Hepatitis B virus infection in Africa

A team of experts discuss the burden of HBV infection, factors enhancing its spread and the challenges of controlling the spread of the infection in Africa. They also recommend some strategies that will help in achieving the 2030 goal of elimination of HBV in Africa.

Hepatitis B, previously known as serum hepatitis, is a serious public health challenge globally. It is a major etiological agent for liver diseases including hepatocellular carcinoma, liver cirrhosis and chronic hepatitis. According to the World Health Organisation (WHO), viral hepatitis is a bigger threat to Africa than the HIV/AIDS, malaria and tuberculosis due to the high rate of hepatitis related deaths that occurs annually within the continent. About 30% of the almost 300 million people with chronic hepatitis B infection are resident in Africa, next to the Western Pacific Region. The importance of innovative strategies to reduce and control the spread of hepatitis B virus infection in the Continent cannot therefore be overemphasized. In this review article, we discuss the burden of HBV infection, factors enhancing its spread and the challenges of controlling the spread of the infection in Africa. We also recommend some strategies that will help in achieving the 2030 goal of elimination of HBV in Africa.

Transmission of HBV

The major modes of HBV transmission are vertical transmission, sexual transmission, and parenteral contact with blood or blood products. In endemic areas of Africa, HBV can be transmitted from an infected mother to the foetus or to the child during pregnancy and in the perinatal periods. Mother-to-child transmission is responsible for most infants' infections at ages 6-12 months of life. Mothers who do not receive appropriate treatment have a very high risk of transmitting the infection to their babies. Infection rates as high as 70%-90% have been recorded for HBeAg-positive mothers, 25% for HBeAg-negative/HBeAb-negative mothers and 12% for HBeAg-negative/anti-HBe-positive. Immunoprophylaxis and maternal antiviral agents in the 3rd trimester have been successful in reducing HBV transmission to new-borns, suggesting that most vertical transmissions occur at or near the time of birth while Intrauterine transmission takes place in less than 15% of pregnant women[1,2].

HBV has been detected and experimentally transmitted through several body fluids of infected individuals such as saliva, urine, tears, sweat, semen, menstrual, and vaginal secretions [3]. HBV infection is therefore spread by unprotected sexual contact and contact with above body fluids contaminated with the virus.[3a-c].

Parenteral contact with blood or blood products via transfusion of unsafe blood have been reported in Africa[4,5]. Practices such as tattooing, piercing, injection drug use and other practices that may result in higher exposure to contaminated equipment and body fluids, have also been implicated in the spread of the infection in the continent. Owing to its high stability and ability to remain infectious for long periods of time outside the body[6], other transmission routes in hospital environment may include the use of inadequately disinfected equipment and or improper reuse of sharps.

Diagnosis and viral markers of HBV

Eliminating viral hepatitis as a public health threat by 2030 is one of the Sustainable Development Goals (SDG). Controlling Chronic HBV (CHB) is an important component of this goal as it contributes to about 50% of all viral hepatitis related deaths. Accurate diagnosis and management of Hepatitis B and detecting the presence and activity of HBV are vital to achieving the elimination of the diseases[8]. A number of viral markers are used in the diagnosis of HB, the disease progression and response to therapy.

Detection of HBsAg indicates HBV infection, quantification of HBsAg can also be used to define the stage of the infection, define truly inactive phase, determine response to treatment and predict the possibility of loss of the surface antigen and to determine possibility of HBV reactivation. This viral marker has been used in various studies in Africa to determine the prevalence of HBV infection[7,9,10]. Anti-HBc indicates an exposure to the virus which may or may not have been cleared and it can also be used to identify possible occult HBV infection, while detection of anti-HBc IgM is used in identifying recent acute infection[8,11]. In occult hepatitis, HBsAg is usually negative while anti-HBcore is positive. This is a challenge in the diagnosis of HBV infection in Africa because in most countries, diagnosis of HBV infection is based mainly on detection of HBsAg. The need to run two different assays to establish occult HBV makes its diagnosis more expensive. Presence of anti-HBs indicates protection to HBV which could have been acquired either from previous infection or vaccination.

HBV disease progression and response to therapy is monitored using markers such as HBeAg, anti-HBe, HBV DNA. Detection of HBeAg indicates active HBV replication and is a marker of HBV infectivity [8,12]. It is

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also associated with high HBV DNA, while anti-HBe is associated with low level of HBV DNA, hence implies a better prognosis. In a study in Nigeria, Odaibo and colleagues detected HBV DNA in over 75% of HBeAb positive but HBeAg negative samples[12]. The implication of this finding in the management and control of HBV in Africa is enormous. Particularly because HBeAg/HBeAb detection assays are used in most African countries for the prognosis of disease and initiation and monitoring of response to therapy. Detection of HBV DNA in an individual indicates HBV infection, and its quantification can be used to define stage of the infection, determine the need for treatment as well as response to therapy[13].

Some other biomarkers are being considered for monitoring disease progression, management as well as determining risk of developing liver cancer. Intrahepatic cccDNA which is maintained in the nucleus of the infected cells and its eradication is required for the permanent cure of HBV infection[14] can be measured to assess viral replication, therapeutic endpoint or cure of HBV infection[15]. Also, detection of serum HBV RNA, transcribed from cccDNA indicates transcription of activities and its level correlates with levels of HBV DNA in treatment naïve patients while it is usually higher in patients on antiviral drug[16]. Similarly, HBV core antigen (HBcAg) is being proposed as a marker for HBV cccDNA transcription. HBcAg can easily be quantified using ELISA or chemiluminescence assay which are relatively cheaper and easier to perform. It will be a good marker for differentiating disease state and to identify patients who can safely discontinue therapy.

Hepatitis B virus (HBV) and Sickle cell disease

Sickle cell disease is a common inherited haematological disorder in Sub-Sahara Africa where HBV is also endemic. The major clinical features of sickle cell disease are lifelong anaemia and recurrent vaso-occlusion, which in addition to infection represent a major cause of morbidity, disability and death. The consequences of the life-long anaemia and vaso-occlusion increases the susceptibility to infections such as HBV as a result of therapeutic interventions[17]. Blood transfusion, a significant therapeutic and prophylactic component of SCD management is a known risk factor for HBV infection. Before the widespread blood bank routine screening of blood units for HBV infection in Africa, the prevalence for HBV among SCD was as high as 22% and HBV was responsible for 50% of post transfusion hepatitis[18].

Several insults to the liver results in liver disease in SCD of which hepatitis due to HBV contributes significantly. The clinical feature of acute and chronic hepatitis due to HBV infection in SCD patients are similar to that in other patients. Chronic hepatitis B (CHB) infection may be asymptomatic, however, progressive disease and advanced liver disease or liver cancer are of concern[18,19]. Fortunately, with universal routine screening of blood units for HBV infection and inclusion of HBV vaccine in the Expanded Programme for Immunization (EPI) in most African countries, the prevalence among SCD patients has reduced to between 1%-5.7% and the prevalence is comparable to the general, population[10,20].

Recent studies have not shown significant correlation with blood transfusion[20-22]. There is no doubt that vaccine confer immunity to acquisition of the virus but there has been reports on some patient having anti-HBs titer below 10 IU/L which is a non-protective titer following HBV vaccination and therefore at the risk of acquiring HBV infection[23,24]. In view of this, it is being suggested that SCD patients should be followed up after HBV vaccine and those identified as not having adequate anti-HBs titre should receive booster dose.

High risk groups and factors enhancing spread of HBV

Although prevalence of the infection varies globally, studies have shown that low resource countries, especially those in sub-Saharan Africa are the most impacted by the infection. The overall prevalence of HBV in most sub-Saharan African countries is between 6-11%, compared to the global 3% prevalence rate[25,26]. The major mode of HBV transmission is percutaneous, although sexual transmission is also very common. Hence, high risk groups include blood donors, pregnant women, sickle cell patients, health workers, untrained community medical providers, people with body scarifications and tattoos, intravenous drug users, persons working with sharps in non- health related occupations and patients that are frequently exposed to sharps like diabetics. Sexually active persons such as teenagers, middle aged individuals, commercial sex workers, and long distance drivers, military and paramilitary officers that lived outside their homes for long periods, as well as HIV infected individuals because of their shared mode of transmission[25,27,30]. Recent studies carried out in Botswana, Ghana and Nigeria showed that the prevalence of HBV among people living with HIV, the general population and health care workers was about 56%, 8.48% and 6% respectively despite the global HBV prevalence of 3%[32-34]. Male infants and toddlers are also known to be at high risk[27]. Under diagnosis of HBV, limited availability of vaccination, screening and treatment in low resource settings are major factors affecting the spread of HBV in Africa[35]. Recently, migration and global travel have also impacted the spread of the virus into regions which hitherto had low prevalence rates[36]. Figure 1 is a word cloud depicting the interactions of HBV high risk groups and factors affecting spread of the virus.

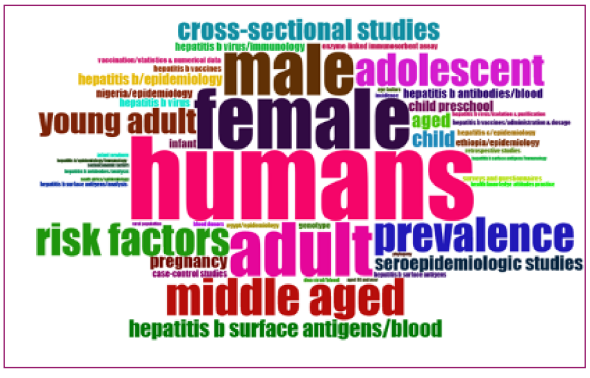

Figure 1: *Word Cloud showing interaction of HBV high risk groups and factors affecting its spread*

DISTRIBUTION OF HBV INFECTION IN AFRICA

Hepatitis B virus was discovered about 50 years ago, and the infection is still endemic in Africa despite the use of vaccines for over 20 years as a preventive measure[37,38]. Around 70% of Hepatitis B infections worldwide occur in Africa. Estimates in 19 African countries show that more than 8% of the population is infected with Hepatitis B. In 2020, the African region accounted for 26% of the global burden for Hepatitis B and C. This can be justified by the recent national estimates made available from the IHM, Schweitzer, the WHO and the CDA for 195, 161, 194 and, 120 countries in the world respectively. Analyzed data from the above 4 research groups indicated that sub-Saharan Africa accounts for the highest prevalence of HBV as presented in Figure 2.

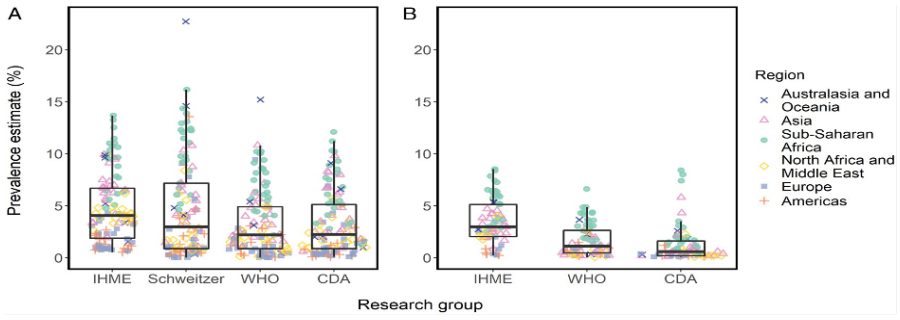

Figure 2: Distribution of country-level estimates of chronic HBV infection prevalence (A) across all ages and (B) in children under 5 years of age in countries covered by the four groups (IHME, Schweitzer, WHO, CDA).

Based on the global viral hepatitis report of 2019, Sub-Saharan Africa is highly affected by HBV with a prevalence in the general population, that ranges from <2% in Seychelles, Botswana and Kenya to ≥10% in countries such as Chad, Liberia, South Sudan, Togo, Mauritania, and Guinea[39]. Prevalence of HBV in specific African countries is shown in Table 1. The differences in prevalence within the African region can be attributed to the fact that by 2018, only 28 countries in Africa had a national strategic hepatitis plan and access to diagnosis and treatment is still limited[39]. Also, many African countries are yet to adopt the policy of vaccination against HBV at birth[40]. There is also a variation in the number of children with chronic HBV infection between countries in Africa (Table 1). WHO classifies the endemicity of HBV infection as low, low intermediate, high intermediate and high. As seen in the map below (Figure 3), most African countries belong to the high intermediate/high endemic areas.

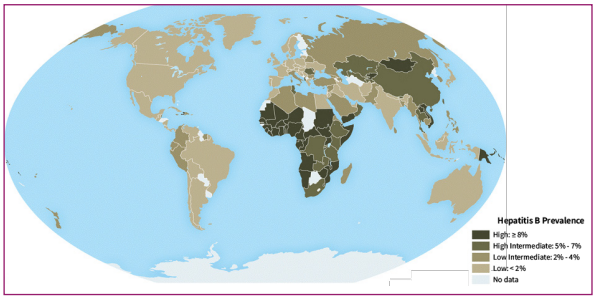

Figure 3: Global distribution of HBV infection (Source-CDC Yellow Book 2020).

Clinical presentation and management of hepatitis B in Africa

Hepatitis B virus infection could present in acute or chronic form. Symptomatic acute hepatitis infection is relatively not common in Africa compared to its prevalence since most infections occur during childhood when there is lack of immunity[41]. However, HBV infections is still a common cause of acute hepatitis in adults in Africa[41,42]. The symptoms of hepatitis B typically involve anicteric phase of fever, body pain, tiredness, etc. and the icteric phase which sometimes may not occur making acute hepatitis B infection in Africa sometimes difficult to distinguish from other common prevalent infections like malaria and enteric infections. Acute hepatitis B infection in Africa rarely progresses to fulminant hepatitis. Chronic hepatitis B infection could be asymptomatic or present with liver cirrhosis and or hepatocellular carcinoma. Chronic hepatitis B infection is the most common risk factor for liver cirrhosis and or hepatocellular carcinoma in sub-Saharan Africa[43]. Mozambique has the highest incidence of hepatocellular carcinoma in Africa and is largely due to hepatitis B infection. Many patients in Africa are not aware of their status until they develop chronic sequalae of the infection making them to present very late[43].

Majority of patents with HBV may not require drug treatment based on the level of detectable DNA[44]. Patients who do not meet criteria for treatment are to be followed up every six months but this is not feasible in many African countries because of cost of HBV DNA assay and the fact that patients pay out of pocket[45]. Available medication for

the treatment of hepatitis B in Africa include pegylated interferon, tenofovir disoproxil fumarate, tenofovir alafenamide, entecavir and lamivudine. Because of high cost, negative e antigen status and normal serum alanine transferase, many patients in Africa with hepatitis B nay not benefit from pegylated interferon[46]. Because majority of the patients with hepatitis B in Africa lack the e antigen, they have to be on oral antivirals for a long time, mostly for life[47].

Challenges with the management of hepatitis B in Africa include out of pocket payment system, non-availability or inadequate facilities for viral DNA quantification in some places and its high cost where available and low adherence to medication for various reasons including cost[48].

Molecular Epidemiology of Hepatitis B Virus in Africa Hepatitis B virus (HBV) has nucleotide sequence heterogeneity because its polymerase, the reverse transcriptase, lacks proofreading ability and the genome has been estimated to evolve at an error rate of approximately 10–3 to 10–6 nucleotide substitutions/site/year[49]. This leads to the occurrence of various genotypes, subtypes, mutants, recombinants, and even quasispecies in the background of the long-term evolution of HBV50. Ten (A to J) genotypes are so far identified which differ in more than 7.5% of their nucleotide sequences (Velkov et al., 2018). Coinfection with different HBV genotypes further leads to intergenotypic recombination of HBV strains and genotypes A and genotype C show a higher trend of recombination than other genotypes (Lin and Kao, 2015).

Globally, genotypes and sub-genotypes are related to disease prognosis and progression, chronicity of disease, response to antiviral and interferon treatment[51]. This is an important feature that must be considered by a physician, particularly for implementation of personalised medicine. The geographic distribution of HBV genotypes could also be possibly linked to route of exposure. Genotypes B and C are more commonly found in high-endemic regions of vertical exposure while other genotypes are predominantly detected in regions of horizontal exposure[51]. HBV genotype distribution may similarly be influenced by socio-demographic, ethnic, or migratory factors[52].

In Africa, the geographical distribution of HBV genotypes assumes a particular pattern in Africa (Table 3). The predominant genotypes present in south-eastern Africa, North Africa, and West Africa are genotypes A, D, and E, respectively. Although genotype E is limited to West Africa, its distribution however, expands to parts of central Africa53,54. A meta-analysis of pooled studies on HBV genotypes conducted in West Africa from 1996 to 2018 reported genotype E with prevalence of 90.6% while genotypes A and D had prevalence of 7.8% and 0.74% respectively. In addition, coinfection between genotypes E and A was reported as 0.86%[55]. In West Africa, one or more A/B, A/C, A/E, C/E, D/E, and D/E/A recombinants have been reported[56].

Conclusion and Recommendations

- There is a need to develop a fourth-generation assay with the ability of detecting HBsAg and antiHBVcore in a single run. This will help to address the challenge of running multiple assays to arrive at an appropriate diagnosis and also reduce cost to patients.
- There is need to develop simple and affordable methods for quantification of HBV DNA in resource limited settings like Africa.
- HBV in Africa needs similar attention given to the control of HIV infection. Awareness in the communities, provision of vaccine and post vaccination test for protective level of anti-HBs titre among high-risk populations such as SCD patients and health care workers, support for testing and provision of drugs for treatment of the infection by governments in the African continent.

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