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SAFETY IN THE WORKPLACE: THE BURDEN AND PATTERN OF MARKERS OF HEPATITIS B VIRUS INFECTION IN ROUTINE BLOOD SAMPLES IN HAEMATOLOGY LABORATORY AT IRRUA, EDO, NIGERIA

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ABSTRACT

Hepatitis B virus [HBV] infection is a worldwide problem resulting in many deaths yearly from cirrhosis and liver cancer. Regrettably also, healthcare workers get exposed to blood-borne pathogens, including hepatitis B virus at work. HBV infection in immuno-competent hosts results in acute fulminant illness which may be fatal, partially resolved to become chronic, or completely resolved. HBV immunization in the country cover neonates and health workers leaving many people uncovered. Lack of monitoring and confirmation of successful HBV immunization in heath workers reduces coverage in this group leaving many susceptible to HBV infection at work. We aimed to determine the magnitude of this risk for occupational exposure to HBV infection. We therefore analyzed sixty nine routine blood samples coming to our Haematology laboratory at Irrua, Edo, Nigeria, using the five parameter hepatitis B virus kit manufactured by Micropoint Diagnostics USA. Results showed that HBsAg, Ant-HBs, HBeAg, Anti-HBe and Anti-HBc were reactive in 11.6%, 23%, 1.4%, 7% and 7% of our study samples indicating that the burden of HBV infectivity is high. We recommend active monitoring and routine confirmation of successful HBV immunization in health workers with expansion of the program to cover more of our population.

Key Words: Chronic HBV Infection, Occupational exposure, Immunization, Management of Chronic HBV infection

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INTRODUCTION

In the line of duty, Health Care Workers are at risk of contacting a number of infectious agents whose concentrations in human body fluids (especially in whole blood, serum or plasma) can be particularly high during the incubation and/or acute stages of these infections. These agents include the Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and types I and II Human Immunodeficiency Virus (HIV I &II) among others.

HBV infection however, is a worldwide health problem. The World Health Organization (WHO) estimates that approximately more than two billion people have been infected with HBV. Of these, approximately 240 million are chronically infected and are at risk of serious illnesses and death from Cirrhosis and Hepato-Cellular Carcinoma (HCC) - diseases that are estimated to cause approximately 600,000 deaths every year worldwide (FitzSimons, *et al*. 2008; CDC 2008; WHO, 2004). Majority of the people infected with HBV live in Asia and Africa; particularly Sub-Saharan Africa (Custer, *et al*., 2004). The routes of transmission of HBV infection include; Mother to child transmission, direct contact with an infected person during early childhood, Hetero- and Male Homo-sexual activity, injection drug use, muco-cutaneous contact with infected body fluids and body fluid contaminated surfaces (occupational exposure) and iatrogenic infections via blood and blood product transfusion and transplantation of solid organs (especially liver) to susceptible individuals (Goldstein, *et al*., 2005; Horvat, *et al*., 2011).

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The HBV virus is a partially double stranded DNA virus of the hepadnaviridae (hepatotropic DNA virus) family (Ganem *et al*., 2004). Hepadnaviridae have a strong preference for infecting liver cells, though small amounts have been found in kidneys, pancreas and mononuclear cells. The virion (Dane particle) is composed a nucleocapsid core surrounded by a host derived lipid membrane containing the Hepatitis B surface Antigen (HBsAg). The nucleocapsid core contains the Hepatitis B core Antigen (HBcAg) surrounding the Hepatitis B e-Antigen (HBeAg), a single molecule of partially double stranded circular DNA, and a DNA dependent polymerase (Horvat *et al*., 2011; Ganem *et al*., 2004). The highly efficient genome of this virus contains four Open Reading frames/regions which code for the viral structural and attachment proteins (HBsAg, HBcAg and HBeAg) and proteins needed for replication (viral polymerase and X protein). Following attachment and entry into the hepatocyte, the virion is un-coated and migrates to the nucleus where it is converted into a covalently closed circular DNA (cccDNA) by the host polymerase. The cccDNA serves as the template for the transcription of the pre-genomic RNA (pgRNA) and mRNA (Ganem *et al*., 2004)

The transcribed pgRNA translocates into the cytoplasm where it serves as the template for the reverse transcription enzyme as well as the core protein. Simultaneously, the polymerase converts some pgRNA into cccDNA, some of which circulate back into the nucleus to build up and maintain the pool of cccDNA in early/acute infection. Four viral mRNA transcripts (transcribed from various promoter regions on the cccDNA) are translated into HBV proteins (Horvat *et al*., 2011; Ganem, *et al*., 2004). The longest mRNA acts as the template for genomic replication (pgRNA) as well as the translation of the precore-core (HBcAg) and polymerase proteins. The HbeAg is cleaved from the HBcAg during viral assembly prior to viral release. The second and third transcripts are translated into proteins (preS1, preS2 and S proteins) that constitute the HBsAg which is usually produced in excess during active viral replication and circulates as non infective immunogenic empty viral particles. The fourth and smallest transcript encodes the X protein which transactivates transcription. The pgRNA and the polymerase protein are packaged into HBcAg within which the reverse transcriptase enzyme synthesizes a new viral DNA genome. These particles are then transported to the HBsAg in the ER of the host cell and HBeAg is cleaved off the HBcAg into the circulation (where it circulates freely, or bound to albumin, globulin or α1 antitrypsin) prior to viral release. Thus during active viral replication, antigens such as HBsAg, HBeAg, and Viral DNA are detectable in the patient's circulations using molecular and serologic assays (Horvat *et al*., 2011; Ganem *et al*., 2004). HBcAg is undetectable because the antigen does not circulate freely in blood (Horvat *et al*., 2011; CDC, 2008). Similarly, with vigorous host immune response, antibodies to HBsAg (Anti-HBs), HBeAg (Anti-HBe) and HBcAg (Anti-HBc) are produced and become detectable by serological assays during various stages of the infection and convalescence as shown in table 1 below.

Mutations within the viral genome could impact on prevention, detection and treatment of HBV infection by causing failure or defect of synthesis of HBeAg (preC gene mutation) or produce viruses that either cause false negative serological assay for HBsAg and/or unresponsiveness to vaccine-induced immunity and HBV immunoglobulin therapy (envelope gene) [Horvat *et al*., 2011; CDC, 2008; Ganem *et al*., 2004).

The disease outcome of primary HBV infections depends on the age and immune status of the patient. Primary infections in immune-competent adults may be symptomatic (usually) or asymptomatic while that in neonates and young children and, immune-compromised adults usually lead to chronicity. Symptomatic infections usually manifest, after an incubation period of 2-3 months (range: 6weeks to 6 months), with non-specific symptoms and signs such as fever, abdominal pains, vomiting, jaundice and hepatomegaly. Acute infection is usually accompanied by high rate of viral replication (with high levels of circulating HBsAg, HBeAg and HBV DNA) and infectivity (Horvat, *et al*., 2011, CDC, 2008; Ganem *et al*., 2004; Liang, 2009). It also provokes vigorous host immune response with production of Anti-HBs and Anti-HBc and liver damage majorly from the effects of inflammatory bye products such as; Tumor Necrosis Factor (TNF), Free Radicals and proteases and, to a lesser extent, direct Lymphocyte cytotoxicity by $CD8^+$ T- cells and Natural Killer cells. This immune response often lead to viral clearance attributable to the immune response cells as well as inflammatory bye products notably TNF-α and Interferon-γ (IFN-γ) which kill the viruses without damaging liver cells (Guidotti, *et al*., 1996;

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Baron, *et al*., 2002). This may be followed by complete recovery (Symptoms, Viral replication and liver damage stops, No HBV antigen in serum and seroconversion to Anti-HBs, Anti-HBe and Anti-HBc), fulminant hepatitis with mortality (continued viral replication, host immune response and liver damage) or progress to a chronic infection. The first two antibodies may wane over time leaving Anti-HBc as the only serologic evidence of the infection (No symptoms but varying level of viral replication and host immune response) (Horvat *et al.*, 2011; Ganem *et al*., 2004). Majority of neonatal and early childhood infections as well as infections in the immune-compromised adults often lead to chronic carriage of the virus. Unfortunately, HBV infections resulting in chronic carriage of the virus are more common in the parts of the world where the disease is more prevalent because infections in these places occur mostly peri-natally and in early childhood (Lok *et al*., 2007; McMahon, 2005).

Table 1: HBV markers in different stages of infection and convalescence [Modified from Horvat *et al.*, 2011]

Stage of Disease	Molecular marker [HBV DNA]	Protein antigen markers		HBV specific antibody markers		
		HBsAg	HBeAg	Anti-HBc	Anti-HBe	Anti-HBs
Susceptible host	-	-	-	-	-	-
Early incubation	+	-	-	-	-	-
Late incubation	+	+	-/+	-	-	-
Acute infection	+	+	+	+	-	-
Recent infection[a]	-/+	-	-	+	+	+++
Remote infection[b]	- or very low	-	-	+	+/-	+
HBsAg negative acute infection	-(<10^3IU/ml)	-	-	+	-	-
HBsAg variant infection	-/+	-	-/+	+	-	-
Immune active carrier	++(>10^5IU/ml)	+	-/+	+++	-	-
Inactive HBsAg carrier	-(<10^3IU/ml)	+	-	+	+	-
Immune tolerant carrier	+++	+	+	+	-	-
Vaccination response	-	-	-	-	-	+

(a) Early convalescence and individuals who remain HBV DNA positive for a long time. (b) Individuals with anti-HBc in the absence of other serologic markers, including DNA. They may or may not have anti-HBs and may reactivate HBV during immunosupression.

Three phases of chronic HBV infection have been recognized; the immune tolerant phase characterized by HBeAg positive with high levels of HBV DNA and hence high infectivity but absence of active liver disease, the immune active or chronic hepatitis phase in which there is high level of HBV DNA and active liver inflammation with positive Anti-HBe and positive or negative HBeAg, and the inactive phase during which anti-HBe is detected but liver aminotransferase levels are normal with low or absent HBV DNA (Horvat, *et al*., 2011; CDC, 2008]. Patients can evolve through these phases or revert from inactive hepatitis to immune active infection at any time. The presence of HBeAg and HBV DNA generally indicate high viral replication and infectivity; the presence of anti-HBe usually indicates decreased or undetectable HBV DNA levels and lower levels of viral replication (Horvat, et al., 2011). However, HBV DNA have been found at infective doses in a small proportion of donors from the Brazilian Amazon designated as having occult HBV infection (Moresco *et al*., 2014).

Health workers are at a high risk of contacting HBV infection in the workplace via muco-cutaneous exposure to infectious blood and blood products (WHO, 2003). Spilled infectious body fluid containing HBV remain infectious on the

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contaminated surfaces for about a week after spillage, if the surface is not appropriately disinfected when spillage occurred (Horvat *et al*., 2011; CDC, 2008). Vaccinations against HBV has been introduced for health workers and neonates for some times now in this country but the vast majority of patients whose body fluids are being processed daily in our laboratories are adults, who escaped the neonatal vaccination coverage, or non health workers, who are thus not covered by the health worker vaccination program. Anecdotal reports unfortunately show that some health workers somehow manage to either not get immunized at all or fail to complete their HBV vaccination. In addition post vaccination screening for and measurement of ant-HBs levels in Health workers to confirm success of vaccination is not routinely done in Nigeria as is recommended in other countries; both the WHO and CDC recognize levels of 10mIU/ml of anti-HBs as protective (CDC, 1991]. We undertake in this study to estimate the burden of and infectivity profile of routine blood samples for HBV in the Haematology laboratory of Irrua Specialist Teaching Hospital with a view to making recommendations on confirmation of successful vaccination and other necessary subsequent interventions.

MATERIALS AND METHODS

Sample Size: A total of sixty Nine (69) consecutive routine blood samples in the Haematology Laboratory of Irrua Specialist Teaching Hospital, Irrua, were selected for this study in May 2012 after the requested test had been performed. The samples were centrifuged and plasma separated into plane bottles and refrigerated at 4^{o}C until analysis.

Exclusion Criteria: The samples sent for HBV screening, HCV screening and, screening for HIV and syphilis were not selected for this study. Also excluded were samples of blood donors.

Ethical Consideration: Ethical approval was sort and obtained from the Research and Ethical Review Committee of the Irrua Specialist Teaching Hospital.

Data Collection: Socio-demographic characters such as the age and sex of the patients as well as the types of tests requested by the clinicians were extracted from the request form which normally accompany each sample and are recorded in a sheet against the sample number. However, the presumptive diagnoses could not be recorded as many forms lack information akin to those documented in studies by Ikponmwen *et al*. (2013) and Nutt *et al*. (2008).

Sample Analysis: The separated plasmas were analyzed for the presence of HBsAg, HBeAg, Anti-HBs, Anti-HBe and Anti-HBc using the five parameter hepatitis B virus kit manufactured by Micropoint Diagnostics USA. Instructions of the manufacturers as contained in the product inserts were strictly followed. Positive samples were tested in duplicates and confirmed using control antigen or antibodies supplied by the manufacturer with the kit. Results were entered into and analyzed on spreadsheets of SPSS version 16.0 alongside the socio-demographic data earlier obtained.

RESULTS

The mean age of patients whose samples were analyzed was 28.30 (SD 19.13) with a range from Five months to Seventy seven years. Forty Two percent (29) and Fifty Eight Percent (40) of these samples belong to male and female patients respectively as show in the pie chart below.

Eight (11.6%) of the samples were reactive for HBsAg, Sixteen (16; 23%) of them were reactive for Anti-HBs. Only one sample (1.4%) was reactive for HBeAg while reactivity for Anti-HBe and Anti-HBc were seven in each case (10.1%) as shown in table 2 below.

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Table 2: Sero-positivity to HBV maker

HBV Maker	Number [%] Positive/Reactive	Number [%] Negative/Non-Reactive
HBsAg	08 [11.6%]	61 [88.4%]
Anti-HBs	16 [23%]	53 [76.8%]
HBeAg	1 [1.4%]	68 [98.6%]
Anti-HBe	7 [10.1%]	62 [89.9%]
Anti-HBc	7 [10.1%]	62 [89.9%]

Keys: HBsAg= Hepatitis B surface Antigen, HBeAg = Hepatitis B envelope Antigen, Anti-HBs = Antibodies to HBsAg, Anti-HBe = Antibodies to HBeAg, Anti-HBc = Antibodies to Hepatitis B core Antigen

Table 3: Sex distribution of HBV markers.

Maker of HBV infection	Number (Percentage) of Males positive [n=29]	Number (Percentage) of Females positive [n=29]	Total Number (Percentage) positive [n=69]	Sig.
HBsAg	2 (6.9)	6 (15)	8 (11.6)	0.260
HBeAg	0 (0)	1 (2.5)	1 (1.4)	0.580
Anti-HBs	2 (6.9)	14 (35)	16 (23)	0.006
Anti-HBe	2 (6.9)	5 (12.5)	7 (10.1)	0.368
Anti-HBc	2(6.9)	5 (12.5)	7(10.1)	0.368

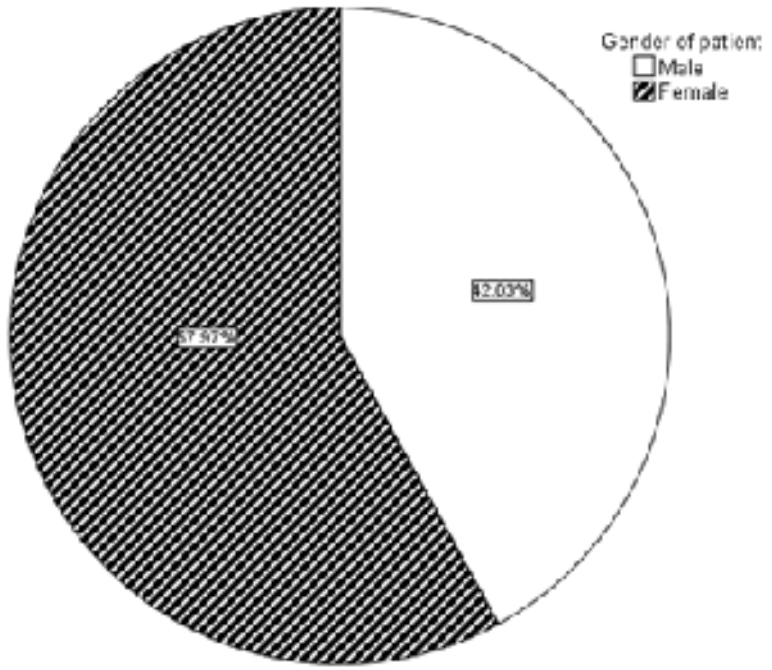

Figure 1: Gender of Patients

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The sex distribution of HBV marker positivity is shown in Table 3 above. Table 3 also shows that even though differences existed in the number of male and female samples that tested positive for various antigens and antibodies, this only reached statistical significance in the case of Anti-HBs were there were significantly more female samples testing positive than males. (p= 0.006)

DISCUSSION

Eleven percent of samples in our study are positive for HBsAg. This is consistent with the population estimate of >8% for regions of the world, with high endemicity for HBV infection, to which Nigeria belong. Our figure is however higher than the overall sero-positivity rate of 4.98% (Ejele and Ojule, 2005) and 4.3% (Akani *et al*., 2005) found in routine samples and pregnant women in Port Harcourt respectively. Any of this patient could be incubating an acute infection, having acute hepatitis or be a chronic carrier all of which are infectious as shown in table 1 above (Horvat *et al*., 2011; CDC, 2008; Ganem, *et al*., 2004).

Twenty-three percent were positive for anti-HBs indicating that they had a recent or remote infection which has just resolve and some of these could still be infectious depending on the circulating HBV DNA level. Positivity for anti-HBe in our study was 10.1%. These patients could be have a resolving acute infection or could be chronic carriers of HBV.

Anti-HBc was detected in 10.1% of our samples. Positivity for this HBV antibody alone could indicate a recent, remote or inactive chronic infection in which anti-HBs had waned, or could be indicative of acute infection by an HBsAg variant in which HBs is not detected (Bertoletti and Gehring, 2007; Heermann, 1999.). It is also important to note that infective doses of HBV DNA were found in a significant proportion of Brazilian donors. The implication is that these samples are still highly infectious.

Health workers are exposed to blood and other body fluids in the course of their work and are consequently at risk of infection with blood borne viruses including HIV; HBV and HCV. The risk of infection for health workers depends on the prevalence of the disease in the patient population and the nature and frequency of exposures. The most common form of occupational exposure to blood and the most likely to result in infection is needle stick injury while health workers who work in areas such as operating, Delivery and Emergency rooms and the laboratory are at a higher risk of exposure. Cleaners, waste collectors and others whose duties involve handling of blood-contaminated materials are also at risk. Among 35 million health workers worldwide, about 3million experience percutaneous exposure to blood borne pathogens every year; two million of those to HBV, 0.9million to HCV and 170,000 to HIV. These injuries may result in 70,000 HBV, 15,000HCV and 1,000 HIV infections. More than 90% of these infections occur in developing countries (WHO, 2003; FitzSimon *et al*., 2008].

CONCLUSIONS AND RECOMMENDATIONS

With the forgoing, it is obvious that the risk of occupational exposure to HBV in our center is enormous considering the positivity rates of the infectivity markers for this virus in our study. We therefore recommend that; the training and retraining of health workers in the use of personal protective wears and, handling and disposal of body fluid and body fluid contaminated materials should be intensified; the routine immunization of health workers against HBV should be continued and properly monitored to prevent cases of default and/or failure to complete the schedule and routine screening and measurement of anti-HBs levels be commenced to monitor and confirm the success and effectiveness of HBV immunization of health workers so that necessary interventions can be instituted in cases of unsuccessful immunization . We also recommend that routine immunization of adults who escaped the routine childhood immunization against HBV should be seriously considered so that the burden of HBV infection in health workers through occupational exposure can be reduced. Finally, we are of the opinion that it is time to start active public health management of HBsAg positive persons through contact management, patient education, dedicated medical management of chronic hepatitis B and development of Surveillance registries for persons with Chronic HBV infection.

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AUTHORS' CONTRIBUTIONS:

Dr Olanrewaju DO was involved in the conception of the study, proposal writing, analysis of samples, and analysis of data, literature review and writing up the work as well as overall supervision. Drs. Ikponmwen OD, Okogun FE, Otumu OS and Ehizogie AO were involved with collection and analysis of samples, and Literature review. Drs. Isoa EM, and Omoifo VO were involved in analysis of samples as well as review of literature.

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