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The S-Gene Mutations in the Circulating HBV Genotypes/Sub-Genotypes Associated with Hepatitis B Infection in Uganda and their Effects on Cytokines Expression in Liver Disease Progression

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Abstract

The causal agent for hepatitis B is called hepatitis B virus (HBV). It is a partially double stranded circular DNA virus of the family Hepadnaviridae. It has been implicated as the leading cause of hepatocellular carcinoma and only second to tobacco among the global human carcinogens. Liver damage as a result of HBV infection is due to host immune response and is modulate by cytokines. The HBV is classified into 10 genotype denoted as A, B, C, D, E, F, G, H, I and J together with several sub-genotypes which have diverse geographical distribution. These genotypes influence liver disease progression and severity as well as response to antiviral therapies. Mutations in the S-gene have been implicated in the paradoxical coexistence of HBsAg and the anti-HBs antibodies which is associated with advanced liver diseases including hepatocellular carcinoma and liver cirrhosis. Management of HBV is by using antiviral therapy but there is no treatment that can cure HBV. Therefore the practical alternative is vaccination but this is genotype specific. It therefore absolutely necessary to match vaccine strains with field strains. Success on this subject is contingent upon accurate diagnosis and routine genotyping. The concept paper also explicates the need for more elucidation of cytokine profiles in HBV virus infection since liver disease progression is cytokine modulated especially in the scenario where mutations are common yet they influence cytokine profiles.

Index terms— hepatitis B virus, genotypes, cytokines, mutations.

I. Section One: Back Ground epatitis B virus (HBV), a member of the Hepadnaviridae, is a circular, partially doublestranded DNA virus and is one of the major causes of chronic liver diseases, including chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (Matsuura et al., 2009, Khamduang et al., 2013). The HBV genomic structure has been exclusively reviewed by Coleman (2006), Suppiah, Mohd Zain, Bahari, Haji Nawi, & Saat (2014), Ding, Miao, Li, Dai, & Yu (2015) as a partially double stranded DNA of genomic size of approximately **??**.2kb with four open-reading frames (ORF). The ORFs encode four genes including the polymerase gene designated as P gene, core (C) gene, large, medium and small surface antigen proteins (S gene) and the X protein **??**Coleman, 2006, Kahila Bar-Gal et al., 2012). The HBV genome S gene is paramount importance in the molecular genetics of the virus since it is concerned with the expression of the surface antigens and classification of the viral strains (Suppiah et al., 2014) as well as the antigenic variation of the virus. The coexistence of the HBsAg and anti-HBs Antibodies is implicated on the mutation in the S-gene encoding for the surface antigen as a result of HBV immune escape election mutations (Ding et al., 2015). This in turn associated with more advanced liver diseases including hepatocellular carcinoma and liver cirrhosis or chronic hepatitis B infection (Seo, Choi,

& Choi, 2014). This is consistent with the earlier study by Svicher, Cento, & Salpin, (2011) who found out that mutations in the Sgene affect pathogenicity and oncogenic potential which in turn affects cytokine profile in HBV infection. Cytokine are critical molecules in progression of the liver disease as reported earlier by **??**kpolat & Joseph Mugambwa ¥ Abstract-The causal agent for hepatitis B is called hepatitis B virus (HBV). It is a partially double stranded circular DNA virus of the family Hepadnaviridae. It has been implicated as the leading cause of hepatocellular carcinoma and only second to tobacco among the global human carcinogens. Liver damage as a result of HBV infection is due to host immune response and is modulate by cytokines. The HBV is classified into 10 genotype denoted as A, B, C, D, E, F, G, H, I and J together with several sub-genotypes which have diverse geographical distribution. These genotypes influence liver disease progression and severity as well as response to antiviral therapies. Mutations in the S-gene have been implicated in the paradoxical coexistence of HBsAg and the anti-HBs antibodies which is associated with advanced liver diseases including hepatocellular carcinoma and liver cirrhosis. Management of HBV is by using antiviral therapy but there is no treatment that can cure HBV. Therefore the practical alternative is vaccination but this is genotype specific. It therefore absolutely necessary to match vaccine strains with field strains. Success on this subject is contingent upon accurate diagnosis and routine genotyping. The concept paper also explicates the need for more elucidation of cytokine profiles in HBV virus infection since liver disease progression is Frodsham et al (2006). Damage to the liver as a result of HBV infection is due to immune response as reported in earlier studies by Racanelli & Rehermann (2006) and in recent studies by Wang & Zhang (2009) and is cytokine modulated but cytokine profiles in HBV virus infection need more elucidation especially in the scenario where mutations are common. The virus interferes with the functioning of liver cells (hepatocytes) causing the innate immunity to release immune mediators particularly chemokines and cytokines to combat the infectious agent (Keating et al., 2014) Matthews et al., (2013) have shown that the use of highly active antiretroviral therapy (HAART) have resulted into hepatotoxicity and has been implicated as the major cause of mortality in HBV-HIV co-infection.

According to the world health organization (WHO), countries of Africa, Asia and South America have carrier rates as high as greater than 8% (Franco et al., 2012) with Sub-Saharan Africa accounting for 20% of global burden (Khamduang et al., 2013). In Uganda the burden of the disease varies from region to region with Nothern Uganda having the highest prevalence of 17.6% as reported in the study by (Ochola et al., 2013).

However the press release from the ministry of health revealed that 10% (more than 3.5 million Ugandans) are living with chronic Hepatitis B infection and the prevalence is region specific with North East 21.7%, North Central 19.4%, West Nile 18.7%, Western 10%, Kampala 5.8%, Central 5.8%, while South West with 2.9%. (MOH), 2015). This challenge is precipitated by lack of advanced clinical laboratory for routine and accurate patient testing (Franco et al., 2012) as well as the limited knowledge about the circulating genotypes and sub genotypes in the developing world (Singhatiraj et al., 2012). Previously, a novel field deployable, rapid, simpler, single temperature, nucleic acid amplification method, termed loop-mediated isothermal amplification (LAMP), has been developed for laboratory diagnosis of many infections (Notomi et al., 2000). However no study has been reported to evaluate the use of LAMP in the diagnosis of HBV in Uganda. It has been used for the timely diagnosis of hepatitis C virus (Nyan et al., 2014), malaria (Hopkins et al., 2013), African Swine fever Virus (Atuhaire et al., 2014), foot-and-mouth disease virus (Kafeero et al., 2016) and Human African Trypanasomiasis (Matovu, Enock,Kuepfer, Boobo, Kibona, & Burri, 2010). This concept paper underpins the urgent need to use rapid diagnostic assays such as LAMP and comparing its diagnostic sensitivity and specificity with the commonly used assays of ELISA and polymerase chain reaction in order to come up with recommendations to the policy makers and the Ministry of Health about the potential benefits of the assay that has received a lot of attention in the recent times.

This concept paper is divided into four sections. After introducing the key conceptual issues in section one, there is section two which provides the conceptual objectives and hypothesis that underpin the development of the whole concept. Section three explicates the conceptual problem which this paper is trying to address. Section four summarizes the literature that informed the design of the concept. The objective of this paper is to elicit Ugandan scientists, physicians and policy makers to appreciate the magnitude of the current and future effect of HBV in our country and think outside the box, using evidence based practice to manage HBV. This is in line with the recently ushered in sustainable development goals as stipulated in goal 3 target 3.3 which is aimed at eliminating hepatitis B by 2030.

1 II. Section Two: Conceptual Objectives and Hypothesis

We hypothesize that mutations have occurred not only in the S-gene implicated in the antigenicity of the virus but also in the entire genome of the hepatitis B virus resulting into evolution and emergency of several HBV genotypes which influence cytokine profiles. Mutations in the S-gene are of paramount significance The S-Gene Mutations in the Circulating HBV Genotypes/Sub-Genotypes Associated with Hepatitis B Infection in Uganda and their Effects on Cytokines Expression in Liver Disease Progression because they have been implicated in the paradoxical coexistence of the HBsAg and the anti-HBs antibodies. This in turn affects the severity of the liver diseases. Immigrants into our country from all other parts of Africa in particular and World over in general have profound effect on the HBV circulating genotypes yet some are issued with immigration documents without valid HBV vaccination documents. This re-affirms our hypothesis of existence of novel genotypes in our region. Liver disease progression, vaccination and antiviral therapy are genotype specific. Unfortunately there is no clear

documentation on the circulating genotypes in Uganda underscoring the burden of the disease and escalating the devastating effects of the epidemic.

2 a) General objective

The main aim of the conceptual paper is to establish the S-gene mutations in the circulating HBV genotypes/ sub-genotypes associated with hepatitis B infection and the role of cytokines in liver disease progression. b) Specific objectives 1. To determine the prevalence of HBV DNA and antibodies in blood/serum of the study subjects. 2. To establish the circulating genotypes and subgenotypes of HBV in Uganda. 3. To determine the mutations in S gene of the HBV genome. 4. To profile the panel of cytokines in patients infected with HBV.

3 III. Section Three: Conceptual Problem

Management of HBV requires the knowledge of mutations particularly the S-gene mutations as well the genotypes and the sub-genotypes because they affect antiviral therapy **??** To date there is no curative treatment to eradicate the HBV but the commonly used therapies such as interferon, pegylated interferon as well as nucleoside / nucleotide analogs prolong the suppression of viral replication and establish host immune control over the virus (Alazawi & Foster, 2008).

The success of these therapies is contingent upon the specific viral genotype infecting the host (Kao et al., 2002, Janssen, van Zonneveld, & Senturk, 2005) as well as the mutations in the genome.

There is paucity of information about HBV genotypes, S-gene mutations, cytokine profiles in HBV infections elsewhere as reported elsewhere in a series of studies by Arauz-Ruiz et al., **??**2002) **??**2016). However no study in Uganda to date on the molecular genomics of the circulating genotypes/ subtypes, mutations and their effects on disease progression in terms of cytokine profiles in pathological conditions. Since migrations and variations in selection pressures affect the circulating genotypes and the subsequent mutations (Kahila Bar-Gal et al., 2012), these affect the efficacy of the antiviral drugs. These challenges underscore the burden of the disease which is a public health concern. The recently ushered in sustainable development goals (SDGs) have emphasized the need to eliminate hepatitis B virus infection by 2030. Therefore this concept paper retaliates for an urgent need for studies on molecular biology of the HBV in order to provide physicians and other health workers with evidence based information particularly in areas of molecular genetics of the virus required in the management of HBV in Uganda.

4 IV. Section Four; Literature Review a) Hepatitis B genotypes and subtypes and their effect on liver disease progression

The HBV genome is composed of approximately 3,200 nucleotides (Matsuura et al., 2009 The other genotypes G-J have no subgenotypes and none of them has been reported in Africa. Countries in Africa where genotyping is routine and thence information about the circulating genotypes and sub-genotypes is available include Tunisia, Gambia, Africa, South Africa and Morocco (Table 1). Uganda and many other countries are missing on this list. The S-Gene Mutations in the Circulating HBV Genotypes/Sub-Genotypes Associated with Hepatitis B b) The HBV S gene mutations and the paradoxical coexistence of HBsAg and anti-HBs in chronic infection with HBV

The HBV genomic structure has been exclusively reviewed by Coleman (2006), Suppiah, Mohd Zain, Bahari, Haji Nawi, & Saat (2014), Ding, Miao, Li, Dai, & Yu (2015) as a partially double stranded DNA of genomic size of approximately 3.2kb with four openreading frames (ORF). The ORFs encode four genes including the polymerase gene designated as P gene, core (C) gene, large, medium and small surface antigen proteins (S gene) and the X protein (Coleman, 2006, Kahila Bar-Gal et al., 2012). Studies on the full genome analysis of hepatitis B genome have given a paucity of information including identification of mutations reported world over in all the four ORFs. (Quer et al., 2008).

The HBV genome S gene is paramount importance in the molecular genetics of the virus since it is concerned with the expression of the surface antigens and classification of the viral strains (Suppiah et al., 2014) as well as the antigenic variation of the virus. These genetic mutations in the S-gene enable the virus to escape the host's immune system as well other selection pressures such as antiviral drugs and vaccines. The immune escape S-gene mutations against the imposed selection pressures have been implicated in the coexistence of the HBsAg and anti-HBs antibodies (Ding et al., 2015) especially in advanced liver damage such in cases of liver carcinoma, fibrosis ,cirrhosis or chronic liver (Seo et al., 2014). Therefore mutations in the S-gene are considered as the culprits in pathogenicity and oncogenicity of viral hepatitis B, an argument consistent with the earlier findings by Svicher, Cento, & Salpin, (2011). The challenge in giving health care services to chronic HBV infections as a result of the antigenic variations of the virus is reduced sensitivity and specificity of the assays used in the diagnosis of the virus giving false negatives, failure of medication, and vaccination if the mutations are not timely identified.

5 c) Cytokine profile in HBV infection

Cytokine are critical molecules in progression of the liver disease as reported earlier by Akpolat, Yahsi, Godekmerdan, Demirbag, & Yalniz (2005), Frodsham et al (2006) and it common knowledge that damage to

the liver as a result of HBV infection is due to immune response as reported in earlier studies by Racanelli & Rehermann (2006) and in recent studies by Wang & Zhang (2009) and is cytokine modulated but cytokine profiles in HBV virus infection need more elucidation especially in the scenario where mutations are common.

6 d) Rapid detection of HBV

The hepatitis B infection is a global public health concern. This is aggravated in countries where health care facilities are poor due to the shrinking resource allocation to the health care services in the national budgets (Nyan et al., 2014). This problem is worsened by the natural coincidence of the disease being endemic in these poor countries (Nyan et al., 2014). According to the world health organization (WHO), countries of Africa, Asia and South America have carrier rates as high as greater than 8% (Franco et al., 2012). This challenge is precipitated by lack of advanced clinical laboratory for routine and accurate patient testing (Franco et al., 2012) as well as the limited knowledge about the circulating genotypes and sub genotypes in the developing world (Singhatiraj et al., 2012). In many countries, HBV diagnosis is based on screening for HBV surface antigen, antibodies to the core HBV, and HBV DNA (Nyan et al., 2014). These tests are performed with enzyme-linked immunosorbent assay (ELISA) and real time polymerase chain reaction (rRT-PCR). These tests are slow and require expensive laboratory equipment such as the ELISA reader, real time PCR machine in addition to specially trained laboratory staff (Caliendo, Valsamakis, & Bremer, 2011 **??** Kao,JH 2008). A recent study in Uganda by Mullis et al., (2013) revealed a high frequency of false-positive hepatitis C virus in Rakai. In their study, the high prevalence of false positive was due to clearance of HCV RNA but not the antibody. However this explanation is invalid since in their study, there was no single sample that was positive by both the HCV RNA Abbot real time HCV assay and ELISA assay suggesting that the positives by ELISA are most likely to be false positive. These studies provide a basis for adopting the use of alternative assays in the detection of HBV with rapidity, high sensitivity, specificity and at lower cost without the need of sophisticated laboratory equipment and trained staff in Uganda. Uganda is a country of high intermediate HBV prevalence (Fig. 1) with a prevalence of 5-7% suggesting that the disease burden is high and needs attention. However little research has been conducted to provide information required to evidence based management of the epidemic. This prevalence may even underestimate the current prevalence in the country because it is not from a local study and was done close to four years ago (Ott et al., 2012). The previous HBV epidemiological survey in Uganda by Pido & Kagimu, (2005) among health workers put the prevalence at 8-11%. This study was conducted 10 years ago and the prevalence must be certainly different though almost consistent with a preceding report from the world health organization (WHO) which reported a prevalence of 8% (WHO, 2004), being the highest in highly endemic countries of sub-Saharan Africa. In the previous study by Watson-Williams & Kataaha, (1990), the prevalence of hepatitis B virus surface antigen in the Ugandan population was then between 6 and 15% among blood donors when screening was introduced. Fortunately, the WHOrecommended strategy for HBV control vaccine was introduced in Uganda in 2002 as part of the expanded Program on Immunization (EPI) and is given at 6, 10 and 14 weeks of age **??**WHO 2004, Pido & Kagimu 2005). The high prevalence then could have been due to inadequate access to the vaccine, limited awareness of the disease, and the value of vaccination against HBV. For the past 20 years massive campaign to vaccinate pregnant mothers and the new borne has been on in our country to prevent parenteral transmission to the new borne. However success of vaccination is largely dependent on matching the vaccine strains with the field strains. This is anchored on the knowledge of the circulating genotypes and sub-genotypes as well as the mutations in the S-gene which influence the HBsAg. This information is not available in Uganda. In case of the sero-positive cases, management is by use of antiviral drugs. However these are also genotype specific. The developing world is challenged with inadequate clinical research in the rapid and accurate diagnosis of HBV, a key feature in the management of the epidemic.

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The concept paper has underlined the need to investigate the S-gene mutations in the circulating hepatitis B viral strains in Uganda. The S-gene encodes for the surface protein coat with has been implicated in antigenicity of the virus which in turn influences the effectiveness of antiviral therapy. It has also highlighted the need to for routine HBV genotyping in order to match vaccine strains with field strains for effective immunization programs in our country. The concept paper has underpinned the need to screen immigrants using HBV genotype specific assays in order to inform the physicians so as to adopt evidence based HBV management.

The paper has outlined the need for rapid and accurate detection of HBV which is paramount in management of the disease. The paper has quoted studies which left several questions unanswered hence leaving knowledge gaps.

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Figure 1:

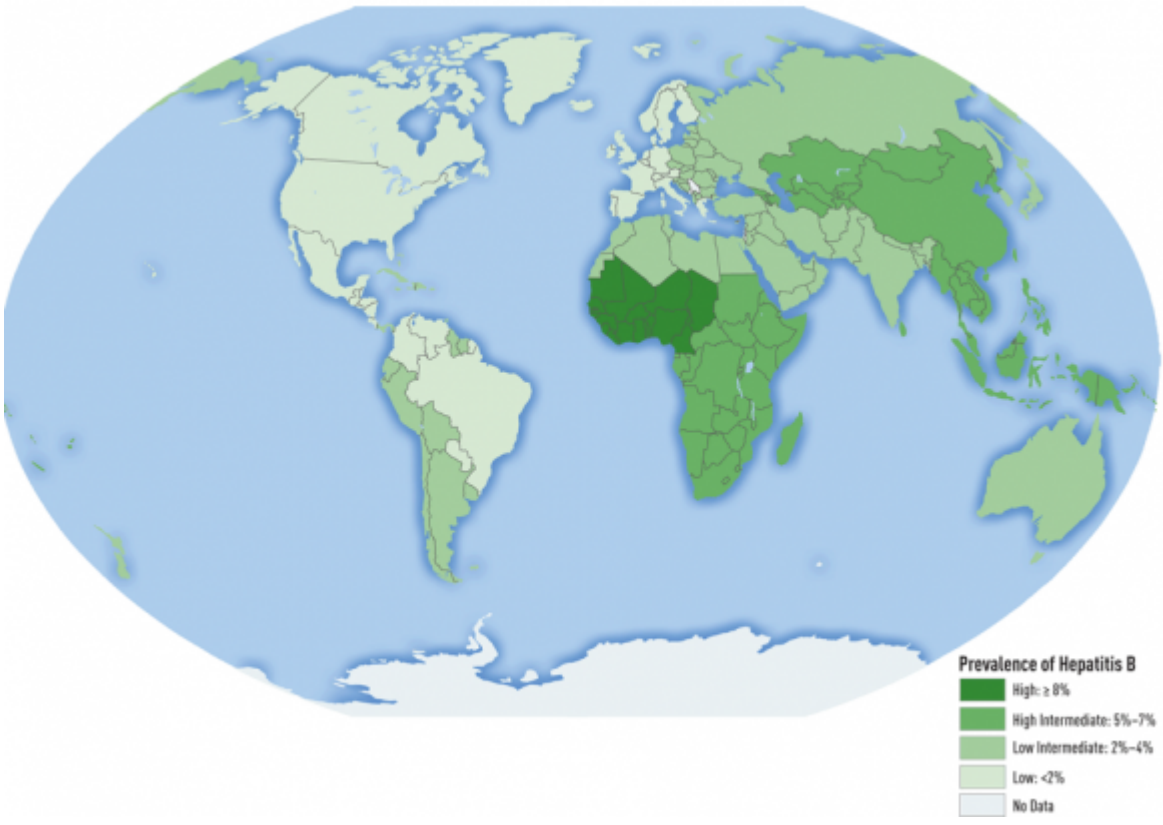

Figure 2:

1

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Figure 3: Table 1)

1

Country	Genotypes	Sub-genotypes	Reference
Tunisia	D, F	-	(Ayari et al., 2012)
Gambia, Nigeria, Congo, Rwanda, Cameroon	A	A4, A5, A6, A7	(Shi, 2012)
Egypt	D	D1	(Ragheb et al., 2012)
Central African	A, D, E	A1,D4	(Komas et al., 2013)
South Africa	D	D3	(Yousif & Kramvis, 2013)
Morocco	D,A	D1, D7, A2	(Baha et al., 2012)

Figure 4: Table 1 :

has shown that patients with HBV/B have more serious liver disease than patients with HBV/C. The HBV genotypes have also been implicated in variations in seroconversion to hepatitis B e antigen (HBeAg) antigen. Studies by Chu, Hussain, & Lok, (2002) have shown that patients with genotype B achieve HBeAg seroconversion 10 years ealier than patients with genotype C. Variations in response to treatment are also affected by genotypes. Evidence from studies by Wai, Chu, Hussain, & Lok, (2002) have shown that patients with genotype B respond better to IFN-? as compared to patients with genotype C.

Figure 5:

216 [1] [2] [3]

[1] © 2016 Global Journals Inc. (US)The S-Gene Mutations in the Circulating HBV Genotypes/Sub-Genotypes Associated with Hepatitis B Infection in Uganda and their Effects on Cytokines Expression in Liver Disease Progression

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.1 Competing interests

We declare that we have no any competing interests.

.2 Authors' contributions

Hussein Mukasa Kafeero, Kawooya Abubakar, Namusoke Mariam, Atiku Saad and Mugambwa Joseph contributed to the conception of the idea, drafting and writing of the manuscript and manuscript preparation.

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