK, Dushimiyimana D, Umutesi J, Nisingizwe MP, et al. Prevalence of hepatitis B surface antigen (HBsAg) positivity and its associated factors in Rwanda. *BMC Infect Dis* 2019; 19(1): 381. [[Crossref](#)]

- 62.** Yambasu EE, Reid A, Owiti P, Manzi M, Murray MJS, Edwin AK. Hidden dangers-prevalence of blood borne pathogens, hepatitis B, C, HIV and syphilis, among blood donors in Sierra Leone in 2016: opportunities for improvement: a retrospective, cross-sectional study. *Pan Afr Med J* 2018; 30: 44. [[Crossref](#)]
- 63.** Samsunder N, Ngcapu S, Lewis L, Baxter C, Cawood C, Khanyile D, et al. Seroprevalence of hepatitis B virus: Findings from a population-based household survey in KwaZulu-Natal, South Africa. *Int J Infect Dis* 2019; 85: 150-7. [[Crossref](#)]
- 64.** Badawi MM, Atif MS, Mustafa YY. Systematic review and meta-analysis of HIV, HBV and HCV infection prevalence in Sudan. *Virology* 2018; 15(1): 148. [[Crossref](#)]
- 65.** Kirbak ALS, Ng'ang'a Z, Omolo J, Idris H, Usman A, Mbabazi WB. Sero-prevalence for Hepatitis B virus among pregnant women attending antenatal clinic in Juba Teaching Hospital, Republic of South Sudan. *Pan Afr Med J* 2017; 26: 72. [[Crossref](#)]
- 66.** Mueller A, Stoetter L, Kalluvya S, Stich A, Majinge C, Weissbrich B, et al. Prevalence of hepatitis B virus infection among health care workers in a tertiary hospital in Tanzania. *BMC Infect Dis* 2015; 15: 386. [[Crossref](#)]
- 67.** Kitandwe PK, Muyanja E, Nakaweesa T, Nanvubya A, Ssetaala A, Mpendo J, et al. Hepatitis B prevalence and incidence in the fishing communities of Lake Victoria, Uganda: a retrospective cohort study. *BMC Public Health* 2021; 21(1): 394. [[Crossref](#)]
- 68.** Vinikoor MJ, Sinkala E, Kanunga A, Muchimba M, Zanolini A, Saag M, et al. Eligibility for hepatitis B antiviral therapy among adults in the general population in Zambia. *PLoS One* 2020; 15(1): e0227041. [[Crossref](#)]
- 69.** Dzingirai B, Katsidzira L, Matyanga CMJ, Postma MJ, van Hulst M, Mafirakureva N. Progress on the elimination of viral hepatitis in Zimbabwe: A review of the policies, strategies and challenges. *J Viral Hepat* 2021; 28(7): 994-1002. [[Crossref](#)]
- 70.** Gerlich WH. Medical virology of hepatitis B: how it began and where we are now. *Virology* 2013; 10: 239. [[Crossref](#)]
- 71.** Liu Z, Zhang Y, Xu M, Li X, Zhang Z. Distribution of hepatitis B virus genotypes and subgenotypes: A meta-analysis. *Medicine (Baltimore)* 2021; 100(50): e27941. [[Crossref](#)]
- 72.** Fujiwara K. Novel Genetic Rearrangements in Hepatitis B Virus: Complex Structural Variations and Structural Variation Polymorphisms. *Viruses* 2021; 13(3): 473. [[Crossref](#)]
- 73.** Tran TT, Trinh TN, Abe K. New complex recombinant genotype of hepatitis B virus identified in Vietnam. *J Virol* 2008; 82(11): 5657-63. [[Crossref](#)]
- 74.** Tatematsu K, Tanaka Y, Kurbanov F, Sugauchi F, Mano S, Maeshiro T, et al. A genetic variant of hepatitis B virus divergent from known human and ape genotypes isolated from a Japanese patient and provisionally assigned to new genotype J. *J Virol* 2009; 83(20): 10538-47. [[Crossref](#)]
- 75.** Sunbul M. Hepatitis B virus genotypes: global distribution and clinical importance. *World J Gastroenterol* 2014; 20(18): 5427-34. [[Crossref](#)]
- 76.** Lin CL, Kao JH. Hepatitis B virus genotypes and variants. *Cold Spring Harb Perspect Med* 2015; 5(5): a021436. [[Crossref](#)]
- 77.** Seo Y, Yano Y. Short- and long-term outcome of interferon therapy for chronic hepatitis B infection. *World J Gastroenterol* 2014; 20(37): 13284-92. [[Crossref](#)]
- 78.** Kurbanov F, Tanaka Y, Mizokami M. Geographical and genetic diversity of the human hepatitis B virus. *Hepatology* 2010; 40(1): 14-30. [[Crossref](#)]
- 79.** Andernach IE, Hübschen JM, Müller CP. Hepatitis B virus: the genotype E puzzle. *Rev Med Virol* 2009; 19(4): 231-40. [[Crossref](#)]
- 80.** Lago BV, Mello FC, Kramvis A, Niel C, Gomes SA. Hepatitis B virus subgenotype A1: evolutionary relationships between Brazilian, African and Asian isolates. *PLoS One* 2014; 9(8): e105317. [[Crossref](#)]
- 81.** Shi W, Zhang Z, Ling C, Zheng W, Zhu C, Carr MJ, et al. Hepatitis B virus subgenotyping: history, effects of recombination, misclassifications, and corrections. *Infect Genet Evol* 2013; 16: 355-61. [[Crossref](#)][81]
- 82.** Pourkarim MR, Amini-Bavil-Olyaei S, Kurbanov F, Van Ranst M, Tacke F. Molecular identification of hepatitis B virus genotypes/subgenotypes: revised classification hurdles and updated resolutions. *World J Gastroenterol* 2014; 20(23): 7152-68. [[Crossref](#)]
- 83.** de Pina-Araujo IIM, Spitz N, Soares CC, Niel C, Lago BV, Gomes SA. Hepatitis B virus genotypes A1, A2 and E in Cape Verde: Unequal distribution through the islands and association with human flows. *PLoS One* 2018; 13(2): e0192595. [[Crossref](#)]
- 84.** Kurbanov F, Tanaka Y, Fujiwara K, Sugauchi F, Mbanya D, Zekeng L, et al. A new subtype (subgenotype) Ac (A3) of hepatitis B virus and recombination between genotypes A and E in Cameroon. *J Gen Virol* 2005; 86(Pt 7): 2047-56. [[Crossref](#)]
- 85.** Olinger CM, Venard V, Njajou M, Oyefolu AOB, Maïga I, Kemp AJ, et al. Phylogenetic analysis of the precore/core gene of hepatitis B virus genotypes E and A in West Africa: new subtypes, mixed infections and recombinations. *J Gen Virol* 2006; 87(Pt 5): 1163-73. [[Crossref](#)]
- 86.** Pourkarim MR, Lemey P, Amini-Bavil-Olyaei S, Maes P, Van Ranst M. Novel hepatitis B virus subgenotype A6 in African-Belgian patients. *J Clin Virol* 2010; 47(1): 93-6. [[Crossref](#)]
- 87.** Hübschen JM, Mbah PO, Forbi JC, Otegbayo JA, Olinger CM, Charpentier E, et al. Detection of a new subgenotype of hepatitis B virus genotype A in

Cameroon but not in neighbouring Nigeria. *Clin Microbiol Infect* 2011; 17(1): 88-94. [[Crossref](#)]

88. Hadziyannis SJ. Natural history of chronic hepatitis B in Euro-Mediterranean and African countries. *J Hepatol* 2011; 55(1): 183-91. [[Crossref](#)]

89. Matthews PC, Beloukas A, Malik A, Carlson JM, Jooste P, Ogwu A, et al. Prevalence and Characteristics of Hepatitis B Virus (HBV) Coinfection among HIV-Positive Women in South Africa and Botswana. *PLoS One* 2015; 10(7): e0134037. [[Crossref](#)]

90. Gopalakrishnan D, Keyter M, Shenoy KT, Leena KB, Thayumanavan L, Thomas V, et al. Hepatitis B virus subgenotype A1 predominates in liver disease patients from Kerala, India. *World J Gastroenterol* 2013; 19(48): 9294-306. [[Crossref](#)]

91. Kramvis A, Kew MC. Molecular characterization of subgenotype A1 (subgroup Aa) of hepatitis B virus. *Hepatol Res* 2007; 37(s1): S27-32. [[Crossref](#)]

92. McMahon BJ. The influence of hepatitis B virus genotype and subgenotype on the natural history of chronic hepatitis B. *Hepatol Int* 2009; 3(2): 334-42. [[Crossref](#)]

93. Forbi JC, Ben-Ayed Y, Xia GL, Vaughan G, Drobeniuc J, Switzer WM, et al. Disparate distribution of hepatitis B virus genotypes in four sub-Saharan African countries. *J Clin Virol* 2013; 58(1): 59-66. [[Crossref](#)]

94. Khatun M, Mondal RK, Pal S, Baidya A, Bishnu D, Banerjee P, et al. Distinctiveness in virological features and pathogenic potentials of subgenotypes D1, D2, D3 and D5 of Hepatitis B virus. *Sci Rep* 2018; 8(1): 8055. [[Crossref](#)]

95. Matlou MK, Gaelejwe LR, Musyoki AM, Rakgole JN, Selabe SG, Amponsah-Dacosta E. A novel hepatitis B virus recombinant genotype D4/E identified in a South African population. *Heliyon* 2019; 5(4): e01477. [[Crossref](#)]

96. Hundie GB, Stalin Raj V, Gebre Michael D, Pas SD, Koopmans MP, Osterhaus AD, et al. A novel hepatitis B virus subgenotype D10 circulating in Ethiopia. *J Viral Hepat* 2017; 24(2): 163-73. [[Crossref](#)]

97. Zampino R, Boemio A, Sagnelli C, Alessio L, Adinolfi LE, Sagnelli E, et al. Hepatitis B virus burden in developing countries. *World J Gastroenterol* 2015; 21(42): 11941-53. [[Crossref](#)]

98. Meldal BHM, Moula NM, Barnes IHA, Boukef K, Allain JP. A novel hepatitis B virus subgenotype, D7, in Tunisian blood donors. *J Gen Virol* 2009; 90(Pt 7): 1622-8. [[Crossref](#)]

99. Abdou Chekaraou M, Brichler S, Mansour W, Le Gal F, Garba A, Dény P, et al. A novel hepatitis B virus (HBV) subgenotype D (D8) strain, resulting from recombination between genotypes D and E, is circulating in Niger along with HBV/E strains. *J Gen Virol* 2010; 91(Pt 6): 1609-20. [[Crossref](#)]

100. Kostaki EG, Karamitros T, Stefanou G, Mamais I, Angelis K, Hatzakis A, et al. Unravelling the history of hepatitis B virus genotypes A and D infection using a

full-genome phylogenetic and phylogeographic approach. *Elife* 2018; 7: e36709. [[Crossref](#)]

101. Shi YH. Correlation between hepatitis B virus genotypes and clinical outcomes. *Jpn J Infect Dis* 2012; 65(6): 476-82. [[Crossref](#)]

102. Odemuyiwa SO, Mulders MN, Oyedele OI, Ola SO, Odaibo GN, Olaleye DO, et al. Phylogenetic analysis of new hepatitis B virus isolates from Nigeria supports endemicity of genotype E in West Africa. *J Med Virol* 2001; 65(3): 463-9. [[PubMed](#)]

103. Suzuki S, Sugauchi F, Orito E, Kato H, Usuda S, Siransy L, et al. Distribution of hepatitis B virus (HBV) genotypes among HBV carriers in the Cote d'Ivoire: complete genome sequence and phylogenetic relatedness of HBV genotype E. *J Med Virol* 2003; 69(4): 459-65. [[Crossref](#)]

104. Bekondi C, Olinger CM, Boua N, Talarmin A, Muller CP, Le Faou A, et al. Central African Republic is part of the West-African hepatitis B virus genotype E crescent. *J Clin Virol* 2007; 40(1): 31-7. [[Crossref](#)]

105. Cuenca-Gómez JÁ, Lozano-Serrano AB, Cabezas-Fernández MT, Soriano-Pérez MJ, Vázquez-Villegas J, Estévez-Escobar M, et al. Chronic hepatitis B genotype E in African migrants: response to nucleos(t)ide treatment in real clinical practice. *BMC Infect Dis* 2018; 18(1): 568. [[Crossref](#)]

106. Hübschen JM, Andernach IE, Muller CP. Hepatitis B virus genotype E variability in Africa. *J Clin Virol* 2008; 43(4): 376-80. [[Crossref](#)]

107. Norder H, Hammas B, Löfdahl S, Couroucé AM, Magnus LO. Comparison of the amino acid sequences of nine different serotypes of hepatitis B surface antigen and genomic classification of the corresponding hepatitis B virus strains. *J Gen Virol* 1992; 73(Pt 5): 1201-8. [[Crossref](#)]

108. André FE. Summary of safety and efficacy data on a yeast-derived hepatitis B vaccine. *Am J Med* 1989; 87(3A): 14S-20S. [[Crossref](#)]

109. Zhao H, Zhou X, Zhou YH. Hepatitis B vaccine development and implementation. *Hum Vaccin Immunother* 2020; 16(7): 1533-44. [[Crossref](#)]

110. Beran J. Safety and immunogenicity of a new hepatitis B vaccine for the protection of patients with renal insufficiency including pre-haemodialysis and haemodialysis patients. *Expert Opin Biol Ther* 2008; 8(2): 235-47. [[Crossref](#)]

111. World Health Organization (WHO), Geneva, Switzerland. WHO: Vaccines and Biologicals: WHO Vaccine-preventable Diseases: Monitoring System: 2002 Global Summary: Department of Vaccines and Other Biologicals, World Health Organization; 2002. [https://apps.who.int/immunization_monitoring/global_summary/]

112. Meireles LC, Marinho RT, Van Damme P. Three decades of hepatitis B control with vaccination. *World J Hepatol* 2015; 7(18): 2127-32. [[Crossref](#)]