

# World Journal of *Hepatology*

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*World Journal of Hepatology* (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

*WJH* covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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## Genetic diversity of hepatitis viruses in West-African countries from 1996 to 2018

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### Abstract

The severity of hepatic pathology and the response to treatment depend on the hepatitis virus genotype in the infected host. The objective of this review was to determine the distribution of hepatitis virus genotypes in West African countries. A systematic review of the literature in PubMed, Google Scholar and Science Direct was performed to identify 52 relevant articles reporting hepatitis A, B, C, D, E and G viruses genotypes.



Hepatitis B virus (HBV) genotype E with a prevalence of 90.6% (95%CI: 0.891-0.920) found in this review, is characterized by low genetic diversity. Hepatitis C virus (HCV) genotypes 1 and 2 represented 96.4% of HCV infections in West African countries, while hepatitis delta virus, hepatitis A virus, hepatitis G virus genotypes 1 and HEV genotype 3 were reported in some studies in Ghana and Nigeria. HBV genotype E is characterized by high prevalence, low genetic diversity and wide geographical distribution. Further studies on the clinical implications of HBV genotype E and HCV genotypes 1 and 2 are needed for the development of an effective treatment against this viral hepatitis in West African countries. Surveillance of the distribution of different genotypes is also needed to reduce recombination rates and prevent the emergence of more virulent viral strains.

**Key words:** Hepatitis virus; Mutations; Genotypes; Recombination; West African Economic and Monetary Union

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**Core tip:** The determination of hepatitis viruses genotypes is very important for the management and treatment of infected patients. Indeed, mutation development, disease progression and antiretroviral response are all dependent on the genotype of the infecting virus. Genotype determination is therefore very important to identify patients who are at increased risk of disease progression and to optimize treatment. The objective of this review was to determine the prevalence and distribution of different hepatitis viruses genotypes in 10 West African countries.

Assih M, Ouattara AK, Diarra B, Yonli AT, Compaore TR, Obiri-Yeboah D, Djigma FW, Karou S, Simpore J. Genetic diversity of hepatitis viruses in West-African countries from 1996 to 2018. *World J Hepatol* 2018; 10(11): 807-821 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v10/i11/807.htm> DOI: <http://dx.doi.org/10.4254/wjh.v10.i11.807>

## INTRODUCTION

Viral hepatitis is an inflammation of the liver that may progress spontaneously to healing or lead to cirrhosis or hepatocellular carcinoma (HCC). Viral hepatitis caused 1.34 million deaths in 2015, a figure comparable to deaths from tuberculosis (TB) and human immunodeficiency virus (HIV). However, mortality attributable to TB and HIV is decreasing, while that due to hepatitis is constantly increasing<sup>[1]</sup>. There are five types of hepatitis viruses designated by the letters A, B, C, D and E. The most common forms of the disease are hepatitis A, B and C. Another human lymphotropic virus belonging to the Flaviviridae family and closely related to hepatitis C virus (HCV) was identified as hepatitis G

virus (HGV) or GB virus C (GBV-C). However, several studies have shown that GBV-C/HGV infection is not clearly associated with any disease and may play a role in modulating HIV disease<sup>[2,3]</sup>. In a study conducted in Burkina Faso, a prevalence of 7.4% of HGV was reported in blood donors<sup>[4]</sup>. Viral hepatitis usually occurs as a result of parenteral contact with infected body fluids: Blood transfusions or contaminated blood products.

Hepatitis B virus (HBV) is ubiquitous, but the prevalence of infection varies across different regions of the world. According to the World Health Organization, about two billion people have been in contact with HBV worldwide, with more than 240 million cases of chronic infections<sup>[5]</sup>. About 80 to 120 million cases of chronic HBV infection occur in sub-Saharan Africa<sup>[6,7]</sup>. According to the carriage of hepatitis B surface antigen (HBsAg), there are zones of low endemicity (< 2%) such as Western Europe or North America; areas of average prevalence (2%-7%) such as North Africa or Eastern Europe and finally high endemic areas (> 8%) such as West Africa or Southeast Asia<sup>[8]</sup>. Indeed, hepatitis B is highly endemic in West Africa, with the highest prevalence in the world (> 8%). In sub-Saharan Africa, about 47% of HCC have been attributed to HBV<sup>[9]</sup>. Despite the availability of a vaccine, HBV remains a major public health problem, with approximately 686 thousand deaths per year worldwide due to the consequences (cirrhosis and HCC) of this infection<sup>[5]</sup>.

More than 71 million people worldwide are chronically infected with HCV and may develop liver cirrhosis and/or HCC<sup>[10]</sup>. There is currently no effective vaccine against HCV; and about 399000 people die each year from hepatitis C, mainly cirrhosis and HCC. In North and West Africa, the prevalence of HCV infection ranges from 0.5% to 1.0%<sup>[10]</sup>. Hepatitis delta virus (HDV) is a small defective ribonucleic acid (RNA) virus that depends on HBV for the assembly of new virions and proliferation of infection to hepatocytes. HDV infection can be therefore prevented through vaccination or any strategy to eliminate HBV infection. Approximately 15 to 20 million people worldwide are co-infected with these two viruses, with a high risk of severe liver disease<sup>[11]</sup>. In a study of pregnant women in Benin, the prevalence of HDV was 11.4% in 15.5% of HBsAg-positive individuals<sup>[12]</sup>.

There are several genotypes of hepatitis viruses with different clinical implications and distinct geographic distributions. HBV is classified into 10 genotypes (A-J) and about 40 subgenotypes with a correlation between genotypes and their modes of transmission<sup>[13]</sup>. In fact, HBV genotype A is found in North America, Europe, South-East Africa and India; genotypes B and C in Asia and Oceania while genotype D is the most common in North America, North Africa, Europe, the Middle-East and Oceania. HBV genotype E is hyperendemic in West Africa; genotype F is found in

South America; and genotypes G and H are in Central and South America<sup>[13]</sup>. HCV has a high genetic diversity with a predominance of genotype 1 and 3 worldwide. The endemic strains of genotypes 1 and 2 are mainly found in West Africa, genotype 3 in Asia, genotypes 4 in Central Africa and the Middle East, while genotypes 5 and 6 are predominant in South Africa and South East Asia, respectively<sup>[14]</sup>. HCV genotype 2 is the most common genotype in West African countries, followed by genotype 1 and genotype 3<sup>[15]</sup>. HDV genotype I is more common in Europe and North America, genotype II is predominant in the Far East and Japan while genotype III is predominant in the Amazonian area and northern South America<sup>[16]</sup>.

The severity of hepatic pathology and the response to treatment depend on the virus genotype in the infected host. For example, HBV genotype A infection tends to chronicity, whereas genotype D has a high frequency of mutation influencing response to treatment. Liver cirrhosis and progression to HCC are strongly associated with HBV genotypes C and D compared to other genotypes<sup>[17,18]</sup>. Furthermore, superinfection of chronic HBV patients by HDV leads to increased liver damage and more rapid progression of cirrhosis in 90% of cases<sup>[16]</sup>. HDV genotype III is thought to be associated with severe forms of liver disease, while a more moderate clinical evolution and a wide variety of clinical conditions are observed with genotypes II and I, respectively. The response to interferon treatments is more effective against HBV genotypes A and B compared to genotypes C, D and I. HBV genotype E seems to have the worst response to treatment<sup>[18]</sup>. Rapid progression of hepatic disease and HCC has also been associated with HBV genotype A1<sup>[13]</sup>. HCV subtype 1b is associated with a high risk of developing HCC compared to other genotypes<sup>[19]</sup>. Early generations of vaccines protected against subtype 1b, while genotype 3, which accounts for 30.1% of HCV global infections, is less likely to respond to first and second generation direct-acting antivirals currently used for HCV treatment<sup>[14,20]</sup>.

Determination of the viral genotype is an essential element of the pre-therapeutic assessment, because it is one of the predictors of the response to treatment and determines the choice of molecules used with the new anti-HCV treatments. It has also been shown that HBV genotypes differ according to disease course, mutation development and response to anti-viral therapy<sup>[21]</sup>. Indeed, genotype determination is important to identify patients who are at increased risk of disease progression and to optimize treatment<sup>[22]</sup>. Here, we review various publications on the genotypes of hepatitis viruses in West African countries [West African Economic and Monetary Union (WAEMU) countries, Ghana and Nigeria] in order to map the genotypes distribution and discuss the infections associated with the different viruses identified.

## HEPATITIS VIRUSES' INFECTION IN WEST AFRICA

### HBV infection

HBV belongs to the *Hepadnaviridae* family and the *Orthohepadnavirus* genus<sup>[23]</sup>. It is a double-stranded circular DNA enveloped virus of small circumference (1.6 million Dalton) associated with a DNA-dependent DNA polymerase that acts as a reverse transcriptase during replication. HBV is highly contagious, 100 times more contagious than HIV and can remain stable at 25 °C for seven days in dried blood. Sexual, parenteral (through the blood), mother-to-child or even close intrafamily non-sexual contact over a long period of time are the different modes of infection. The most common modes of spread of hepatitis B in endemic areas are mother-to-child transmission and exposure to infected blood. The appearance of a chronic infection is very common for infants infected by their mother before the age of 5 years.

Markers, such as the HBsAg, the HBs antibody (anti-HBs), the core antigen (HBcAg), the HBe antigen (HBeAg) and the HBe antibody (anti-HBe) make it possible to monitor the evolution of this virus. Despite the small size of the genome and the constraints imposed by its organization, HBV is highly variable.

HBV strains are divided into several genotypes. These genotypes are defined by a divergence of at least 8.0% of the whole genome nucleotide sequence and at least 4.1% in the S gene<sup>[24]</sup>. The main genotypes were divided into subgenotypes based on the divergence between 4.1% and 8.0% of their complete nucleotide sequence<sup>[25]</sup>. In the last decade, phylogenetic studies of sequences of different viral genomes have tentatively classified HBV into 10 genotypes (A-J)<sup>[26]</sup>. Genotypes and subgenotypes have a distinct geographic distribution<sup>[27]</sup>. Genotype A is the only predominant genotype in East Africa, where the prevalence of other genotypes is less than 5%<sup>[24,28]</sup>. The subgenotype A1 is predominant in Africa, while subgenotypes A3-A6 are found in Central and West Africa<sup>[29]</sup>.

Subgenotype D1 is highly prevalent in East Africa<sup>[30]</sup>; D7 has been isolated in Tunisia<sup>[31]</sup>; and D8 has been characterized in Niger<sup>[32]</sup>. West Africa is the main focus of genotype E. Vaccination is the safest way to prevent HBV infection<sup>[33]</sup>. Major advances in the treatment of chronic HBV have been made with the development of nucleoside reverse transcriptase inhibitors with anti-HBV activity, such as L-nucleosides (lamivudine 3TC) or alkylphosphates (tenofovir disoproxil fumarate)<sup>[34]</sup>.

### HCV infection

HCV belongs to the family *Flaviviridae* and the genus *hepacivirus*<sup>[35]</sup>. HCV mainly infects hepatocytes but may also be present in blood mononuclear cells and dendritic cells<sup>[36]</sup>. HCV is a small single-stranded RNA virus of positive polarity, enveloped 55-65 nm in diameter.

Parenteral route is the major mode of transmission of HCV. Transfusion and intravenous drug addiction are also routes of transmission. To this day, the main cause of HCV transmission in developed countries is drug abuse<sup>[37]</sup>. The HCV genome shows a high rate of mutations with considerable genetic heterogeneity of the virus in infected people worldwide. Phylogenetic approaches made it possible to classify HCV into 11 major genotypes (designated by the Arabic numerals from 1 to 11), with many subtypes (indicated by lower case letters a, b, c, etc.)<sup>[38]</sup>.

Subgenotypes 1a, 1b, 2a, 2b and 3a are widely distributed worldwide<sup>[39]</sup>, while 5a and 6a are common in South Africa and Southeast Asia<sup>[40,41]</sup>. Genotype 4 is predominant in Central Africa<sup>[42,43]</sup> and in North Africa<sup>[44]</sup>. In Africa, divergent HCV genotype 1 and 2 strains were found endemic in the West African subregion<sup>[45-47]</sup>. Recently, analysis of the epidemic history of HCV infections has traced modern HCV lines in West Africa to the 17<sup>th</sup> and 20<sup>th</sup> centuries<sup>[46]</sup>. The current standard treatment for chronic infection is the combination of pegylated interferon alpha (pegIFN $\alpha$ ) and ribavirin (RBV)<sup>[48]</sup>. Currently, new therapeutic approaches using direct-acting antivirals have been developed for the treatment of chronic hepatitis C. These molecules inhibit certain stages of the viral cycle and prevent the production of viral particles by infected hepatocytes.

#### **Others hepatitis virus infection (HDV and HGV)**

**HDV infection:** HDV is an infectious agent that can only infect patients previously or simultaneously infected with the HBV<sup>[49]</sup>. It is a single-stranded RNA negative polarity virus, 1700 nucleotides in size, which encodes a single structural protein, the hepatitis delta antigen (HDAg), and requires HBV to replicate. HDV infection can only occur with simultaneous coinfection with HBV or superinfection<sup>[1]</sup>. HDV transmission is predominantly parenteral, and the sexual route is less effective than HBV. Mother-to-child transmission is rare. Hepatitis D is a liver disease that can take the acute form and chronic form. There can be no hepatitis D in the absence of HBV. Co-infection with HBV or HDV superinfection results in more severe disease than HBV mono-infection<sup>[1]</sup>. HDV infection is diagnosed by high titers of immunoglobulin G (IgG) and immunoglobulin M (IgM) anti-HDV and confirmed by serum detection of HDV RNA by polymerase chain reaction<sup>[1]</sup>. HDV isolates in the world are divided into at least eight phylogenetically distinct genotypes<sup>[50]</sup>.

Genotype 1 is the predominant form of HDV with worldwide distribution, while genotypes 2 and 4 are present in Japan and Taiwan and are often associated with a milder form of disease<sup>[50]</sup>. Genotype 3 has been reported in the Amazonian region<sup>[51]</sup>. Genotypes 5-8 were detected in the sera of patients of African origin<sup>[52]</sup>. In addition, genotype 8 infection was also

detected in the state of Maranhão in northeastern Brazil<sup>[53]</sup>. Some studies have shown that genotypes 3 and 4 can be associated with particularly severe clinical forms of hepatitis (fulminant hepatitis)<sup>[51]</sup>. HDV infection is rarely studied in West Africa despite the high prevalence of HBV. There is currently no effective antiviral therapy for hepatitis D. The prevention of hepatitis D involves vaccination against hepatitis B. pegIFN $\alpha$  is the only effective anti-HDV drug; nucleoside analogues active against HBV have little or no effect on HDV replication<sup>[1]</sup>.

**HGV infection:** The HGV, called GBV-C or HGV, is a flavivirus, such as HCV, that causes spontaneously resolving acute hepatitis or fulminant hepatitis. It can cause chronic infections. HGV is a single-stranded positive-strand RNA virus<sup>[54]</sup>. Its transmission is mainly parenteral. Maternal-fetal and sexual transmissions are higher than those seen with HCV. IFN is effective in normalizing hypertransaminasemia in infected patients, but relapse appears to be common when treatment is discontinued.

## **METHODOLOGY**

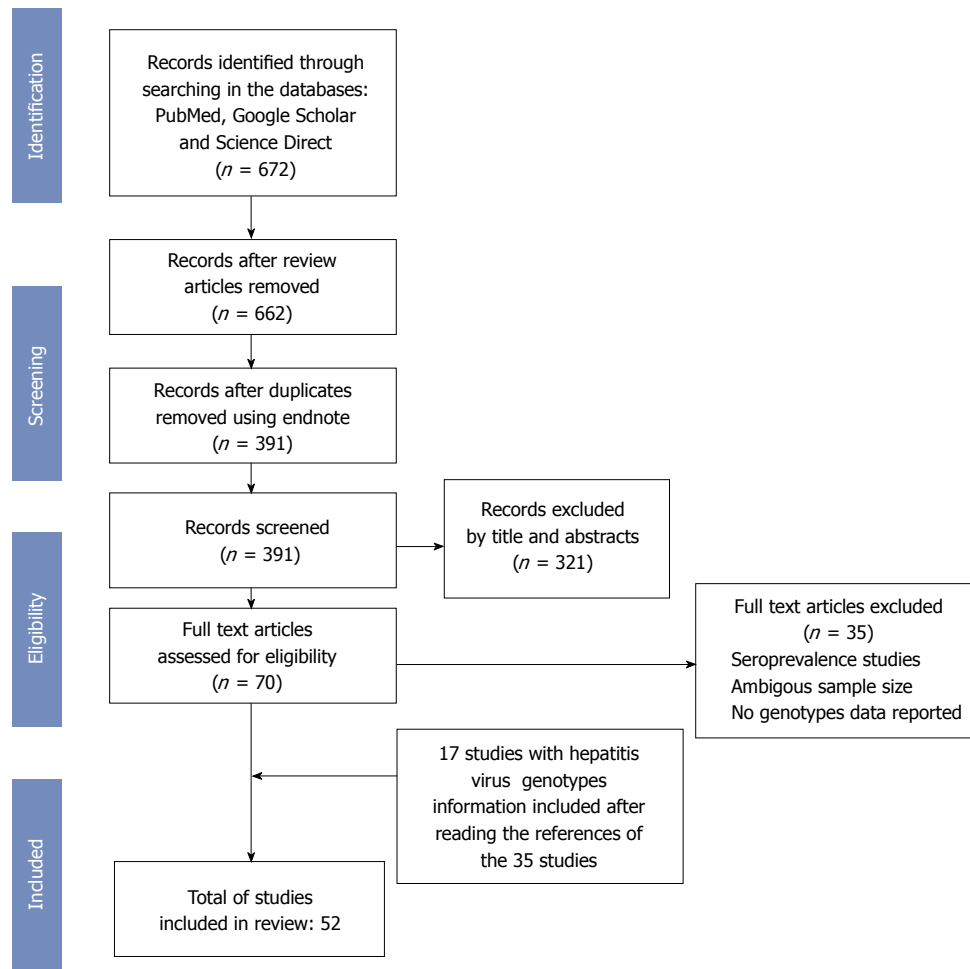
### **Research strategy and selection criteria**

A systematic review of the literature was conducted to identify relevant articles reporting genotypes of hepatitis viruses in WAEMU countries including Ghana and Nigeria from 1996 to 2018. The research was conducted in French and/or English in three databases: PubMed, Google Scholar and Science Direct. The keywords used were "HBV and/or HBV and other viruses "+" the name of each of the 10 countries included in the study". A filter limiting the search for keywords in the title and/or abstract of articles was used [PubMed: (tiab); Google Scholar: Allintitle and Science Direct: TITLE-ABSTR-KEY]. Searches with similar terms such as "hepatitis virus", "hepatitis virus", "hepatitis virus genotypes" or "hepatitis virus genotype" were also conducted.

The studies were then selected on the basis of the following criteria: (1) data published in a peer-reviewed scientific journal; (2) only patients residing in one of the WAEMU countries, Ghana or Nigeria; and (3) patients from these countries infected with hepatitis viruses whose genotypes have been identified. All scientific publications (52) that reported data on genotypes of hepatitis viruses in populations from WAEMU countries, Ghana and Nigeria, between 1996 and 2018 and met the selection criteria were included in this systematic review (Figure 1). Eligible studies had to report the genotype of viral hepatitis in populations from included countries regardless of method used for viremia detection. Both risk groups or general population were eligible for inclusion.

HBV and HCV viremia detection were based on





**Figure 1** Flow diagram showing the method for the study selection. The database search for the search strategy described in the section was cleaned up to exclude review articles and duplicates. Titles and abstracts were included in the literature review. Seroprevalence articles, articles with ambiguous data that did not meet the inclusion criteria were then excluded during the full-text review. Fifty-two (52) relevant articles were finally included for this review.

DNA/RNA amplification. Genotypes detection was performed using polymerase chain reaction or direct sequencing. HCV genotype classification was considered because in many studies, HCV cases were classified at the genotype level but not at the subtype level. Journal articles, publisher correspondence, news, letters, book chapters and studies whose data were ambiguous or could not be extracted were systematically excluded. The search and selection of the relevant articles in the three databases were carried out by two independent reviewers. The inclusion of a study by both reviewers was a requirement. In case of disagreement on the eligibility of a study, the problem was solved through a discussion and/or consensus with a third reviewer.

### Extractions of data and analysis

The genotyping data were extracted from the different studies carried out in Ghana, Nigeria and WAEMU countries. The data extracted from the various studies included in this review are: The first author, the year of the data publication, the study population, the type of study or data collection (prospective or retrospective),

the country, the number of samples successfully genotyped and the results of identified genotypes.

In multi-center studies, only data from the countries included in this mini-review were considered. Prevalence was determined by making the ratio of the genotype considered to the total number of samples tested for that genotype. Confidence intervals were calculated using the R software. Phylogenetic analysis was performed with 53 HBV sequences using the neighbor-joining algorithm based on the Kimura two-parameter distance estimation method. Only bootstrap values of > 80% are shown (1.000 replicates). The maps were made using genotyping data from each country (source: Dr. Ouattara AK).

## SEARCH RESULTS

### Selection of studies

The initial search in the three databases, according to the search strategy described in the methodology, found 391 articles after elimination of reviews and duplicates. Examination of titles and abstracts led

to the elimination of 321 studies that did not meet the inclusion criteria of this review. Only 70 studies were considered eligible after full text review. This step allowed the exclusion of 35 articles presenting data reporting only seroprevalences or presenting ambiguous genotyping data. Finally, 52 studies, 35 of which were obtained after the full text examination and 17 after references examination of the 35 articles selected, were included in this systematic review.

### Characteristics of included studies

Tables 1 and 2 present the characteristics of the different studies included in this systematic review. The majority of included studies used a prospective method of sample collection. A case-control study, two Cas reports, two multi-center studies and four cohort studies were included in the review, while the rest were cross-sectional or prospective studies. Twelve studies were performed in HIV-infected individuals compared to 11 in blood donors and seven in pregnant women, while populations and age groups were variable for the rest of the studies.

### HBV genotypes

The frequency of the different genotypes was determined by dividing the number of samples presenting the genotype considered by the total number of successfully sequenced samples. In this systematic review, the largest number of successfully sequenced samples were recorded in Ghana (457/1620), followed by Nigeria (269/1620) and Côte d'Ivoire (251/1620). Genotyping studies of hepatitis viruses were rare in Guinea-Bissau and almost non-existent in Togo. The HBV genotype E was the predominantly isolated genotype in the various studies conducted in the WAEMU countries, Ghana and Nigeria (Table 1).

Indeed, out of a total of 1620 successfully sequenced HBV samples, E genotypes were individually isolated in 90.6% (1468/1620, 95%CI: 0.891-0.920) of HBV infection cases. In addition, its prevalence of recombination or coinfection with genotypes A and D was estimated at 0.86% (14/1620, 95%CI: 0.005-0.014) in our study area. HBV genotype E is characterized by low genetic diversity compared to other genotypes, including genotype A (Figure 2). The second HBV genotype reported in terms of frequency in the countries included in this review was genotype A with an individual prevalence of 7.8% (126/1620, 95%CI: 0.065-0.092), while a prevalence of 0.74% (12/1620, 95%CI: 0.004-0.013) of genotypes D was observed in the study area. A slight decrease in the overall frequency of HBV genotype E in West African countries was found between 2003 and 2010 (94.4%) compared to 2011-2018 (90.0%) with emergence of genotypes A and D. Some studies have focused on the genotyping of other hepatitis viruses with a predominance of HCV

infections (528/570, Table 2). Figure 3 shows the geographical distribution of the different HBV genotypes in the countries included in this review.

### Genotypes of other hepatitis viruses (HCV, HDV, HAV)

Of the 535 strains of HCV isolated and sequenced successfully, genotype 1 was found in the majority of cases of infections (56.4% or 298/528) against 40.0% (211/528) for genotype 2 while 3.6% (19/528) of the samples had genotypes 3 (9/19), 4 (7/19) and 5 (3/19) of HCV. HCV genotype 2 was most common in Benin, Burkina Faso, Ghana Guinea Bissau and Mali, while genotype 1 was predominant in Côte d'Ivoire, Senegal and Nigeria (Figure 4), with a high number of sequenced samples. Genotypes 1 of other hepatitis viruses such as HDV, a satellite virus still found in coinfection with HBV, HAV, HGV, and HEV genotype 3, have been reported in some studies in Ghana and Nigeria (Table 2).

## DISCUSSION

### Selection of studies

The aim of this review was to map the genotypes of the different hepatitis viruses identified in WAEMU countries, Ghana and Nigeria. The systematic review in the PubMed, Google Scholar and Sciences Direct databases included 52 studies reporting genotypes of hepatitis A, B, C, D, E and G. The availability of genetic data varied across country due to the prevalence or clinical relevance of the virus or the difficulty of sequencing in a context of limited resources. Indeed, most of the genotyping studies (29/52) focused on HBV because of its endemicity in sub-Saharan Africa and its clinical implications<sup>[1]</sup>. In West Africa, chronic carriage of HBV in the general unvaccinated population is estimated to be between 10% and 18%<sup>[55]</sup>. Several studies (18/52) have also provided HCV genotype data, which is the second virus of clinical interest in this West African sub-region after HBV, while very little genetic data is available on HDV, a satellite of HBV. The genetic data on HAV come only from Nigeria where it is endemic<sup>[56]</sup>, while the genotypes of hepatitis E and G viruses, very scarce in WAEMU countries<sup>[57]</sup>, were reported respectively in Nigeria and Ghana.

### HBV genotypes

Knowledge of hepatitis viruses genotypes is of great epidemiological and clinical interest. Indeed, genotypes are responsible for variable clinical manifestations with differences depending on the stage of the disease, mutations and response to treatments<sup>[58,59]</sup>. They are also an invaluable tool for mapping the molecular evolution and dynamics of infection transmission because the different genotypes have a distinct geographic distribution. The study of Archampong *et al*<sup>[59]</sup>

**Table 1** Distribution of hepatitis B virus genotypes in West African Economic and Monetary Union countries, Ghana and Nigeria

Ref.	Year	Countries	Patients	Type of study	Samples	HBV genotypes ( <i>n</i> )
Diarra <i>et al</i> <sup>[80]</sup>	2018	Burkina Faso	Occult HBV	Cross-sectional	21	E (17) and A3 (4)
Archampong <i>et al</i> <sup>[59]</sup>	2017	Ghana	HBV-HIV coinfected	Cross-sectional	63	E (58), A (4) and D (1)
Boyce <i>et al</i> <sup>[58]</sup>	2017	Ghana	HBV-HIV coinfected	Case reports	3	D/E (3)
Cella <i>et al</i> <sup>[63]</sup>	2017	Mali	Malian refugees	Cross-sectional	16	E (16)
Lawson-Ananissoh <i>et al</i> <sup>[81]</sup>	2017	Côte d'Ivoire	Chronic HBV	Prospective	33	E (27), A (6)
Dongdem <i>et al</i> <sup>[73]</sup>	2016	Ghana	Chronic Hepatitis B	Cross-sectional	58	E (47), A (8) and D (3)
Opaleye <i>et al</i> <sup>[82]</sup>	2016	Nigeria	HBV+	Cross-sectional	17	E (17)
Compaore <i>et al</i> <sup>[62]</sup>	2016	Burkina Faso	HIV-1+ and HIV-1-	Case-Control	120	E (120)
Candotti <i>et al</i> <sup>[83]</sup>	2016	Burkina Faso	Blood donors	Prospective	99	E (71) A3QS (28)
Brah <i>et al</i> <sup>[84]</sup>	2016	Niger	HBV infected	Prospective	23	E (21), A3E (1) and D/E (1)
Boyd <i>et al</i> <sup>[85]</sup>	2016	Côte d'Ivoire	HBV-HIV coinfected	Prospective	100	E (98) and A (2)
Ampah <i>et al</i> <sup>[61]</sup>	2016	Ghana	Randomized volunteers	Prospective	52	E (52)
Traore <i>et al</i> <sup>[55]</sup>	2015	Mali	Adults volunteers	Cohort study	90	E (82), D/E (5), D (1) and A (2)
Faleye <i>et al</i> <sup>[86]</sup>	2015	Nigeria	Pregnant women	Cross-sectional	6	E (6)
Faleye <i>et al</i> <sup>[87]</sup>	2015	Nigeria	Asymptomatic individuals	Cross-sectional	13	E (13)
Maylin <i>et al</i> <sup>[88]</sup>	2015	Senegal	Chronic HBV	Cohort study	87	E (65), A (22)
Honge <i>et al</i> <sup>[76]</sup>	2014	Guinea-Bissau	HIV+	Cross-sectional	26	E (25) and D (1)
De Paschale <i>et al</i> <sup>[12]</sup>	2014	Benin	Pregnant women	Prospective	19	E (19)
Forbi <i>et al</i> <sup>[56]</sup>	2013	West Africa <sup>1</sup>	Pregnant women and HIV+	Multicenter	83	E (74) and A (9)
Hübschen <i>et al</i> <sup>[89]</sup>	2011	Nigeria	Cohorts samples	Cohorts study	163	E (154) and A (9)
Geretti <i>et al</i> <sup>[90]</sup>	2010	Ghana	HIV+	Cross-sectional	86	E (82) and A (4)
Forbi <i>et al</i> <sup>[69]</sup>	2010	Nigeria	Asymptomatic volunteers	Cross-sectional	55	E (53) and A3 (2)
Chekaraou <i>et al</i> <sup>[32]</sup>	2010	Niger	Blood donors	Cross-sectional	24	E (20), D/E (4)
Candotti <i>et al</i> <sup>[91]</sup>	2007	Ghana	Pregnant women	Cross-sectional	70	E (69) and A (1)
Vray <i>et al</i> <sup>[92]</sup>	2006	Senegal	Blood donors	Cross-sectional	32	E (23) and A (9)
Huy <i>et al</i> <sup>[60]</sup>	2006	Ghana	Blood donors	Cross-sectional	12	E (12)
Candotti <i>et al</i> <sup>[66]</sup>	2006	Ghana	Blood donors	Cross-sectional	100	E (87), A (10) and D (3)
Fujiwara <i>et al</i> <sup>[65]</sup>	2005	Benin	Blood donors	Cross-sectional	21	E (20) and A (1)
Mulders <i>et al</i> <sup>[64]</sup>	2004	West Africa <sup>2</sup>	Measles or HIV+	Multicenter	79	E (78), and A (1)
Suzuki <i>et al</i> <sup>[70]</sup>	2003	Côte d'Ivoire	HBV carriers	Cross-sectional	48	E (42), A (3) and D (3)

<sup>1</sup>Ghana 13 (E = 100%), Côte d'Ivoire 70 (E = 87%); <sup>2</sup>Benin 13 strains, Burkina Faso 11 with 1 case of HBV-A genotypes (BFA-S121), Mali 18 strains, 15 strains from Nigeria and Togo 22 strains. WAEMU: West African Economic and Monetary Union; HBV: Hepatitis B virus; HIV: Human immunodeficiency virus.

demonstrated that the majority of HBV-positive and patients co-infected with lamivudine 3TC resistance were infected with HBV genotype E. This review confirms the endemicity of HBV genotype E, with a pre-

valence of 90.6% (1468/1620, 95%CI: 0.891-0.920) and a predominance of serotype awy4. Indeed, some studies conducted in Ghana<sup>[60,61]</sup>, Burkina Faso<sup>[62]</sup> and Mali<sup>[63]</sup> exclusively reported the HBV genotype E in

**Table 2** Distribution of non-hepatitis B virus genotypes in West African Economic and Monetary Union countries, Ghana and Nigeria

Ref.	Year	Countries	Patients	Type of study	Samples	Others hepatitis genotypes (n)
Abubakar <i>et al</i> <sup>[93]</sup>	2017	Nigeria	HCV+	Prospective	173	HCV G1 (159) and G2 (14)
Ndiaye <i>et al</i> <sup>[94]</sup>	2015	Senegal	Drug users	Cohort study	25	HCV G1 (21), G2 (1), G3 (1) and G4 (2)
Henquell <i>et al</i> <sup>[95]</sup>	2016	Burkina Faso	woman	Case report	1	HCV G5 (1)
Opaleye <i>et al</i> <sup>[82]</sup>	2016	Nigeria	HBV+	Cross-sectional	14	HDV G1 (14)
De Paschale <i>et al</i> <sup>[112]</sup>	2014	Benin	Pregnant women	Prospective	6	HCV G1 (1), G2 (5)
Honge <i>et al</i> <sup>[76]</sup>	2014	Guinea Bissau	HIV+	Cross-sectional	8	HCV G2 (8)
Zeba <i>et al</i> <sup>[96]</sup>	2014	Burkina Faso	Blood donors	Cross-sectional	36	HCV G1 (4), G2 (22), G3 (8), G4 (2)
Forbi <i>et al</i> <sup>[56]</sup>	2013	Nigeria	Apparently healthy adult	Cross-sectional	12	HAV sub-G1A (12)
Diarra <i>et al</i> <sup>[97]</sup>	2013	Mali	Diabetic	Prospective	25	HCV G1 (7) and G2 (18)
Bouare <i>et al</i> <sup>[98]</sup>	2013	Mali	Old women	Prospective	14	HCV G1 (2) and G2 (12)
Forbi <i>et al</i> <sup>[47]</sup>	2012	Nigeria	Asymptomatic indigenes	Prospective	60	HCV G1 (51) and G2 (9)
Sombie <i>et al</i> <sup>[99]</sup>	2011	Burkina Faso	HCV+	Prospective	38	HCV G1 (10), G2 (27) and G5 (1)
Bengue <i>et al</i> <sup>[100]</sup>	2008	Côte d'Ivoire	Blood donors	Prospective	27	HCV G1 (21), G2 (5) and G5 (1)
Plamondon <i>et al</i> <sup>[101]</sup>	2007	Guinea Bissau	Adult volunteers	Cross-sectional	57	HCV G1 (1) and G2 (56)
Simpore <i>et al</i> <sup>[102]</sup>	2005	Burkina Faso	Pregnant women	Prospective	5	HCV G1 (2) and G2 (3)
Rouet <i>et al</i> <sup>[103]</sup>	2004	Côte d'Ivoire	HIV+/Pregnant women	Cross-sectional	6	HCV G1 (3) and G2 (3)
Agwale <i>et al</i> <sup>[104]</sup>	2004	Nigeria	HIV+ under ART	Prospective	12	HCV G1 (9) and G2 (3)
Candotti <i>et al</i> <sup>[45]</sup>	2003	Ghana	Blood donors	Cross-sectional	23	HCV G1 (3) and G2 (20)
Buisson <i>et al</i> <sup>[105]</sup>	2000	Nigeria	Acute hepatitis	Cross-sectional	7	HEV G3 (7)
Saito <i>et al</i> <sup>[79]</sup>	1999	Ghana	HIV+ and HIV-	Cross-sectional	9	HGV G1 (9)
Wansbrough-Jones <i>et al</i> <sup>[106]</sup>	1998	Ghana	Blood donors	Cross-sectional	7	HCV G1 (2) and G2 (5)
Oni <i>et al</i> <sup>[107]</sup>	1996	Nigeria	blood donors	Cross-sectional	5	HCV G1 (2) and G4 (3)

WAEMU: West African Economic and Monetary Union; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HDV: Hepatitis D virus; HEV: Hepatitis E virus; HGV: Hepatitis G virus; HIV: Human immunodeficiency virus; ART: Antiretroviral treatment.

their study populations.

In addition to the presence of other genotypes, including HBV genotypes A and D, studies have reported a strong predominance of genotype E<sup>[64-66]</sup>. Similar observations have led several authors to support further the common presence of HBV genotype E in West African populations<sup>[24]</sup>. Indeed, the predominance and almost exclusive circulation of genotype E in sub-Saharan Africa certainly indicates its West African origin<sup>[67-69]</sup>. Its distribution is limited to West Africa, unlike other HBV genotypes, despite the migration of slaves from West Africa to North America<sup>[66]</sup>. This review also reports low genetic diversity of HBV genotype E in West Africa (Figure 2)<sup>[64,66]</sup>. The low genome diversity and large distribution of genotype E in West Africa suggests a recent introduction of this genotype in the human host<sup>[64,70]</sup>. It is possible that it has been introduced relatively recently into an animal reservoir (the chimpanzee) as well as for HIV or that variant of genotype D (the closest to genotype E) has acquired an evolutionary advantage<sup>[66]</sup>. HBV genotypes A and D were also reported in this review with respective prevalence of 7.8% (126/1620, 95%CI: 0.065-0.092) and 0.74% (12/1620, 95%CI: 0.004-0.013). HBV genotype A, which is also found in sub-Saharan Africa, has been reported in eight of the 10 countries included in this review. Indeed, genotype E is predominant in West Africa, while genotype A has a relatively high prevalence in East Africa<sup>[71]</sup>.

In 2006, Candotti *et al*<sup>[66]</sup> reported a prevalence of 10% and 3%, respectively, for HBV genotypes A

and D in blood donors in Ghana. Similar results have also highlighted the cocirculation of genotypes A and D in Ghana, Mali, Côte d'Ivoire and Nigeria<sup>[59]</sup>. The majority of genotypes A identified in Burkina Faso are quasi-A3 genotypes (A3Q) documented in West African populations<sup>[72]</sup>. Indeed, data from previous studies suggest a predominance of the A1 genotype in East Africa and the A3 genotype in West and Central Africa, while the A2 subgenotype has a high frequency in North Africa where the genotype D is predominant. Africa has a high diversity of HBV genotypes and subgenotypes displaying distinct geographical distributions. Genotype A is found mainly in south-eastern Africa, genotype E in western and central Africa and genotype D prevails in northern Africa. Genotype E is rarely found outside Africa, except in individuals of African descent.

Characterization of HBV genotypes allows clinicians to determine patients' response to treatment and potential risks of complications<sup>[58,73]</sup>. Flink *et al*<sup>[74]</sup> have indeed reported that genotype A responds better to interferon alpha and pegIFN $\alpha$  than genotype D. Genotype recombination occurs in areas where multiple genotypes are in co-circulation, thus facilitating diversification between individuals within the general population. Our review reports a recombination prevalence of HBV genotype E with genotypes A and D of 0.87% (14/1599, 95%CI: 0.005-0.015). A/B, A/C, A/E, C/E, D/E and D/E/A recombination have been reported in West Africa<sup>[58]</sup>. Recombination requires co-infection with more than one genotype in the same patient. Appropriate treatment and elimination of risky



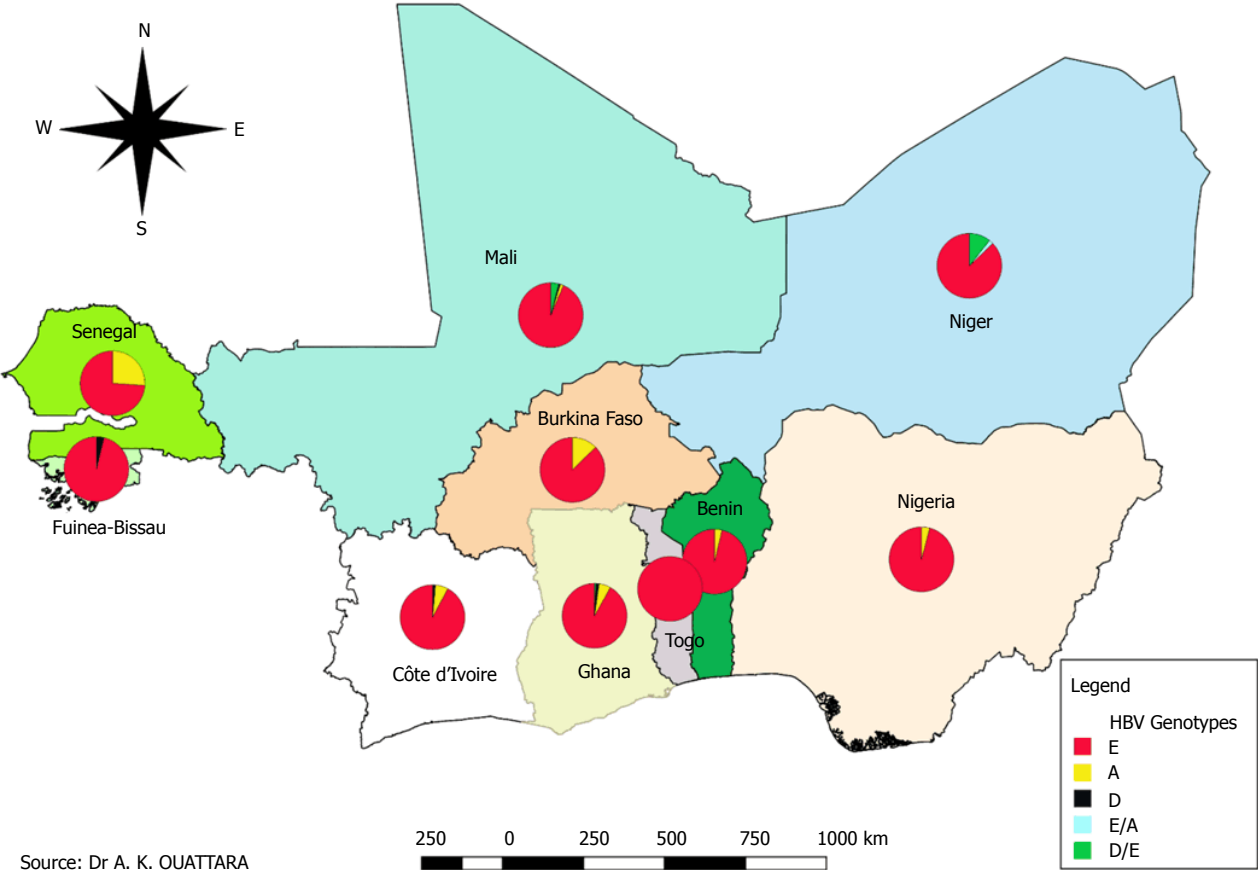


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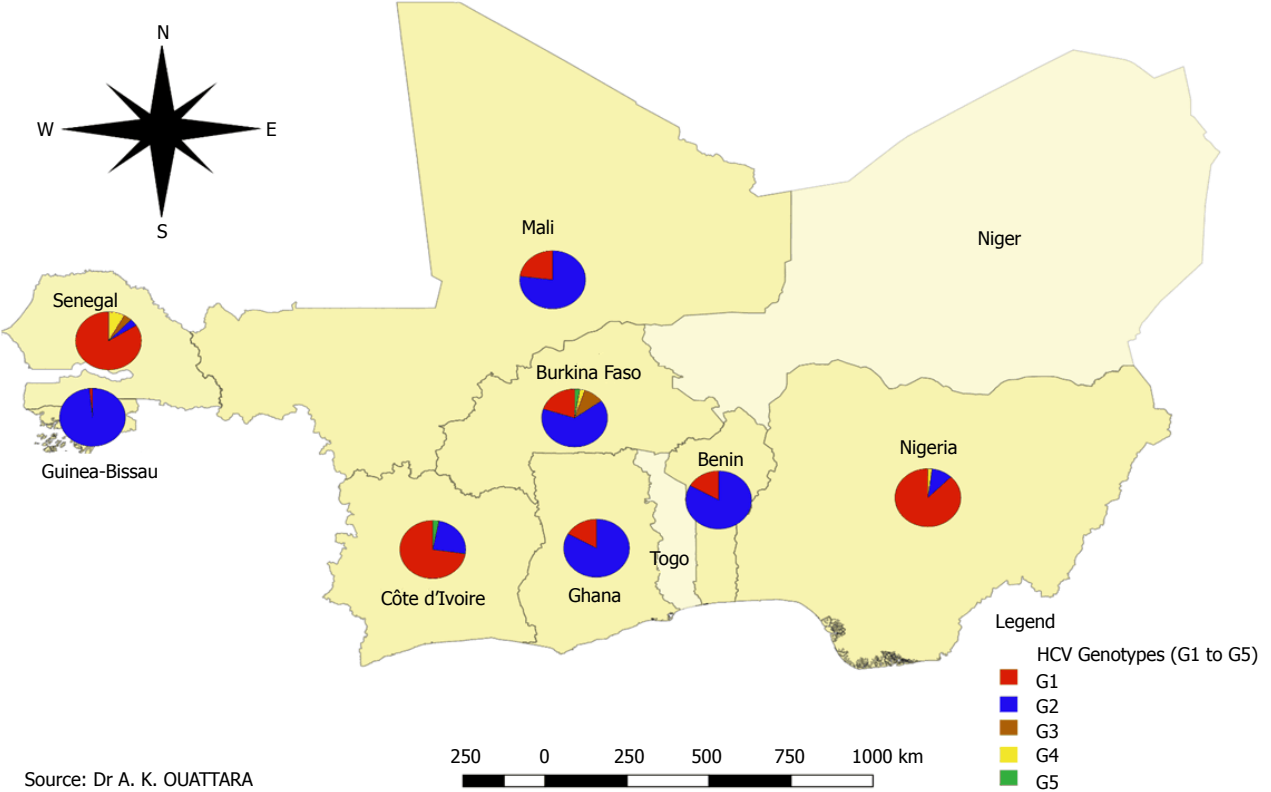
Guinea-Bissau report an almost exclusive predominance of genotype 2<sup>[76]</sup>. Candotti *et al*<sup>[45]</sup> reported 87.0% of genotype 2 was associated with chronic HCV infection with 13% of cases for genotype 1. In a study in Ghana in HCV/HIV coinfecting patients, HCV sequences were phylogenetically assigned genotype 2 and subtypes 21 and 2r<sup>[77]</sup>. Although no published data on HCV genotypes were found in Togo, genotypes 2 and 1 were the most frequently isolated, with respective prevalence 73.2% and 17.1%, in a study conducted in 2014 in the Togolese general population.

Genotype 2 is, therefore, predominant in Togo, as it is in most parts of West Africa (unpublished data). In Martinique, where three quarters of the slaves sent in the 17th and 18th centuries came from West Africa, there is a great diversity of genotype 2<sup>[78]</sup>. The majority of molecular and epidemiological studies suggest that HCV genotype 2 has been present in West Africa for several centuries.



Source: Dr A. K. OUATTARA

**Figure 3** Hepatitis B virus genotypes reported in West African Economic and Monetary Union countries, Ghana and Nigeria. Pie charts show the proportion of different hepatitis B virus genotypes in West African countries according to the data in Table 1.



Source: Dr A. K. OUATTARA

**Figure 4** Hepatitis C virus genotypes reported in West African Economic and Monetary Union countries, Ghana and Nigeria. Pie charts show the proportion of different hepatitis B virus genotypes in West African countries according to the data in Table 2.

Data on the genotypes of other hepatitis viruses that are very infrequent or with relatively high frequencies in some areas have also been reported in this review. HAV genotype 1 and HEV and HDV were reported in Nigeria, while genotype 1 of HGV was found in Ghana. HAV, whose transmission is closely associated with lack of clean drinking water, unsuitable food, inadequate sanitation and poor personal hygiene, is prevalent in parts of Nigeria (World Health Organization). HDV is a satellite virus of HBV, because HDV only infects people with HBV. Limited data is available on circulating HDV genotypes. In a study in Togo, it was reported that 94.3% of the general population was infected with genotype 1, and 5.7% was infected with genotype 5. Studies on HGV are very limited<sup>[57,79]</sup>. The analysis of the 5% untranslated region nucleotide sequence of the genome of the HGV shows that the nine Ghanaian isolates of the HGV belong to genotype 1, the West-African type of the HGV<sup>[79]</sup>.

## CONCLUSION

The complexity of hepatitis virus genotypes often leads to a specificity of treatment associated with the genotype. The present review reporting a mapping of genotypes of hepatitis viruses A, B, C, D, E and G in the WAEMU, Ghana and Nigeria, reveals that the majority of studies conducted in Ghana and Nigeria have very little information on hepatitis D and G. In the WAEMU area including Ghana and Nigeria, HBV strains were classified as genotypes E, A, D with a predominance of genotype E and serotype ayw4. Genotype E is characterized by a high prevalence, low genetic diversity and wide geographical distribution.

The majority of HCV genotype data came from Nigeria, Senegal and Côte d'Ivoire were characterized by a predominance of genotype 1, while a high prevalence of genotype 2 was found in Benin, Burkina Faso, Ghana, in Guinea-Bissau and Mali. Further studies on the clinical implications of HBV genotype E are needed for the development of an effective treatment for HBV in West Africa. Monitoring the distribution of the different genotypes is also needed to reduce recombination levels and prevent the emergence of other viral strains. There is a diversity of genotypes and subtypes of hepatitis viruses with risks of recombination and emergence of even more virulent forms. Hepatitis viruses do not need a passport or visa to move from one country to another, and they have preceded us in WAEMU or ECOWAS. It is therefore appropriate for us to develop the adequate means to prevent, treat and even eradicate these viral infections using a vaccine covering all variants.

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