CHAPTER ONE

INTRODUCTION

1.1.Introduction

Hepatitis B viral infection is a major global health problem with predilection for the liver and is known to commonly lead to chronic infection after acute infection. The chronic infections increases risk of death from childhood hepatic failure, cirrhosis of the liver and liver cancer (Shepard *et al.*, 2006; Mustaphas *et al.*, 2007). The earliest recognition of the public health importance of hepatitis B virus infection is thought to have occurred when it appeared as an adverse event associated with a vaccination campaign (WHO, 2011).New WHO data reveal that an estimated 325million people worldwide are living with chronic hepatitis B virus (HBV) infection, indicate that large majority of these people lack access to life-saving testing and treatment. As result, millions of people at risk of a slow progression to chronic liver disease, cancer and death. (WHO,2017). Approximately three million health care workers (HCW) are exposed to percutaneous blood – borne viruses each year. It is estimated that 66000 hepatitis B virus (HBV) are acquired annually (Kermode*et al*., 2005).The infections are important risk factors for hepatocellular carcinoma and other liver related morbidity (Omer*et al.*, 2001). The HBV carrier rate varies widely from 0.01% to 20% in different geographical regions of the world. The HCW including clinicians, nurses, laboratory technicians, other hospital technicians, administration and cleaning staff are exposed to an increased risk of occupational infection with HBV (Tarantola*et al.*, 2006). Health care workers (HCWs) are defined as all paid and unpaid persons working in health-care settings who have the potential for exposure to patients and/or

to infectious materials, including body substances, contaminated medical supplies and equipment, contaminated environmental surfaces, or contaminated air. HCWs might include physicians, nurses, nursing assistants, therapists, technicians, emergency medical service personnel, dental personnel, pharmacists, laboratory personnel, autopsy personnel, students and trainees, contractual staff not employed by the healthcare facility, and persons (e.g. clerical, dietary, housekeeping, laundry, security, maintenance, administrative, billing and volunteers) not directly involved in patient care but potentially exposed to infectious agents that can be transmitted to and from HCWs and patients (CDC,2011). While performing their duties, healthcare workers (HCWs) are frequently exposed to dangerous infectious agents. The risk oftransmission of vaccine-preventable infections, both from patients to HCWs and from personnel to patients, other HCWs, and visitors is substantial (Almuneef *et al*., 2006).Health care workers are at a high risk of exposure to blood and body fluids. Needle stick injuries, cuts and splashes are common occupational accidents exposing health care providers to different blood borne pathogens. Transmission of hepatitis B virus, human immune deficiency virus (HIV), and hepatitis C virus (HCV) has been related to injuries and frequency of exposure. According to world health organization (WHO)As many as 2.2 million persons in the United States are chronically infected with hepatitis B virus (HBV) and approximately 15%–25% of persons with chronic HBV infection will die prematurely from cirrhosis or liver cancer Since 2006, the overall U.S. incidence of acute HBV infection has remained stable; the rate in 2013 was 1.0 case per 100,000 persons. Hepatitis B vaccination is highly effective in pre-venting HBV infection and is recommended for all infants (beginning at birth), all adolescents, and adults at risk for HBV infection (e.g., persons who inject drugs, men who have sexual contact with men, persons

infected with human immunodeficiency virus [HIV], and others). Hepatitis B vaccination coverage is low among adults: 2013 National Health Interview Survey data indicated that coverage with ≥3 doses of hepatitis B vaccine was 32.6% for adults aged 19–49 years. Injection drug use is a risk factor for both hepatitis C virus (HCV) and HBV(CDC,2016) Adherence to standard precautions, awareness about post exposure prophylaxis is poor in developing countries amongHCWs and documentation of exposures is suboptimal (WHO, 2002).Healthcare workers have been historically recognized as being at increased risk of HBV infection, effective vaccines are available to prevent HBV infection and universal immunization programs are now advocated, needle stick injuries are one of the most efficient modes of HBV transmission, most transmission in the healthcare setting probably occurs in the absence of adocumented percutaneous injury, there is evidence from a Cochrane Library systematic review to support occupational health guidelines that all healthcare workers should be offered HBV vaccination and that the vaccine is safe(Jefferson *et al.*, 2003). Healthcare workers who have not been immunized, HBIG and HBV vaccine are recommended after a significant exposure. Although the effectiveness of HBIG and HBV vaccine has not been evaluated in the occupational health setting, the increased efficacy of this combination compared with HBIG alone in preventing prenatal transmission is presumed to apply to the occupational health setting(Beasly *et al.*, 1983).

1.2. Rationale

Health care workers have a high risk of occupational exposure to many blood borne viruses, hepatitis B virus is a major health problem and causessignificant morbidity and mortality rate.the observation

that needle-stick injuries can transmit the virus indicates that only very small amounts of blood are necessary to transmit the disease. The prevalence of disease is associated with a proper understanding of the mode of transmission of the disease. Moreover, little is known about the situation and prevalence of the disease in White Nile State especially among health workers whom may represent a source of infection. Furthermore, the proper understanding of the prevalence in study area may help in setting further control programs.The aim of this studywas to determine the prevalence of HBV among health care workers in ALdueim locality.

1.3 Objectives

1.3.1General objective

To detection HBV among healthcare workers in ALdueim locality**.**

1.3.2 Specific objectives

To detect hepatitisB surface antigen (HBsAg), among health workers in AL dueim locality by using ELISA technique.

To correlate the possible association between hepatitis B virus and selected risk factors.

CHAPTER TWO

LITERATURE REVIEW

2.1HBV properties

The hepadnaviruses got their name because they cause hepatitisand they have DNAgenomes.They are known as hepatitis B viruses (HBVs) and are classified in the familyHepadnaviridae. Some members infect mammals and some infect birds; examples include woodchuck HBV and heron HBV. The best known hepadnavirusis that which infects humans; it is commonly referred to as HBV, and is of major importance as an agent of disease and death. Duck HBV,on the other hand, is non-pathogenic in its natural host (Carter and Saunders,2007).Hepatitis B virus is a member of the hepadnavirusfamily, it is a 42, nm enveloped virion with icosahedral nucleocapsid core containing partially double strand circular DNAgenome (Levinson,2014).

2.1.1 Genome

Hepatitis B virus is a small DNA virus and belong to a group of hepatotropic DNAviruses (hepadnaviruses). The virus consists of nucleocapsid and an outer envelopecomposed mainly of three antigens (HBs Agthat play a central role in the diagnosis ofHBV infection). The nucleocapsid contains HBc Ag, and DNA polymerase reverse transcriptase, the viral genome as well as cellular proteins (Seto*utet al.*, 2011) Genome made up of two strands of DNA, one of which is incomplete; hence the DNA is partly singlestrandedand partly double-stranded, a short sequence is triple-stranded as a result of a complementary sequence at the 5 ends, and this results in the DNA having a circular conformation, the genome is very small, with a length of about3.2 kb (p). At the

5 end of each of the DNA strands there isa covalently linked molecule: a capped RNA on the short strand and a protein (P) on the long strand. (Carterand *Saunders*2007). Three types of viral particles can be visualized in the infectious serum by electron microscopy: the infectious virions and the subviral particles. The infectious virus particles are the so-called Dane particles (Dane *et al.,* 1970), have a spherical, doubleshelledstructure of 42-44 nm containing a single copy of the viral DNA genome, covalently linked to the terminal protein of the virus. A hallmark of HBV infection is the presence of two additional types of particles, the spheres and the filaments, which are exclusively composed of hepatitis B surface proteins and host-derived lipids (Glebe*et al*., 2007). Since they do not contain viral nucleic acids, the subviralparticles are non-infectious. The spherical structures measure around 22 nm in diameter, while the filaments are of similar width, but of variable lengths. The viral membrane contains three viral surface proteins and is acquired by the virus during budding into the endoplasmic reticulum, whereas the viral particles are transported via the secretary pathways through the ER and Golgi. The surface proteins are named the preS1 (or large), the preS2 (or middle) and the S (orsmall), which correspond to the HBsAg. As with nearly all enveloped viruses, theHBV particle also contains proteins of host origin (Glebe, 2007;GlebeandUrban, 2010). The HBV genome consists of a partially double-stranded relaxed circular DNA of approximately 3200 nucleotides in length, varying slightly from genotype togenotype, that in concert with the core protein (HBcAg) forms the nucleocapsids(Nassal *et al.,*2008). Within the Dane particle the negative strand of the viral DNA ispresent in full-length,

carrying the complete genetic information. In contrast, thepositive strand spans only ~ 2/3 of the genome in length, whilst its 3' end is variablein size (Summers *et al.*, 1988*)*. The viral polymerase is covalently bound tothe negative strand by a phosphotyrosine bond. At the 5' end of the positive strand ashort RNA oligomer originating from the pre-genomic RNA residually remains bound covalently after the viral DNA synthesis. The negative strand also contains small redundancy of 8-9 nucleotides in length on both the 5' end and the 3' end, named the R region. These redundant structures are essential for viral replication (Nassal, 2008).

2.2. Replication:

Hepatocytes (liver cells) are the host cells for having the body. In the laboratory, primary cell cultures of human hepatocytes support replication, but unfortunately none of the established cell lines derived from livertumors can be infected by HBV visions. Some cell lines, however, can be infected using HBV DNA (a procedure known as transfect ion) **(**CarterandSaunders, 2007*)*. Life cycle of the HBV is complex. Hepatitis B is one of the few knownnonretroviralviruses which used reverse transcription as a part of its replication process. The virus gain entry in to the cell by binding to an unknown receptor on the surface of the hepatocytes and enter it by endocytosis. Because virus multiplies via RNA made by host enzyme, the viral genomic DNA has to be transformed to the cell nucleus by host protein called chaperones. The partially double stranded viral DNA is then made fully double stranded and transform in covalently closed circular DNA (cccDNA) that serves as template, for transcription of four viral mRNAs. The largest mRNA, (which is larger than the viral genome), is used to make the new copies of the genome the capsid

core protein and the viral DNA polymerase. These four viral transcripts undergo additional processing and go on to form progeny virions which are released from the cell or returnedto the nucleus and recycled to produce even more copies. The long mRNA is thentransported back to the cytoplasm where the virion p protein synthesized DNA via itsreverse transcriptase activity (Levinson,2014). Hepatocytes (liver cells) are the host cells for HBVin the body(*Carter*and Saunders,2007).

2.3HBV Transmission

The three main modes of transmission are via blood, during sexual intercourse, andperinatally from mother to newborn (Levenson,2014).

2.3.1Risk groups for hepatitis B in developedCountries

Intravenous drug abusers, homosexual men, sexual contacts of antigen-positive persons, residents in long-stay homes for mentally handicapped

People, renal dialysis patients, recipients of multiple blood products (e.g. haemophiliacs), surgeons, dentists and morticians, and infants of infectious HBsAgpositive mothers, (Bannister*et al.*, 2006).

2.4HBV Genotype and Its Clinical Significance

Based on an intergroup divergence of 8% or more of the complete genomes, HBV can be classified in to 7 genotypes, i.e. A-G(Okamoto*etal.*,1988; Norder*etal.*,1992). Genotype H was recently identified in central America (Arauz-RuizP*etal.*,2002), is well known that HBV genotypes have distinctgeographical distributions. The prevalent HBV strains in China are genotype B and C (Zhu*etal.*,1999). but the two genotypes distribute unevenly in China. We studied 1096 Chinese chronic HBVcarriers from 9

provinces in Mainland China. Four major genotypes A, B, C and D were found and their prevalence were 1.2%,41%, 52.5% and 4.3%, respectively. In northern China,genotype C is predominant(85.1%), while in southern China, genotype B ispredominant (55.0%).Genotypes A and D are also found in other areas of China. However, thegenotypes E-H have not been reported in China. Recently, genotype C/D hybrid was identified in Tibet (Cui*etal.*,2002) and genotype B wasfound recombinated with preC/C region of genotype C in China (Luo*etal.*,2004). Accumulated data suggest the importance of genotype,subgroup and recombination that may influence the biological characteristics of virus and clinical outcome of HBV infection.Several studies reported a correlation of HBV genotypes with HBeAg clearance, liver damage, and the response to IFN treatment. Itwas reported that HBeAg carrier status tends to be longer and the prevalence of HBeAg appears higher in patients with genotype Cthan with genotype B (Orito*etal*, 2001). HBV carriers with genotype B have lower histological activity scores and genotype C is more prevalence in patients with cirrhosis (*Kaoetal.*,2000). Furthermore, a retrospective study showed that HBV genotype B is associated with a higher rate of IFN-induced HBeAg clearance compared with genotype C (Kao*etal.*,2000). However, whether patients with genotype B differfrom those with genotype C in development of hepatocellular carcinoma remains controversial. The response of different HBVgenotypes to interferon-alfa treatment is of increasing interest because the benefit of interferon-alfa or its pegylated form in combination with other antiviral agents is being explored in the treatment of chronic hepatitis B. In a homogeneous group ofprospectively

followed patients from Europe, a recent study demonstrates that genotype A responds better than other HBVgenotypes to standard interferon therapy and represents an independent predictor of a therapeutic success, with a greater impact thanother pre-treatment characteristics, such as HBV DNA or ALT levels (Hou*et al.*,2000).

2.5 Epidemiology

There are around 350 million chronic carriers of the hepatitisB virus worldwide. The incidence of acute disease andprevalence of carriage varies considerably from country tocountry. In parts of south-east Asia, 10–20% of the population may be carriers, whereas most countries in Europeand North America have carriage rates below 2%.Where carriage rates are high, acute infection occurs mainly in infants and young children, mostly via intrapartumand horizontal transmission within households. Skindisease and biting arthropods may facilitate the transfer of body fluids from person to person.Those most at risk include intravenous drug abusers, homosexualmen, residents and staff of institutions for thementally handicapped, surgeons, dentists, laboratoryworkers, morticians, renal dialysis patients and recipientsof unscreened blood and blood products (Bannister *et al.*, 2006). Hepatitis B is highly endemic indeveloping regions with large population such as South East Asia, China, sub-Saharan Africa and the Amazon Basin, where at least8% of the population are HBV chronic carrier. In these areas, 70–95% of the population shows past or present serological evidenceof HBV infection. Most infections occur during infancy or childhood. Since most infections in children are asymptomatic, there islittle evidence of acute disease related to HBV, but the rates of chronic liver disease and liver cancer in adults are high (Alter,2003)Hepatitis B virus is spread from person to person primarilyby blood and blood

products. Blood transfusionremains a major mode of transmission in the UnitedStates; however, screening of donors has reduced the riskto 1 in 63,000 transfusions. Screening tests fail to exclude small percentage of donors who have infectious viral particlesin their blood despite being negative for HBsAg.Hepatitis B virus is also found in other body fluids,including urine, bile, saliva, semen, breast milk, and vaginalsecretions. It is not found in feces, however. Membranecontact with any of these body fluids can result in transmission.The virus can be spread to sexual partners, and its prevalent in homosexual men and heterosexuals withmultiple partners. It can be readily spread from mother toneonate at the time of vaginal delivery—a common modeof transmission in developing countries. Intravenous drug abusers have a high incidence of hepatitis B. Reuse of needleshas also led to transmission of the virus duringplacement of tattoos and ear-piercing. Crowded environments such as institutions for the mentally handicapped, (Frederick and Southwick, 2007).

2.6Pathogenesis and immunity

After entering the blood, the virus infects hepatocytes, and viral antigens aredisplayed on the surface of the cells. Cytotoxic T cells mediate an immune attackagainst the viral antigens, and inflammation and necrosis occur. Immune attackagainst viral antigens on infected hepatocytes is mediated by cytotoxic T cells. Thepathogenesis of hepatitis B is probably the result of this cell-mediated immuneinjury, because HBV itself does not cause a cytopathic effect. Antigen–antibodycomplexes cause some of the early symptoms (e.g., arthralgias, arthritis, andurticaria) and some of the complications in chronic hepatitis (e.g.,glomerulonephritis, cryoglobulinemia, and vasculitis), (Levension,2014). Fullydifferentiated hepatocytes are the primary cell type infected

byHBV. The primary cause of hepatic cell destruction appears to bethe cell-mediated immune response, which results in inflammationand necrosis. The cells involved are cytotoxic T cells, which reactspecifically with the fragments of nucleocapsid proteins (HBcAg andHBeAg), expressed on the surface of infected hepatocytes. Thisresponse also contributes to control of the infection by eliminatingvirus-producing cells. Enhanced natural killer cell activity, as well asproduction of interferon-γ also contributes to limiting the extent ofinfection. Anti-HBsAg antibody, which is the neutralizing antibody,does not appear until well into the convalescence period, when itmay aid in clearing any remaining circulating free virus (Harvey*et al*., 2007).

2.7Clinical Presentation/NaturalHistory

2.7.1Acute Infection

After exposure to the virus, there is a long, asymptomatic incubation period, which may be followed by acute diseaselasting many weeks to months. The naturalcourse of acute disease can be tracked using serum markers(Kumar*et al*.,2013).

• HBsAg appears before the onset of symptoms, peaks during overt disease, and then declines to undetectable levels in 3 to 6 months.

• Anti-HBs antibody does not rise until the acute diseases over and usually is not detectable for a few weeks toseveral months after the disappearance of HBsAg. Anti-HBs may persist for life, conferring immunity; this is thebasis for current vaccination strategies using noninfectious. HBsAgHBeAg, HBV-DNA, and DNA polymerase appear inserum soon after HBsAg, and all signify active viralreplication. Persistence of HBeAg is an important indicatorof continued viral replication, infectivity, andprobable progression to chronic hepatitis. The

appearanceof anti-HBe antibodies implies that an acute infectionhas peaked and is on the wane(Kumar*et al*.,2013).

IgM anti-HBc becomes detectable in serum shortlybefore the onset of symptoms, concurrent with elevationof serum aminotransferase levels (indicative of hepatocytedestruction). Over a period of months, the IgM anti-HBc antibody is replaced by IgG anti-HBc. As in the caseof anti-HAV, there is no specific assay for IgG anti-HBc,but its presence is inferred from decline of IgM anti-HBcin the face of rising levels of total anti-HB (Public Health Agency of Canada,2008).Initial infection with hepatitis B virus (HBV) maybe asymptomatic in up to 50 per cent of adults and90 per cent of children,When symptomsoccur, they may include anorexia, vague abdominalpain, nausea, vomiting and jaundice,Fevermay be absent or mild (Heymann,2008). Extrahepaticmanifestations such as arthralgias, arthritis, macularrashes, thrombocytopenia or papular acrodermatitis(Gianotti-Crosti syndrome) can occur early in thecourse of the illness and may precede jaundice, Acute HBV infection cannotbe distinguished from other forms of acute viralhepatitis on the basis of clinical signs andsymptoms or nonspecific laboratory findings (American Academy of Pediatrics, 2012).

2.7.2Chronic Infection

While the majority of individuals infected withHBV are able to clear the virus, some individualsfail to mount an adequate immune response,leading to chronic infection (Conlyand Johnston,2007). The exactmechanisms by which chronic liver injury occurs inHBV infection are not known (Kozieland *Siddiqui*,2010). Hepatitis Bvirus infection becomes chronic in approximately90 per cent of infants infected at birth (American Academy of Pediatrics,2012) If chronic infection is established, the spectrumof illness ranges from the healthy carrier state to allof the sequelae of

chronic hepatitis, including mildto moderate fibrosis, compensated cirrhosis, hepaticdecompensation and hepatocellular carcinoma(HCC), The single most important riskfactor for HCC is cirrhosis (Pungpapong *et al.*,2007). Individuals who areimmunosuppressed or have an underlying chronicillness are at increased risk of developing chronicinfection (Heymann, 2008;American Academy of Pediatrics,2012). Factors that may influence thenatural history of chronic infection include gender,race, alcohol use, and co-infection with hepatitis A,hepatitis C or hepatitis D viruses or humanimmunodeficiency virus (HIV) (American Academy of Pediatrics,2012). Antiviraltherapy can modify the natural history of chronic HBVinfection (Yimand Lok ,2006).Superinfection or co-infection is not uncommon in patients with chronic HBV infection. Acutehepatitis delta virus (HDV) may be acquired as co-infection simultaneously with HBV or as asuperinfection in a patient who is already a carrierof HBV (Sherman*et al.*, 2007). Infection with HDV in HBVinfected individuals is associated with more severe and/or progressive liver disease than is HBVmonoinfection.The natural course following acute hepatitis C virus(HCV) superinfection has not been well studied.The long-term prognosis following acute HCVsuperinfection is worse than that following HDVsuperinfection (Liaw*et al.*,2004). Individuals co-infected withthe parasite *Schistosoma* (Schistosomiasis) are morelikely to have more severe hepatitis B manifestationsand become chronic carriers of HBV (Plourde,2008).

2.8HBV and Hepatocellular Carcinoma

Epidemiologic studies have demonstrated that there is a consistent and specific causal association between HBV infection

andHCC(Beasley*etal.* 1981;Chen*etal.*1996). In patients with persistent HBV infection, the risk of HCC was 100 times higher than in non-infected individuals (Beasley*etal.* 1981).The global distribution of hepatocellular carcinoma correlates with the geographic prevalence of chronic carriers of HBV, whonumber 400 million worldwide. The highest rates are in Southeast Asia and sub-Saharan Africa, with the HCC incidence >50/100,000 populations (Bosch*et al.,*1999).Virological factors in the pathogenesis of hepatocellular carcinoma have recently been defined. Both retrospective andprospective studies strongly supported the relation between positive HBeAg and the risk of HCC (Lin*etal.*,1991). A prospective study inTaiwan showed that relative risk of HCC among men who were positive for both HBsAg and HBeAg were muchhigher than that among men who were positive for HBsAg alone . HBV DNA was identified as the most importantpredictor of the development of hepatocellular carcinoma in HBsAg-positive patients with different clinical conditions,therefore, efforts at eradicating or reducing the viral load may reduce the risk for HCC. Additionally, HBV genotype might play arole in the development of HCC. The data from Taiwan showed that genotype C is associated with more severe liver disease including cirrhosis and hepatocellular carcinoma (HCC), whereas genotype B is associated with the development of HCC in youngnoncirrhotic patients (Ishikawa*etal.*,2001;Ikeda*etal.*,2003;Ohata*etal.*,2004).

2.9Occult Hepatitis B

Occult hepatitis B is defined by the presence of HBV DNA in serum or liver in the absence of HBsAg (Hou*etal,* 2001;Hu*et al.*,2002). Serum HBVlevel is usually less than 104 copies/ml.

Although occult HBV infection has been identified in patients with chronic liver disease twodecades ago (Brechot*etal*.,1985), its precise prevalence remains to be defined. Occult HBV infection has been found in patients with HCC, pastHBV infection, or chronic hepatitis C, and individuals without HBV serological markers. The frequency of the diagnosis depends onthe relative sensitivity of HBV DNA assays and the prevalence of HBV infection in the population. Collectively, around 30% to35% of HBsAg-negative subjects with chronic hepatitis with or without HCC have positive serum HBV DNA (range from 5% to55%). The prevalence of HBV DNA is higher in anti-HBc positive, but anti-HBs-negative patients, ranging from 7% to 60% inpopulations highly exposed to HBV. HBV DNA is much less frequently identified in HBsAg-negative patients with acute, andparticularly fulminant hepatitis at around 10% and 7% in serum and liver samples (Brechot*etal*., 2001). Viral DNA persistence is not, however,restricted to patients with liver disease and may be observed in subjects with normal liver parameters, including blood and/or organ donors. Overall, occult HBV infection is seen in 7%-13% of anti-HBc-positive and/or anti-HBs-positive subjects, and in 0% to 17%of blood donors.The clinical significance of occult HBV infection remains unclear. Occult HBV infection represents a potential transmissionsource of HBV via blood transfusion or organ transplantation. In addition, occult HBV infection has been associated withcryptogenic chronic hepatitis and hepatocellular carcinoma. Furthermore, some studies suggested that occult hepatitis B might affectresponsiveness of chronic hepatitis C to interferon therapy and disease progress (Brechot*etal*., 2001).

2.10 Laboratory Diagnosis

2.10.1Serologic and Virologic Markers

The two most important serologic tests for the diagnosis of early hepatitis B are thetests for HBsAgand for IgM antibody to the core antigen. Both appear in theserum early in the disease (Levenson,2014).After a person is infected with HBV, the first virologicmarker detectable in serum within 1–12 weeks, usuallybetween 8 and 12 weeks, is HBsAg(Dan and Fauci,2010)Both acutely and chronically infected individuals have HBsantigenaemia. The diagnosis of acute disease is confirmedby demonstrating IgM anti-HBc in the serum. This appears2 weeks after HBsAg, and disappears a fewmonths after uncomplicated infection. IgG anti HBc persistsprobably lifelong, and is a marker of previous infection.The stage of evolution of antigenaemia and antibodyproduction is determined by EIA tests. Viral persistencecan be confirmed by PCR-based detection of HBV DNAin serum. Detection of HBe is still used as a marker of enhancedinfectivity and risk of chronic liver disease. (Bannister*et al.*,2006).

1.10.1.1Viral capsid surface antigen and the antibodydirected against the surface antigen (anti-HBs)

The HBsAg test was the first available for detectinghepatitis B. HBsAg appears in serum within 1 to 10weeks after exposure; its disappearance within 4 to6 months indicates recovery.The persistenceof HBsAg beyond 6 months indicateschronic disease. The disappearance of HBsAg maybe preceded by the appearance of anti-HBs, anddduring this period, patients may develop a serumsickness-like illness. In a large percentage ofpatients, anti-HBs does not rise to detectable levelsfor several weeks to months

after the disappearanceof HBsAg. During this window HBsAg and anti-HBs are both negative, and if these twotests alone are used for screening blood donors, a small percentage of infected donors may be missed.To prevent this occurrence, blood banks also testfor IgM antibody directed against HBcAg. Anti-HBs rises slowly over 6 to 12months and usually persists for life, providing protectionagainst re-infection(Frederick and Southwick,2007).

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2.10.1.2 Antibody directed against the core antigen (anti-HBc)

HBcAg is detected in infected hepatocytes, butis not released into serum; however, IgM antibodydirected against HBcAg (anti-HBc) is usually the earliestanti-hepatitis B antibody detected in the infectedpatient.The IgM anti-HBc is usually interpreted as a marker for early acute disease; however,in some patients, anti-HBc IgM levels can persistfor up to 2 years after acute infection, and in patientswith chronic active hepatitis, IgM antibody levels canrise during periods of exacerbation. An anti-HBc IgMtiter is particularly helpful for screening blood donors,because this antibody is usually present during thewindow between HBsAg disappearance and anti-HBsappearance. The IgG antibodies directed against thecore antigen develop in the later phases of acute diseaseand usually persist for life(Frederick and Southwick,2007).

Secreted core antigen (HBeAg) and its antibody(anti-HBe)

Naked DNA strands and associated proteinsmake up HBeAg.The presence ofHBeAg in serum indicates active viral replication,and it persists in patients with chronic disease, itspresence correlating with infectivity. As the patientwith acute hepatitis B recovers, HBeAg disappears,and anti-HBe appears. Seroconversion from

HBeAgto anti-HBe usually corresponds with the disappearanceof hepatitis B virus DNA from the serum(Frederick and Southwick,2007).

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2.10.3Polymerase chain reaction (PCR) test

It is based on the use of DNA fragment called the gene probe (39). Gene probe isrelatively small, single stranded DNA segment that can hunt for complementary fragmentof DNA (Mumtaz*et al*,2011).To use a gene probe effectively, it is valuable to increase the DNA to be searched.Thepolymerase chain reaction (PCR)accomplishes this task (Pommerville, 2004).

2.10.3.1 Hepatitis B viral DNA (HBV-DNA)

Quantizationof viral DNA in serum is most commonlyused in the assessment of patients with chronicactive hepatitis. In the patient with acute hepatitis,this test provides no significant advantagesover that for HBeAg. Both tests indicate activeviral replication. In patients with fulminanthepatitis, assays for HBV-DNA has been positive in the absence of other positive markers forHBV(Frederick and Southwick,2007).

2.11 Treatment

No antiviral therapy is typically used in acute hepatitis B. For chronic hepatitis B,entecavir (Baraclude) or tenofovir (Viread) are the drugs of choice. They arenucleoside analogues that inhibit the reverse transcriptase of HBV. Interferon in theform of peginterferon alfa-2a (Pegasys) is also used. Other nucleoside analoguessuch as lamivudine

(Epivir-HBV), adefovir (Hepsera), and telbivudine (Tyzeka) areused less frequently. A combination of tenofovir and emtricitabine (Emtriva) is alsoused (Levenson,2014).

2.11.1Drugs active against HBV

Lamivudine, 100 mg daily, orally (also used for HIV), **a**defovir dipivoxil, 10 mg daily, orally, tenofovir (used for HBV/HIV co-infected patients), alternative: interferon alpha, 5–10 MIU three times weekly,subcutaneously for 6 months.If an antiviral drug effective against HBV is also beingused to treat HIV co-infection, the HIV-treatment doseshould be given (this is often higher than the dose for HB) (Bannister *et al.*, 2006).

2.12Prevention

Prevention involves the use of either the vaccineor hyperimmune globulinor both (Levenson,2014).

2.12.1Passive Immunoprophylaxis

Hepatitis B immune globulin (HBIG) contains a high titer of HBsAb. It isused to provide immediate, passive protection to individuals known to be exposedto HBsAg-positive blood (e.g., after an accidental needle-stick injury) (Levenson,2014).Immunoprophylaxis is recommended for allinfants born to HBsAg positive mothers. Current dosing recommendations are 0.13ml/kg HBIG immediately after delivery or within12 hours after birth in combination with recombinant vaccine. The combination results in a higher-than-90% level of protectionagainst perinatal acquisition of HBV (Stevens., Taylor. And Tong. 1987). Between 3.7% to 9.9% of infants still acquire HBV infection perinatally from HBVinfectionmothers, despite immunoprophylaxis. Failure of passive and active immunoprophylaxis in this setting may be theresult of in utero transmission of HBV infection, prenatal transmission related to a high inoculums, and/or the presence of surfacegene escape mutants. To

study the interruptive effect of HBIG before delivery in attempt to prevent intrauterine transmission ofHBV, a large-scale, random-control study was conducted in China (Zhou*etal.*,2003). In this study, nine hundred and eighty HBsAg carrierpregnant women were randomly divided into HBIG group and control group. Each subject in the HBIG group received 200 IU or400 IU of HBIG intramuscularly at 3, 2 and 1 months before delivery, in addition to newborns receiving HBIG intramuscularly. Bythis way, the rate of intrauterine transmission in this group fall to 5.7%, compared to 14.3% in control group. ($P < 0.001$). However,the preventive effect of HBIG administration before delivery needs to be confirmed by more study in the future.Hepatitis B immune globulin remains a central component of prophylaxis in HBV-infected patients undergoing livertransplantation. HBIG monotherapy given at a high dosage can prevent recurrence in 65% to 80% of patients. Because the cost oflong-term prophylaxis with high-dose HBIG is extremely high and combination therapy using HBIG with a nucleoside analog ismore uniformly effective, the current protocol is combination HBIG with a nucleoside analog after liver transplantation. Thesecombination protocols have reduced the rate of virologic breakthrough to 10% or less (Terraultand Vyas, 2003).

2.12.2Active Immunization

Prevention of primary infection by vaccination is an important strategy to decrease the risk of chronic HBV infection and itssubsequent complications. The first-generation hepatitis B vaccine, an inactive plasma-derived vaccine, became available in 1982.Consequently, the second generation of HB vaccine, a DNA

recombinant HB vaccine was also available for general use in 1986.Both of the vaccines were proven to be safe and efficacious in preventing HBV infection. (WHO) recommended that hepatitis B vaccination should be included in national immunization system in all countries with ahepatitis B carrier prevalence (HBsAg) . By May 2002, 154 countries hardoutine infant immunization with hepatitis B vaccine (Lavanchy,2004).The world's first universal vaccination program for HBV infection was launched in 1984 in Taiwan (Ni*et al.* 2001). During the first 2years of the program, coverage was provided mainly for infants whose mothers were carriers of HBsAg. Vaccination wassubsequently extended, first to all newborns and then to unvaccinated preschool-age and elementary school-age children. Since1991, catch-up vaccinations have been given to children in the first grade. This program reduced the overall HBsAg prevalence ratefrom 9.8% in 1984 to 1.3% in 1994 among children <15 years of age. The HBV carrier population was further reduced through improved maternal screening (Chen*et al.*,1996). In 1999, vaccination rates were 80–86% for young children and higher than 90% for olderchildren; the prevalence of HBsAg was reduced to 0.7% for children younger than 15 years of age (Ni *et al.*,2001). To evaluate the long-termefficacy of hepatitis B (HB) vaccination in newborns, one of the longest HB vaccine follow-up studies in the world was conducted inShanghai, China (Zhou*etal.*, 2003). Children who were born in 1986 and immunized with hepatitis B vaccine at birth were followed up at leastonce a year. Serum HBsAg, anti-HBc and anti-HBs were tested. The positive rates of HBsAg in the vaccine group with the period of16 years were 0.46%-0.97%, the average being 0.61%, which was much lower than those of

baseline before vaccination and externalcontrol. The long-term efficacy of newborn vaccination was 85.42%. In countries such as Italy and the United States, the incidenceof acute hepatitis B has declined dramatically during the past decade after vaccination program for HBV infection, particularlyamong persons in younger age group (Da villa,2000).Universal HB vaccination was proven to be effective in the prevention of HCC in several large cohort studies in SoutheastAsia(Chang *et al.*,1997).

CHAPTER THREE

MATERIAL AND METHODS

3.1. Study design

This study was a descriptive cross-sectional study**.**

3.2. Study area:

This study was conducted in ALdueimlocality, is on west bank of the White Nile in Sudan, about 190 km from Khartoum.

3.3Study duration

The study was carried out between January 2017and May2017

3.4. Study population

Health care workers including (Laboratory technologist, Nurses, Laboratory assistant, Pharmacist and Cleaning staff).

3.5. Sample size

Ninety-two(n=92) health care workers were recruited for this study.

3.6 Ethical consideration

Ethical approval to conduct this study in the region was obtained from the Health Services Director in AL dueim locality and verbal consent was obtained from participants before collection of the blood samples.

3.7. Data collection

A structured questionnaire was used to collect demographic and clinical data.

3.8 Collection of blood specimens

Under sterile condition Five ml of venous blood sample was withdrawn from each participant, then waited until sample clotted the serum was separated by centrifugation at 5000rpm for five minutes, serum wasseparated into plain vacutainers then stored at -20C˚ until used.

3.9 Laboratory investigation

HBV surface antigen (HBsAg) was screened by HBsAg (high sensitivity) - ELISA Kit.

3.9.1ELISA technique:

Method:ELISA (Enzyme linked immune sorbent assay)

Fortress HBsAg is an in vitro diagnostic kit for the detection of hepatitis B surface antigen (HBsAg) in human serum or plasmaIntended use: -

For screening of blood donors

For monitoring individuals with a higher than normal risk of contracting hepatitis e.g. patients, Technicians or nursing personnel in renal dialysis units or clinical laboratories as an aid the diagnosis of liver disease

3.9.1.1. Principle

The test is an enzyme linked immune sorbent assay based on sandwichprinciple. Polystyrenemicrotiter wells have been coated with a monoclonal HB antibodies to HBsAg patterns serum or plasma sample is added to the micro wells. During incubation the specific –immune complex formed in the case of presence of

HBsAg in the sample, iscaptured on the solid phase. After washing to remove sample serum proteins ,Second antibody conjugate to the enzyme HRP and directed against different epitopes of HBsAg is added to the conjugated antibodies will be bound to any ant-HBs-HBsAg complexes previously formed during the first incubation ,and The un bound HRP conjugate is then removed by washing after washing to unbound HRP conjugate,chromogen solutions containing TMB and urea peroxidas are added to the wells .in the presence of antibody-antigen , antibody HRP sandwich immune- complex ,the colorless chromogen are hydrolyzed by the bound HRP conjugate to blue colored product .The blue colure turns yellow after stopping the reaction by using the stop solution. The color intensity can be measured and it is proportional to the amount of the antigen captured in the wells and it is amount respectively. wells containing samples negative for HBsAg remain colorless.

3.9.1.2. Assay procedure:

The reagent and samples were allowed to reach room temperature Numbered of wells including two negative control e.g. (B1, C1) and one blank (e.g. A1) and one blank (e.g. A1, neither samples nor HPR conjugate should be added into the blank wells). Then added 20ul of sample diluents to each well except the blank and mixed by toping the plate gently.and added 100ul of positive control and negative control and specimen to their respective wells by using separate disposable tip for each specimen negative control and positive control to avoid contamination.Then added 50 ul HRP conjugate to each well except the blank and mixed tapping the plate gently. Andcovered the plate with plate cover and incubated for 30 minutes for 37˚Cat the end of the incubation removed and

discard the plate coverWashed each well 5 times with diluted wash buffer. Each time allowed the micro wells to soaked for 45 second, Afterthe five washing and plotting paper or clean towel,and tap it to remove any remainders.After washing dispense 50ul of chromogen A and 50ul of chromogen B solutions was added into each well including the blank and mixed by tapping the plate gently. incubated the plate at 37˚C for 15 minutesStopped the reaction by using a multichannel pipette, added 50ul stop solution into the each well and mixed gently the absorbance measured at 450 nm. and calculated the cut-off value and evaluated the result and read the absorbance within 5 minutes after the stopping the reaction.

Interpretation of results:

Each micro plate should be considered separately when calculated and interpreting result of the assay ,regardless of the number of the plate concurrently processed the results are calculated by relating each samples optical density (OD) value to the cut-off (C.O.) of the plate .if the cut-off reading spaced on single filter plate reader ,results should be calculated by subtracting the blank well OD value from the print report value of samples and controls , In case the reading spaced on dual filter plate reader , don't subtract the blank well OD from the print report values of samples and controls.

Cutoff value (C.O.) =*NC*2.1

*__NC__=the mean absorbance value of two negative controls**Negative result:** sample giving an absorbance less than the cut off value are considered negative, which indicate no HBVsurface antigen has been detected with this HBsAg ELISA kits.

Positive result:sample giving an absorbance greater than the cut off value are considered initially reactive, which indicate HBVsurface antigen has been detected with this HBsAg ELISA kit.

3.10. Statistical analysis

The data analysis was done through Statistical Package for the Social Scinces (SPSS)version22and *Chi-square* test was used to assess the association between various variables.

CHAPTER FOUR

RESULTS

4.1 Results

A total ninety- two health care workers (HCWs)who were considered at occupational risk of contracting HBVinfection were enrolled in this study.Fourty seven (51.1%)were male and 45/92(48.9%) were female, the sero-positivity among males was 2 (2.2%) and among females was 6 (6.5%)from the total infected participants 8 (8.7%).

Table 4.1 The distribution of HBsAg positive according to gender

SEX	HBVresult		
	Positive	Negative	Total
Male	2	45	47
	2.2%	48.9%	51.1%
Female	6	39	45
	6.5%	42.4%	48.9%
Total	8	84	92
	8.7%	91.3%	100.0%

Result indicated insignificant p-value = 0.122 (p-value >0.05).

Twenty three (25%) of the participants were vaccinated and 69/92 (75%) were not vaccinated (by using questionnaire)

Table 4.2 HBV result and vaccination

HBV results	vaccine		
	Vaccinated	Non vaccinated	Total
Positive	3/3.3%	5/5.4%	8/8.7%
Negative	20/21.7%	64/69.6%	84/91.3%
Total	23/25%	69/755	92/100%

p-value = 0.393 insignificant.

while47 (51.1%) were married and 45(48.9%) were single.

Table 4.3 frequency of HBV results among marital status

HBV result	marital status		
	married	single	Total
Positive	3/3.3%	5/5.4%	8/8.7%
Negative	44/47.8%	40/43.5%	84/91.3%
Total	47/51.1%	45/48.9%	92/100%

p-value = 0.421 insignificant .

Table 4.4: Frequency of Hepatitis B virus result among health care workers

Health care workers	HBV positive result	HBV negative result
Lab technologist	3/3.3%	19/20.7%
Lab assistants	0/.0%	1819.6%
Nurse	2/2.2%	31/33.7%
Pharmacist	0/0%	3/3.3%
Cleaning staff	3/3.3%	13/14.1%

p-value = 0.289(p-value > 0.050 result indicated that in significant association between occupation practice.

Twenty four 24 out of 92 were exposed to an accidental injury

Table 4.5 Distribution of HBV infection according to accidental injury

	Injury		
HBV results	Yes	no	Total
Positive	4/4.3%	4/4.3%	8/8.7%
Negative	20/21.7%	64/69.6%	84/91.3%
Total	24/26.1%	68/73.9%	92/100%

p-value 0.107 (p-value >0.05) insignificant.

Table 4.6 Association of HBsAg results and blood transfusion

HBV results	Blood transfusion Yes	no	Total
Positive	0/.0%	8/8.7%	8/8.7%
Negative	2/2.2%	82/89.1%	84/91.3%
Total	2/2.2%	90/97.8%	92/100%

p- value = 0.569 (p-value >0.05) insignificant**.**

Table 4.7: Distribution of HBV infection according to age groups

AGEGROUP	**HBVresults** Positive	Negative	Total
20-40 years	8 8.7%	70 76.1%	78 84.8%
41-60 years	0 .0%	14 15.2%	14 15.2%
Total	8 8.7%	84 91.3%	92 100.0%

p-value = 0.210 (p-value > 0.05) insignificant.

CHAPTER FIVE

DISCUSION,CONCLOSIONS, &RECOMMENDATIONS

5.1 Discussion

In this study the sero-prevalence of HBsAg was assessed for 92 (HCWs) atAD duwaymlocality hospital and selected health centers. Only 8(8.9%) were positive for HBsAg andthis result is similar to those reported from Tanzania where the prevalence of hepatitis B virus among HCWs in tertiary hospital was (7%) (Mueller *et al.*2015) and the results are similar to those reported from Yemen and Palestinewhich were (9.9%) and (9.60) respectively (Alhurabi*et al.*, 2004; Jadallah *et al.*, 2005). While, they disagree with other report from White Nile State, Sudan which was (27%) (Abuelgasim *etal.*, 2013).The result is higher than other studies done in Koreawhich was (2.4 %) (Shin *et al.*,2006), Morocco which was (1%) (Djeriri *et al.*, 2008), Khartoum which was (4.4%)(Abdalwhaband Nafi, 2014) and Lagos State in Nigeria which was (1.5%)(Abiola *et al.* 2016). The variation between some of the results particularly that carried at White Nile State could be attributed to the difference in the population and the sample size.

The incidence of infection in laboratory technologist (3 participants), nurses (2 participants), and cleaning staff (3 participants) could be justified by the frequent contact of those HCWs with sources of infection (e.g., accidental needle stick injuries).Such incidents might occur while giving an injection or after injection , including recapping contaminated needle, and handling infected sharps before and after disposal, contaminated blood during sampling, unsafe sharps waste management, and reuse of injection equipment to administer injection to more than one

person. Although majority of the participants in this study were not vaccinated against Hepatitis B virus infection25% only. Some of the vaccinated participants were infected by HBV andthis could be due to poor response to vaccine, theparticipantswere immunosuppressed, or they were vaccinated with non-effective vaccine.In this study onlyeight were positive for HBsAg which represent(8.7%) and this couldbe due understanding of HCWs to the safety protocols that prevent against blood borne infections.

5.2 Conclusions

In conclusion, this study has shown that only 8.7% of the HCWs at AD= duwaym locality were positive for HBsAg. Laboratory technologist were the most affected and only one from those who had blood transfusion was positive. HCWs with frequent injuries had higher prevalence of HBV infection than others.

5.3. Recommendations

1- HCWs should be screened regularly for Hepatitis B virus and other blood-borne infections.

2- Further studies should be conductedwith larger sample size to confirm these results.

3- HCWs should be vaccinated against Hepatitis B virus (HBV) and ensure they are assessed for immunity (post-vaccination management).

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جامعة السودان للعلوم والتكنولوجيا

كلية الدراسات العليا

استبيان

APPENDICES (1)

الكشف عن فيروس الكبد الوبائي (النوع ب) بين العاملين في مجال الرعاية الصحية الأولية في محلية الدويم. ولاية النيل الأبيض

Questionnaire on Detection of Hepatitis B Virus among health care workers in AD DUWAYM locality , White Nile State –Sudan.

Data collection Sheet

General data

1. ID. number……
2. Gender

Male ( ) female( )

3.Age……..

4.locality ……..

Urban ( ) rural ( )

5.Marital status

Married( ) single( )

6.Type of occupation……...

7. duration in hospital…….

8. Vaccine

Yes ( ) No( )

9.Have you taken a sharp instrument?

Yes( ) No( )

If the answer is yes ,what is the procedure used in the hospital to treat the injured person?.....

10.Blood transfusion

Yes( ) No( )

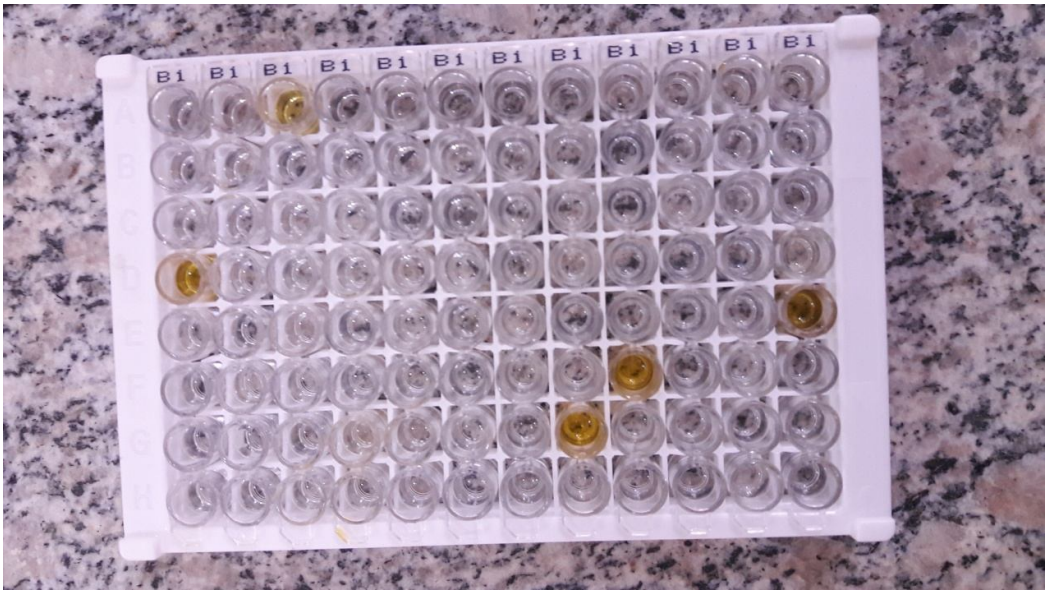
11.Surgical operation

Yes ( ) No( )

12.Renal dialysis

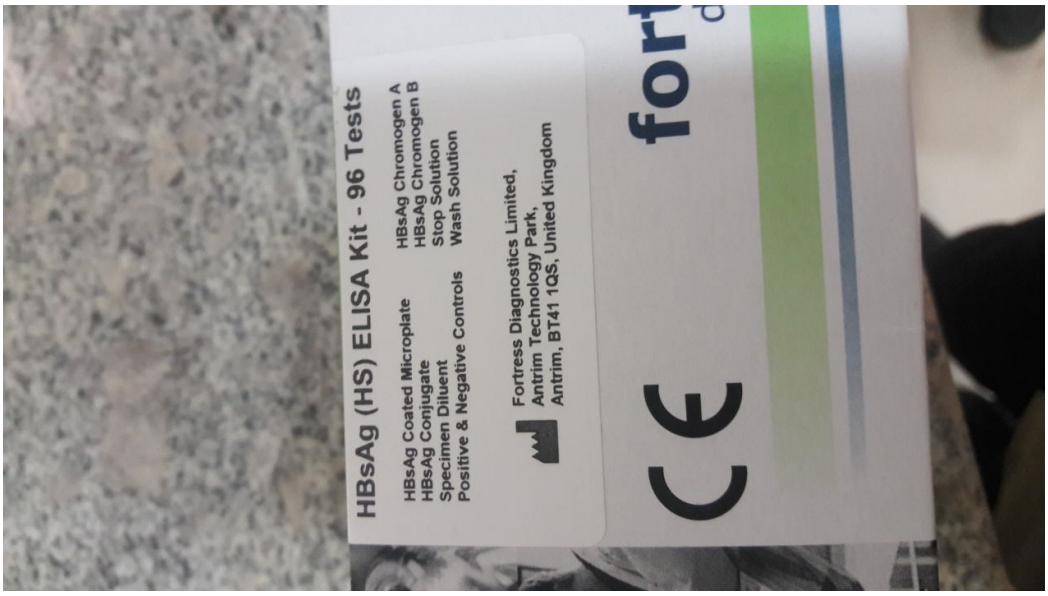
Yes( ) No( ).

Appendix (2)



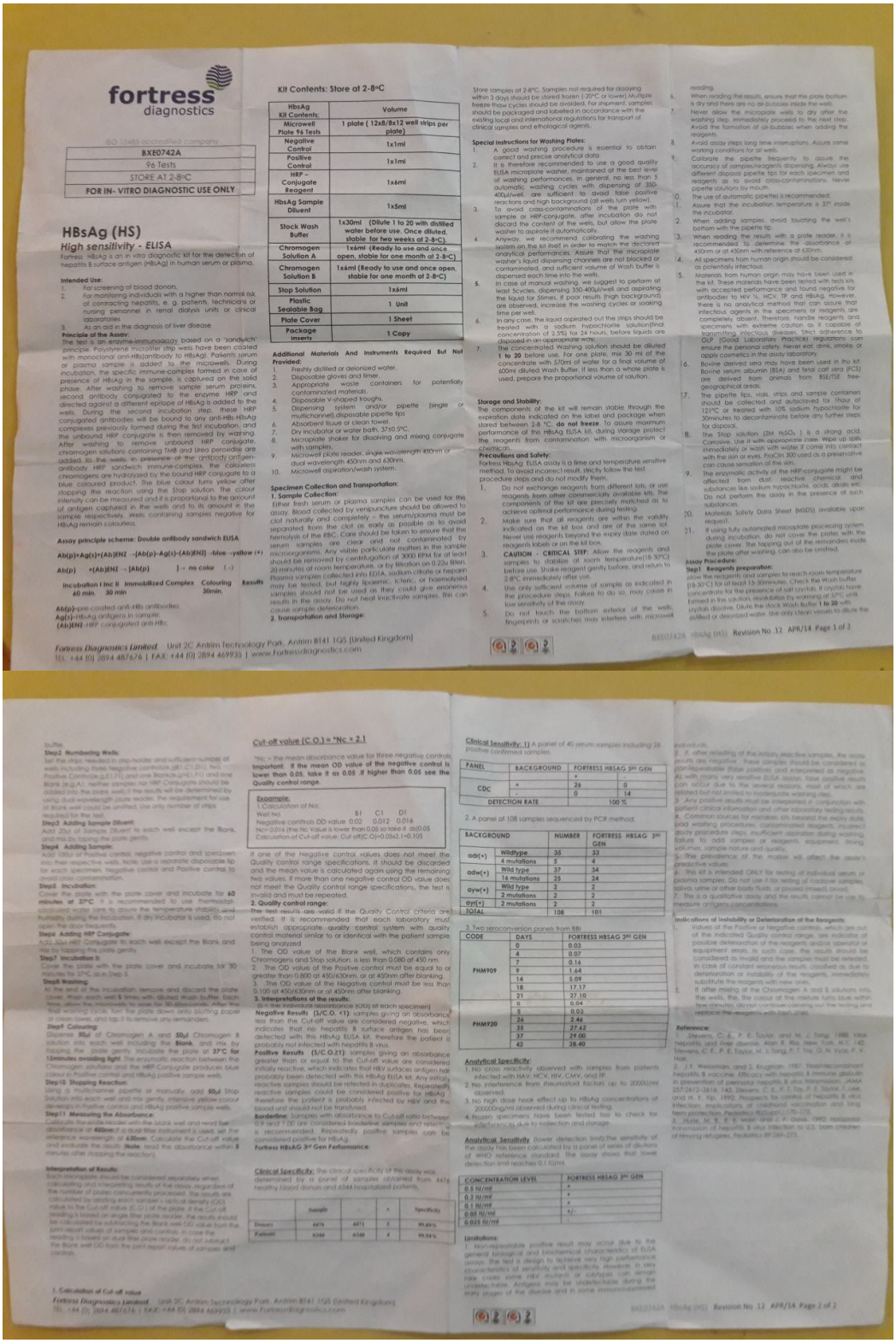
ELISA Results

Appendix (3)



ELISA Kit in study

Appendix (4)



ELISA sheet