Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature

_____ _____

Homoud Saad Algarni Date

Trends of Reported Cases of Hepatitis B Virus Infection, Kingdom of Saudi Arabia, 2009 – 2013

by

Homoud Saad Algarni

Master of Public Health

Hubert Department of Global Health

Scott J. N. McNabb, Ph.D., M.S.

Thesis Committee Chair

Trends of Reported Cases of Hepatitis B Virus Infection, Kingdom of Saudi Arabia, 2009 – 2013

by

Homoud Saad Algarni

MD, 2005 (King Abdul Aziz University, Jeddah)

SBFM, 2010 (Saudi Commission for Health Specialties)

ABFM, 2010 (Arab Board Of Health Specializations)

Thesis Committee Chair: Scott J. N. McNabb, Ph.D., M.S.

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

Global Health

2014

ABSTRACT

PURPOSE: Hepatitis B virus (HBV) infection is widespread globally and a serious public health threat. Understanding the distribution of HBV is important to policymakers to evaluate public health surveillance and develop prevention and control policies. Therefore, we studied the trends of reported HBV infection in the Kingdom of Saudi Arabia (KSA) during the 5-year period from 2009 – 2013.

METHODS: Laboratory-confirmed HBV cases reported to the KSA Ministry of Health (MoH) National Hepatitis Program (NHP) were analyzed by year, gender, nationality, region, and age group.

RESULTS: There were 23,236 cases of HBV infection reported to the KSA MoH during the 5-year period 2009 – 2013. In 2009, the incidence rate (IR) of HBV infection was 19.3 (95% CI = 18.8, 19.9) per 100,000 population. The IR significantly decreased to 14.7 (95% CI = 14.2, 15.1) in 2013. The IR was consistently greater among males than females (in 2013, 16.7 versus 12.2). Over the study period, Saudi citizens had a 2- to 3-fold greater IR than non-Saudis (in 2013, 18.7 versus 5.9). There was a large variation among HBV infection IRs across regions, with Tabouk having the highest. The greatest number of cases was found among those aged 15 to 44 years, followed by those > 45 years of age.

CONCLUSION: Despite the significant decrease in the IRs over the 5-year period from 2009 – 2013, HBV infection remains a major public health problem in KSA. Therefore, there is a need for continuous monitoring and evaluation of the disease's observation protocols and prevention strategies. Various strategies and preventive measures should be implemented to control HBV infection, and well-designed research programs should be carried out in different regions of KSA to improve planning and define the priorities in tackling this health issue.

Trends of Reported Cases of Hepatitis B Virus Infection, Kingdom of Saudi Arabia, 2009 – 2013

by

Homoud Saad Algarni

MD, 2005 (King Abdul Aziz University, Jeddah)

SBFM, 2010 (Saudi Commission for Health Specialties)

ABFM, 2010 (Arab Board Of Health Specializations)

Thesis Committee Chair: Scott JN McNabb, Ph.D., M.S.

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

Global Health

2014

Table of Contents

ABBREVIATIONS

GCC-Gulf Cooperation Council

HAV-hepatitis A virus

HBV- hepatitis B virus

HCC- hepatocellular carcinoma

HCV-hepatitis C virus

HBeAg-hepatitis B e-antigen

HBsAg-hepatitis B surface antigen

IR-incidence rate

KSA-Kingdom of Saudi Arabia

MoH-Ministry of Health

NGHA-National Guard Health Affairs

NHP-National Hepatitis Program

PCR-polymerase chain reaction

WHO- World Health Organization

Chapter I: INTRODUCTION

Hepatitis B virus (HBV) infection remains a major health problem that leads to substantial morbidity and mortality (1). More than 350 million people worldwide carry HBV. Many die from long-term effects: cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC) (2). HBV is a major risk factor for liver cancer and is responsible for a substantial portion of cancer worldwide (3). The virus causes an infection endemic in many parts of the world. Infection rates are greatest in developing countries, especially among people who are considered at high risk of acquiring HBV (4).

Transmission occurs when a healthy person comes in contact with infectious blood, vaginal fluids or semen, and sometimes saliva, urine, or the tears of chronic carriers (5). HBV is also transmitted from chronically infected mothers to their newborns, who consequently develop chronic HBV infection. The virus infects liver cells and can cause acute liver damage (6). The majority of adults exposed to HBV suffer acute infections, while a minority proceeds to develop chronic HBV infection.

No effective treatment for HBV infection has been discovered, so control and prevention are essential. The people who become infected with hepatitis B surface antigen (HBsAg) and remain asymptomatic are called silent carriers (7). These silent carriers are mainly young and are responsible for transmitting the virus to unsuspecting healthy individuals.

The Kingdom of Saudi Arabia (KSA) healthcare system has effective methods for dealing with most of the acute infections; however, the system still has a problem dealing with chronic infections (7). The Ministry of Health (MoH) in the KSA vaccinates all newborns for

HBV in accordance with the World Health Organization (WHO) guidelines; screens blood donors, pregnant women, couples planning for marriage, and health care staff; and educates the population about HBV and its modes of transmission.

Background

KSA has one of the best medical systems in the Middle East due to well-trained doctors and nurses. Medical care in KSA is of the required standard and is available in all major cities. The increased risk of hepatitis B and other bloodborne diseases like HIV – transmitted via poorly sterilized equipment – is worrisome (8). The increasing incidence rate (IR) of chronic infections is a big challenge for the KSA healthcare system, and healthcare officials must therefore be in a position to deal with the challenges.

Contact with infected blood, the use of contaminated needles, and sexual intercourse with someone infected can cause HBV (9). HBV infections are transmissible through blood exchanges and transfusions, inoculation with unsterilized instrument, breastfeeding, and sexual intercourse (10). The disease causes jaundice and affects the liver, potentially causing its failure. People are advised to get vaccination when travelling in and out of the country since the disease has no cure and can only be prevented.

HBV infection is a leading health risk in KSA; it has claimed a number of lives there and in other parts of the world (11). HBV infection and other chronic diseases contribute to a large percentage of the disease burden in most countries, raising concerns about its management. The prevalence of HBV infection varies significantly across the world, with Western Europe and the United States recording the lowest prevalence; Africa and Asia record the highest.

HBV is a major cause of chronic liver disease complications, which include cirrhosis and hepatocellular carcinoma (HCC). The people who are infected with HBV show a wide spectrum of disease manifestations ranging from no symptoms to HCC.

The prevalence of HBV infection in KSA has declined considerably since the introduction of the immunization program in 1989. Before the program began, it was 7% in 1989, and by 1997, it had fallen to 0.3% (12). Children are vaccinated at birth and while at school. Studies show that the efficacy of the HBV vaccine diminishes as one grows (13). The long-term hepatitis B program in KSA exists to prevent virus transmission among all age groups with the ultimate aim of eliminating and eradicating it. This has proved difficult due to the more than 300 million world carriers and the variety of HBV genotypes that have distinct geographic distribution (2). The declining prevalence of the infection among Saudi Arabia's population can be attributed to the increase in preventive measures such as vaccination, investigation of blood donations, maternal screening, pre-marital screening, and health education of the population through the media and social networks.

Statement of the problem

The increasing numbers of HBV chronic infections has led to the need to understand the distribution and prevention opportunities. This may require changing the KSA healthcare system's approach to hepatitis B infection. The KSA healthcare system must develop a better surveillance system to diagnose and follow up on the HBV infection cases. HBV continues to be a problem as there is no effective treatment (14). There have been numerous studies regarding its danger and how it is transmitted. Many have been conducted in KSA describing the prevalence of hepatitis B among children and the general population, including blood donors.

Rationale

This study analyzed the trends of reported hepatitis B infections in KSA. One investigation analyzed the causes of infection; in that study, the incubation period for patients with HBV was determined and symptoms were studied. However, there were not sufficient data available for the Middle East (15). In our study, we will explore the distribution of HBV infection in KSA. We hope this study will help program planners and policymakers to evaluate the HBV surveillance program and develop policies for preventing HBV infection in KSA.

Objectives

1. Evaluate the trends of HBV in KSA during a 5-year period from 2009 to 2013;
2. Analyze HBV IR by gender and nationality;
3. Analyze HBV IR by the 13 KSA administrative regions (provinces);
4. Compare the number of reported HBV cases by age group.

Chapter II: LITERATURE REVIEW

HBV infection occurs when there is exposure to the virus through one of the transmission pathways (16); specifically, when a healthy person comes into contact with infected blood, vaginal fluids or semen, and sometimes with saliva, urine, or the tears of chronic carriers. Also, perinatal infection serves as a significant transmission route, particularly in developing nations (17).

Consequently, working in healthcare settings or undergoing procedures like blood transfusions, dialysis, or acupuncture are risk factors for the transmission of HBV. Infected persons may transmit the virus through the sharing of toothbrushes or razors. Moreover, healthy people who travel in nations where hepatitis B is endemic are more susceptible to infection (18). Various researchers have established that the risk of transmitting HBV by way of holding hands, kissing, coughing, hugging, breastfeeding, sneezing, or sharing drinking glasses and utensils is very small (19).

Once a healthy individual acquires the disease, an acute illness develops, which in turn triggers liver inflammation, jaundice, vomiting, or anemia. As the disease progresses, the chronic form of HBV infection may develop, causing cirrhosis or HCC (20). It is possible to prevent HBV infection with vaccination, which can be administered to infants and adults, as well as to those travelling to areas where it is endemic. Although hepatitis B is not curable, it is possible to prevent the disease's complications by using antiviral medications such as lamivudine, tenofovir, adefovir, entecavir and telbivudine (21). Moreover, immunomodulators such as Pegasys and

interferon alpha-2a have shown efficacy in controlling the disease. Eventually, if complications such as cirrhosis or liver cancer develop, the disease can become untreatable due to medication resistance (21).

The structure of the hepatitis B virus is a circular, double-stranded DNA virus that has around 3200 nucleotides (22). Normally, the genome contains reading frames such as core (precore and core), polymerase, and X proteins. Research indicates that HBV genotypes represent naturally occurring HBV strains, which have changed drastically and are reflected in the worldwide HBV distribution (23). Currently, there are eight distinct HBV genotypes clustering in various parts of the world (24).

Epidemiology of HBV Infection and Scope of Study

HBV infection is a major global health issue, with about 2 billion exposed individuals, 350 million estimated carriers, and over 240 million who are chronically infected (25). This is a communicable disease affecting the liver. HBV carriers are predisposed to developing cirrhosis, chronic hepatitis, and HCC (26). Due to its global presence, HBV infection has had an overwhelming and dramatic impact on many nations, including the KSA.

Many researchers in KSA are committed to studying the epidemiology of HBV infection to understand its distribution. This information is significant for health planners, program managers, and policymakers. The current study focused on describing the distribution of HBV infection in KSA and the incidence among different populations. The latter remains to be more thoroughly explored.

HBV Infection in KSA

Different reports highlight HBV infection as a major burden on the KSA healthcare system due to its high morbidity and mortality (27). According to a 2008 KSA study, out of 74,662 persons who underwent premarital screening from January to May 2008, 1.3% tested HBV positive (28). Another study done in the same year indicated that HBV infection prevalence rates ranged from 1.5 to 2.6% among adults who had blood transfusions during the study period (29). In 2007,data monitoring the effectiveness of HBV childhood immunizations showed a prevalence of 0.22% in children and 0.05% in adults (30). From another perspective, the mean IR of HBV infection was around 0.15%, with massive variations ranging from 0.03 - 0.72% among regions (31).

To study the incidence of HBV infection in KSA as a whole, it is essential to understand past studies in the region. As will be shown in the following sections, several investigators have examined the epidemiologic picture of HBV infection in KSA, but did not address it in a comprehensive manner, nor did they compare the IR across the country's diverse populations and regions.

Literature on the Regional Distribution of HBV Infection in KSA

A study was undertaken to determine the specific viral hepatitis incidence trends in populations served by National Guard Health Affairs (NGHA) health facilities in eastern, western, and central KSA. The researchers performed an 8-year study for the data of surveillance

on the target population. The study was carried out in response to the fact that viral hepatitis is the second most common reportable viral infection in the region (32).

To obtain the data on IR, researchers analyzed surveillance data on viral hepatitis in the region's hospitals from Jan 2000 to Dec 2007. The surveillance system that helped in the data generation was located in King Abdulaziz City in Riyadh (32). The surveillance team was notified with weekly laboratory reports of confirmed cases of HBV, hepatitis C virus (HCV), as well as hepatitis A virus (HAV), from all the NGHA-served regions. According results, the mean annual seropositivity incidences per every 100, 000 persons were highest for HBV (104.6), followed by HCV (78.4), then HAV (13.6).

In addition, Saudi citizens showed a higher HBV IR than non-Saudis. Another observation from the results was a declining IR for the three viruses (32). However, despite the minor decline, HBV, as well as HCV, continued to be a significant public health challenge in the region. The study showed clearly that HBV had become a bigger health threat than the other hepatitis viral strains. To contain the disease, researchers recommended the comprehensive and improved implementation of preventive strategies, particularly vaccination.

In another report, Aljarbou (2009) studied the specific prevalence of HBV and HCV in Qassim region, from 2008 to 2010. To conduct the study, they obtained serum samples from 8,082 participants (4041 females and 4041 males). They focused on adults > 20 years of age who visited the King Fahad Healthcare Hospital before they got married. After analyzing the collected data, the researchers concluded that there was a higher prevalence of HBV than HCV (33). Here is a breakdown of the study's key findings. In 2008, 0.7% of participants had HBV compared to 0.1%of participants who had HCV. In contrast, 1.5% of participants had HBV in

2009, compared to 0.3% of participants with HCV. In 2010, 2.04% of participants had HBV compared to 0.8% of participants who had HCV. The findings reveal the incidence of HBV and HCV increased from 2008-2010. In light of this trend, the researchers predicted that the two viral infections would increase in prevalence in 2011, 2012, and 2013 (33).

Even though the researchers focused on young couples planning to marry, the data indicate how serious HBV and HCV are in Qassim region. In addition, the results highlight the need for cross-sectional research studies of HBV infection in Qassim and KSA, while at the same time indicating the need to reinforce vaccination programs to combat viral hepatitis (33). The researchers highlighted that for the effective control of the viral hepatitis especially with respect to HBV infection, there is a need for continuous monitoring and evaluation of surveillance and prevention strategies.

Hepatitis B Studies Comparing Saudis and Non-Saudis

As research in KSA explored the epidemiology of HBV infection, patterns indicated that Saudis were more affected than non-Saudis. For example, a study about viral hepatitis prevalence rates in the Quwayiyah Governorate took blood specimens drawn in 2012 from patients in Al-Quwayiyah hospital (34), and investigators identified patients by Saudi/non-Saudi and male/female. They show that among 2400 specimens tested, 2.12% were HBV positive. Saudi patients represented 84.3% of the HBV cases, while non-Saudis represented 15.7% of the cases. Additionally, males were the most affected, representing 80.4% of the HBV cases, with females representing 19.6% (34). After analyzing IR for HBV and the HCV, the researchers found that viral hepatitis in the area had decreased over the past three decades. These positive findings were attributable to substantial improvements in personal and public hygiene in Saudi

population (34). The researchers recommended more studies on the cause of the higher prevalence among Saudis, especially males. Our study will include the entire Kingdom to examine the IR between Saudis and Non-Saudis, in addition to examining the IR between males and females.

HBV Infection, by Age

As Abdo, *et al*. (2012) indicates, age is a determinant of HBV distribution in KSA. Compared to children, the infection rates among adults have a greater regional variation. This is attributable to the fact that immunization is mandatory for all children (since 1990) but not for the adults. In addition, the groups at higher risk of HBV infection are adults (31).

In a study to establish hepatitis B profile in KSA, and examine the commonly affected age groups, Alshabanat, *et al*. (2013) carried out a retrospective analysis of viral hepatitis cases. Researchers used KSA Ministry of Health (MoH) reports from 2006 – 2010 for the study. They found that the viral hepatitis incidence seems to decrease over time, with the exception of hepatitis B, which showed a slight increase over time. In fact, among hepatitis A, B, and C infections, researchers found HBV to be the most prevalent. It accounted for 53% of cases, while HAV accounted for 17% and HCV 30% of the cases (25).

In this study HBV infection was predominant in adults aged 15 – 44 years, who accounted for 69% of cases. In the study's conclusion, the researchers indicated that the slight viral hepatitis decline may be attributed to improved health care facilities and vaccination programs (25). However, they indicated the need to conduct further studies on specific risk factors, which put some age groups at higher risk for HBV. Actually, their latter recommendation supports the need for the current study.

Al-Ajlan, *et al*. (2010) described a study in which he evaluated hepatitis B, and C prevalence among the health college students in KSA. The researchers used student health records to obtain the data for calculating the prevalence. The 7-year study involved 16,570 students (9,852 male and 6,718 females). The average age of the participants in the study was 21 years; researchers divided them in two groups aged 18 – 21 and 22 – 30 years. Every participant's residence, urban or rural was included in the study variables.

From the data gathered on hepatitis B alone, hepatitis B surface antigen (HBsAg) prevalence for males within the age range of 18 – 21 years was 0.2% while that of those within 22 – 30 years was 0.4%. By contrast, females within ages 18 – 21 had HBsAg prevalence of 0.8% while that of those aged 22 – 30 years was 0.9%. Apparently, the results indicated a higher HBsAg prevalence among older students. A similar pattern of results was recorded for HCV (35). From another perspective, it was clear that females had a higher prevalence compared to males. Furthermore, after statistical analysis, age, residence, and HBsAg had a significant linkage at 95% confidence level. In order to understand more about the distribution of HBV across different ages, further studies on HBV among youths and in the entire KSA population should be conducted.

HBV Infection, by Gender

In terms of gender as a determinant factor in HBV distribution, Abdo (2012) highlights how the transmission rates vary among males and females. For instance, in a retrospective evaluation of patients visiting Aramco organization in KSA, which is in KSA's eastern province, males had a 1.8 times higher likelihood of transmission than females.

In the same study, when HBV incidence was stratified by gender, it was higher among males, with an incidence of 123 per 100,000 persons, compared to females, who had an incidence of 85.5 per 100,000 persons. As shown in the study, males seem to be more affected by HBV than females (31). However, because of the shortage of data on the gender as a determinant of hepatitis B epidemiology, it is important to carry out more studies to examine the incidence rate by gender over the entire country.

Pregnancy as a Determinant in Hepatitis B Infection

Among the determinants of hepatitis B infection and its distribution in KSA, pregnancy seems to play a role (36). In a 2012 report, national epidemiologic data indicated that Saudi women who are pregnant represent around 4% of the overall hepatitis B infection prevalence in KSA. Among younger women the prevalence was lower as shown in a recent research study conducted in five KSA regions. Researchers found insignificant HBsAg seroprevalence among pregnant women < 18 years of age. From the blood samples of 755 pregnant participants in one center, there were reports of similarly low HBsAg prevalence for the pregnant sub-population (31). In fact, the sub-population of the pregnant minors had a hepatitis B e-antigen (HBeAg) prevalence of < 5%. So, for this population of pregnant minors, vertical hepatitis B virus transmission was an insignificant transmission route among newborns.

In another study involving pregnant mothers in the Jazan region, researchers sought to establish the prevalence and risk factors for developing hepatitis B infection during pregnancy. Viral hepatitis among the pregnant mothers was linked to many maternal complications (37). To carry out the study, the researchers randomly selected 537 pregnant women attending Jazan hospital before the 38th week of pregnancy and screened every eligible participant for HBsAg.

The results showed that HBV prevalence in pregnancy was 4.1% among women < 20 years old. The prevalence among pregnant females increased as the age of a participant increased. Moreover, a history of any hospitalization or jaundice had a significant association with HBV development. However, this study neglected to show any significant associations with dental histories, surgeries, and blood transfusion (37), which are acknowledged risk factors. After analyzing the results, the researchers recommended an expansion of vaccination programs for HBV infection as a way of decreasing the predisposition to HBV acquisition in pregnancy.

Another study focusing on pregnancy as a determinant of the HBV distribution was conducted by Dwivedi, *et al*. (2011). They examined seroprevalence of the HBV in pregnancy and the risk of the perinatal transmission. In the study, 4000 pregnant mothers were assessed using medical history, physical examination, and the tests for HBsAg. Every HBsAg-positive female had to undergo Liver Function Tests as well as an HBeAg test. The researchers also conducted an HBV DNA evaluation utilizing polymerase chain reaction (PCR).

After data analysis, the researchers found that 37 (0.9%) of the participants were HBsAg positive. The women from 21 – 25 years old had an HBsAg positive rate of 1.2% while those aged 26 – 30 had a rate of 0.9%. In addition, 21 of the 37 positive women had HBeAg, with five of them having HBV DNA. It was found that the vertical transmission to newborns was significant in women having HBeAg in combination with HBV DNA (38).

Gasim, *et al*. (2013) published a report on a review he conducted about the epidemiology and risk factors linked with maternal development of the hepatitis B in African and Arab Countries. Gasim, *et al*. realized that there was limited data on the topic in Arab countries, including KSA. However, from the little data gathered, there was a clear indication that hepatitis

varied across the study countries, and viral genotypes changed frequently. The researchers attributed the variations to varied risk factors in the studied countries. Importantly, among the significant risk factors for HBV, the researchers noticed that HBV among the pregnant females imposed substantial political and socioeconomic burdens on the society (1).

In the current study, it will be possible to shed more light on how HBV is distributed among females of reproductive age, which may help in indicating how pregnancy forms a significant determinant of the HBV distribution. Also, further studies about the HBV incidence among women in KSA may reveal more information on HBV in pregnancy.

The Role of Genetics in HBV Epidemiology

In a study aimed at the identification of the commonest kind of HBV genotype in KSA, and consequently correlating predominant genotypes to patient consequences, Al-Faleh, *et al*. (2006) recruited participants from hepatology clinics in two referral centers. In total, 70 eligible patients participated in the study. After screening for the participants' genotypes, they found that 81.4% of patients had HBV genotype D, 10% had a mixed kind of genotype, 5.7% had genotype E, 1.4% carried genotype A, and 1.4% carried genotype C. The researchers suggest that most KSA patients with HBV infection have genotype D (39). Consequently, they recommended further studies to examine any relationship between HBeAg status and genotype D (39).

Other Factors in HBV Epidemiology

Apart from the above-mentioned determinants that influence HBV infection distribution in KSA, having sickle cell disease also seems to predict hepatitis B specific prevalence, according to a study conducted in KSA's eastern province. The sickle cell treatment protocol of

frequent transfusions and surgical interventions puts those who have it at higher risk of acquiring the HBV infection, particularly through a blood exchange.

In order to establish the relationship that exists between sickle cell and HBV infection, Al-Suliman, *et al*. (2012) conducted a retrospective study at King Fahad Hofuf health facility. In the study, researchers selected 211 adults with sickle cell disease. The researchers took the patients through tests to determine levels of the hepatitis B markers alkaline phosphatase, bilirubin, and transaminase. In the results, 2 of 211 eligible participants showed positive signs of HBsAg, indicating HBV. As expected, patients with sickle cell had higher infection rates than healthy participants (40). This study highlighted the need for HBV screening among patients with sickle cell. Due to higher HBV incidence among the sickle cell patient population, the researchers recommended that policymakers create an HBV screening policy for sickle cell patients (40).

Researchers in KSA have also studied HBV infection trends among health practitioners (41). For example, studies on attitude have been conducted among general dentists and other dental specialists. Of concern is the finding that most health providers, like dentists, understand the health consequences of acquiring HBV during service provision but do not seek prophylactic vaccination before practicing (42). What this means is that the health workers' attitudes towards HBV, especially vaccination, may also influence transmission rates. Perhaps many health workers miss getting vaccinations due to their negative attitude towards them; it is possible that they become infected later on.

Finally, blood donation rates may also determine the epidemiologic picture of the HBV infection in different nations, including KSA. Alshehri, *et al*. (2013) conducted a study between

2012 and 2013 that aimed to determine HBV (and HCV) risk factors and prevalence among blood donors in Aseer region, KSA. The data for the study specifically originated from random samples of blood from the healthy donors referred to the transfusion centers in Aseer. After screening the samples for different hepatitis viral strains, 71 of 7267 participants were HBsAg positive, with 66 of them having HBV-DNA. Most of the positive HBsAg cases were reported among the male volunteers (43). According to this study's results, blood donation proved to be a significant HBV transmission route among KSA residents. However, the pattern that was found involving more infections among male donors requires further studies for verification (43).

It is clear from the above studies that the distribution of the HBV infection varies greatly among different regions in KSA. In addition to the geographical variances in HBV infection distribution, there are also certain patterns observed among Saudi and non-Saudi populations. Furthermore, the literature review highlights the fact there has been a slight decline in hepatitis B prevalence in KSA (44). However, in spite of the decrease, Saudi people continue to get sick and die from HBV infections.

From another perspective, there is an indication that HBV infection is determined by different factors define its transmission or distribution patterns. As an example, age, gender, genetics, pregnancy and blood donation are significant determinants of the HBV epidemiologic picture in KSA. Nevertheless, from a comprehensive analysis of the literature, there are gaps in research on HBV infection. A major gap identified is lack of comprehensive comparisons of incidences of the HBV infection by year, age, region, gender, occupation, and nationality. Moreover, the published data on the HBV incidence among Saudis, as well as non-Saudis is insufficient. Lastly, there is no a single comprehensive document comparing the incidence rates across various KSA regions.

This study will establish the incidence rates with respect to the identified gaps. It will be possible to understand more about HBV infection in the entire KSA. This study will describe the epidemiology of HBV infection from 2009 to 2013.

Chapter III: MANUSCRIPT

Trends of Reported Cases of Hepatitis B Virus Infection,

Kingdom of Saudi Arabia, 2009 – 2013

ABSTRACT

PURPOSE: Hepatitis B virus (HBV) infection is widespread globally and a serious public health threat. Understanding the distribution of HBV is important to policymakers to evaluate public health surveillance and develop prevention and control policies. Therefore, we studied the trends of reported HBV infection in the Kingdom of Saudi Arabia (KSA) during the 5-year period from 2009 – 2013.

METHODS: Laboratory-confirmed HBV cases reported to the KSA Ministry of Health (MoH) National Hepatitis Program (NHP) were analyzed by year, gender, nationality, region, and age group.

RESULTS: There were 23,236 cases of HBV infection reported to the KSA MoH during the 5-year period 2009 – 2013. In 2009, the incidence rate (IR) of HBV infection was 19.3 (95% CI = 18.8, 19.9) per 100,000 population. The IR significantly decreased to 14.7 (95% CI = 14.2, 15.1) in 2013. The IR was consistently greater among males than females (in 2013, 16.7 versus 12.2). Over the study period, Saudi citizens had a 2- to 3-fold greater IR than non-Saudis (in 2013, 18.7 versus 5.9). There was a large variation among HBV infection IRs across regions, with Tabouk having the highest. The greatest number of cases was found among those aged 15 to 44 years, followed by those > 45 years of age.

CONCLUSION: Despite the significant decrease in the IRs over the 5-year period from 2009 – 2013, HBV infection remains a major public health problem in KSA. Therefore, there is a need for continuous monitoring and evaluation of the disease's observation protocols and prevention strategies. Various strategies and preventive measures should be implemented to control HBV infection, and well-designed research programs should be carried out in different regions of KSA to improve planning and define the priorities in tackling this health issue.

INTRODUCTION

Hepatitis B virus (HBV) infection is a major health problem leading to substantial morbidity and mortality (45). Currently, about 2 billion individuals have been exposed, 350 million persons are estimated to be carriers HBV, and over 240 million persons are chronically infected (25). HBV infection rates are generally greatest in developing countries, especially among people considered to be at high risk (4). Disease transmission occurs when a healthy person comes in contact with infected blood, vaginal fluids or semen, or sometimes the saliva, urine, or tears of chronic carriers (5). HBV is also transmitted from chronically infected mothers to their newborns, who consequently develop chronic hepatitis B. The virus infects liver cells and can cause acute liver damage (6). Due to its widespread nature at a global level, HBV infection has had an overwhelming and dramatic impact on many nations, including the Kingdom of Saudi Arabia (KSA).

The prevalence of HBV infection has declined considerably in KSA since the introduction of the immunization program in 1989. Specifically, it fell from 7% before the program in 1989 to 0.3% by 1997 (12). However, different reports have shown that HBV infections continue to be a major burden on the KSA healthcare system due to its high morbidity and mortality (27). As reported in a 2008 KSA study, out of 74,662 persons who underwent premarital screening from January to May 2008, 1.31% of the subjects tested positive for HBV infection (28). In terms of HBV infection prevalence, another study done in the same year indicates that the HBV infection prevalence rates were reported to be between 1.5 and 2.6% among adults, specifically those who had blood transfusions during the study period (29). In 2007, cross-community data monitoring the effectiveness of HBV childhood immunizations showed a prevalence of 0.22% in children and 0.05% in adults (30). From another perspective,

the mean incidence of HBV infection was around 0.15%, with massive variations ranging from 0.03% to 0.72% across regions (31).

The long-term HBV program in KSA exists to prevent virus transmission in all age groups with the ultimate goal of eliminating the virus. This has proven to be difficult due to the more than 300 million carriers worldwide and the HBV genotypes, which have distinct geographical distribution (25). The declining prevalence of infection in KSA's population can be attributed to an increase in preventive measures such as vaccination, screening of blood donations, maternal screening, pre-marital screening, and health education of the public through the media and social networks.

The increased number of cases of chronic infection has led to the need to understand how they are distributed and how they can be prevented. This requires a change in the healthcare system's approach to infections like HBV. The purpose of this study was to examine the distribution and trends of HBV in KSA during a five-year period from 2009 to 2013 and to analyze HBV IRs by gender, nationality, and region. In addition, the study compared reported HBV cases among different age groups during this 5-year period. This study can serve program planners and policymakers by evaluating the HBV surveillance program and develop policies for preventing HBV infections in KSA.

METHODS

Data Sources

Surveillance teams in each KSA region send monthly reports of laboratory-confirmed HBV infections to the MoH's National Hepatitis Program (NHP). These case reports include clinical and epidemiologic data, including age, gender, and nationality. KSA population data

were obtained from the Ministry of Economy and Planning, Central Department of Statistics and Information. This statistical information was drawn from registers, census and field surveys, and statistical studies. These population data include age, gender, and nationality, by region for the years 2009 to 2013 (46).

Case Definition of Hepatitis B Virus Infection

The NHP defines HBV infection using the standard case definition for suspected and confirmed cases approved by the World Health Organization (WHO). Suspected cases have an acute illness featured by a discrete onset of symptoms, jaundice, or elevated serum aminotransferase levels (>2.5 times the upper limit of normal); confirmed cases are laboratory confirmed by hepatitis B surface antigen (HBsAg) positive or anti-hepatitis B core immunoglobulin M (anti-HBc-IgM) positive results (47). Laboratory-confirmed HBV cases were studied in this report.

Study Variables

The independent variables in this study included age group, gender, nationality, and administrative region. The age groups are divided into < 1 year, 1 to 4 years, 5 to 14 years, 15 to 44, and > 45 years of age. Nationality was defined as Saudi or non-Saudi. There are 13 administrative regions: Riyadh, Makkah, Madinah, Qasim, Eastern, Asir, Tabouk, Hail, Northern Border, Jizan, Najran, Al-Baha, and Al-Jouf (48).

Statistical Analyses

Incidence rates (IRs) were calculated per 100,000 people by gender, nationality, and region. IRs were analyzed over a 5-year period (2009 – 2013) using Poisson regression and

classified as increasing, decreasing, or stable; this was determined by positive, negative, or non-significant coefficients. Significance was determined at the 5% level using two-sided P values. Rates were compared using rate ratios and 95% confidence intervals (CIs).

Ethics

This research involved secondary data analyses without personal identifiers. Thus, it did not meet the definition of human subjects research and was classified as exempt by the Emory University Institutional Review Board.

RESULTS

The total number of reported HBV infection was 23,236 cases. Over a 5-year period of monitoring for HBV infection from 2009 to 2013, there is significant decrease in the IRs from 19.3 per 100,000 in 2009 (95% CI = 18.8. 19.9) to 14.7 in 2013 (95% CI = 14.2. 15.1) (Table 1). The rates were 18 in 2010, 16.1 in 2011, 15.9 in 2012, and 14.7 in 2013.

Table 1. Reported cases of hepatitis B virus infection and incidence rates, Kingdom of Saudi Arabia, 2009 – 2013

Year	# Cases (IR°)	95% CI*
2009	5020 (19.3)	18.8 – 19.9
2010	4854 (18)	17.5 – 18.5
2011	4494 (16.1)	15.6 – 16.5
2012	4609 (15.9)	15.4 – 16.4
2013	4259 (14.7)	14.2 – 15.1
Total	23,236	

°IR = incidence rate per 100,000 population
*CI = confidence interval

When we studied the IRs of hepatitis B according to gender, we found that the rate among males and females was somewhat comparable in 2009, 2010, and 2011. However, in 2012 and 2013, the IR was significantly higher among males than females: in 2012, the incidence rate was 17.2 (95% CI= 16.6, 17.9) per 100,000 men compared to 15.43 (95% CI= 14.7, 16.1) per 100,000 women. In 2013, the difference in the incidence rate was more marked. It was 16.7 (95% CI= 16.1, 17.3) among men compared to 12.2 (95% CI= 11.6, 12.8) among women (Table 2).

Table 2. Incidence rates of reported cases of hepatitis B virus infection, by year and gender, Kingdom of Saudi Arabia, 2009 – 2013

Year	Male		Female	
	# Cases (IR°)	95%CI*	# Cases (IR°)	95%CI*
2009	2905 (19.4)	18.7 – 20.1	2115 (19.2)	18.4 – 20.1
2010	2816 (18.8)	18.1 – 9.5	2038 (18.5)	17.7 – 19.4
2011	2614 (16.3)	15.7 – 17	1880 (15.7)	15 – 16.4
2012	2758 (17.2)	16.6 – 17.9	1851 (15.4)	14.7 – 16.1
2013	2677 (16.7)	16.1 – 17.4	1582 (12.2)	11.6 – 12.8
Total	13,770		9,466	

°IR = incidence rate per 100,000 population
*CI = confidence interval

By nationality, we found that Saudi citizens had a two- to threefold greater HBV incidence than non-Saudis over the five-year surveillance period. The greatest difference in incidence rates between Saudis and non-Saudis occurred in 2013: the rate among Saudis was 18.7 (95% CI= 18.1, 19.3) per 100,000 compared to 5.9 (95% CI= 5.4–6.4) among non-Saudis. The smallest difference in the incidence rates occurred in 2011: the rate among Saudis was 19.8 (95% CI= 19.2, 20.4) compared to 9.2 (95% CI= 8.6, 9.9) among non-Saudis (Table 3).

Table 3. Reported cases of hepatitis B virus infection and incidence rates, by year and nationality, Kingdom of Saudi Arabia, 2009 – 2013

Year	Saudi		Non-Saudi	
	# Cases (IR°)	95%CI*	# Cases (IR°)	95%CI*
2009	4361 (24.2)	23.5 – 25	659 (8.2)	7.6 – 8.9
2010	4115 (22.9)	22.2 – 23.6	739 (9.2)	8.6 – 9.9
2011	3758 (19.8)	19.2 – 20.4	736 (9.2)	8.6 – 9.9
2012	3899 (20.5)	19.9 – 21.2	710 (7.9)	7.3 – 8.5
2013	3731 (18.7)	18.1 – 19.3	528 (5.9)	5.4 – 6.4
Total	19,864		3,372	

°IR = incidence rate per 100,000 population
*CI = confidence interval

Breaking down the hepatitis B incidence rates by administrative region, we found massive variations (Figure 4). The highest incidence rate for over the 5-year surveillance period was found in Tabouk region (37.4 in 2009, 37.2 in 2010, 26.3 in 2011, 13.7 in 2012, and 21.8 in 2013); the second highest overall was Madinah region. The lowest IR over the study period was seen in Al-Jouf region, followed by Al-Baha and Hail regions (Figure 4).

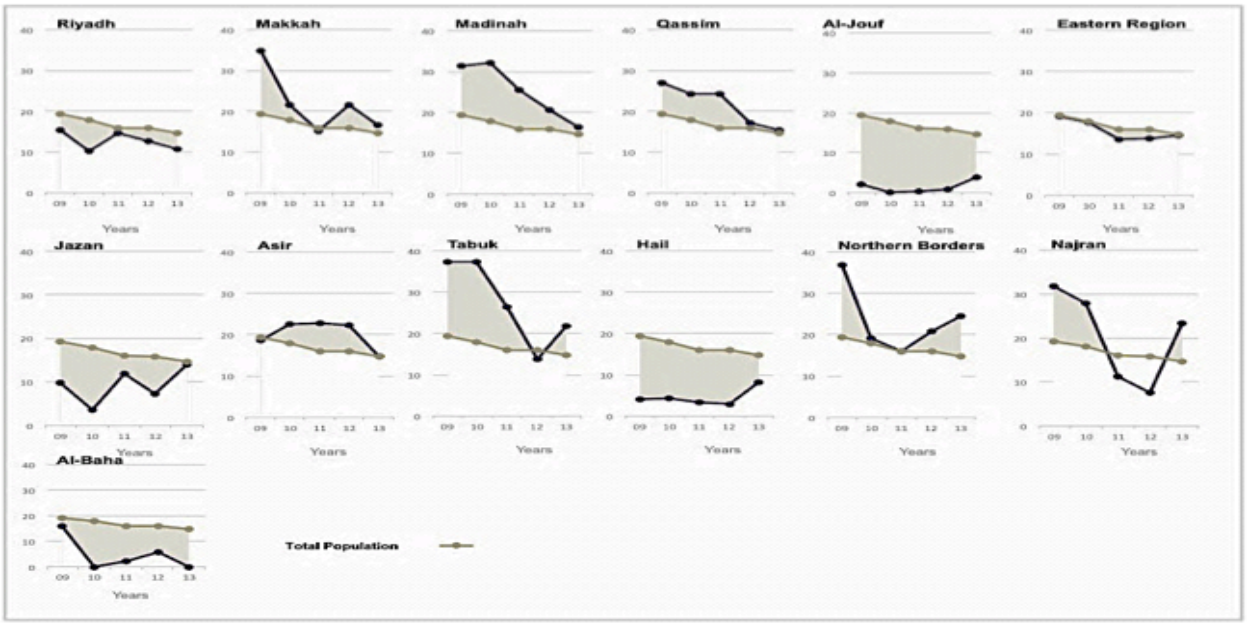
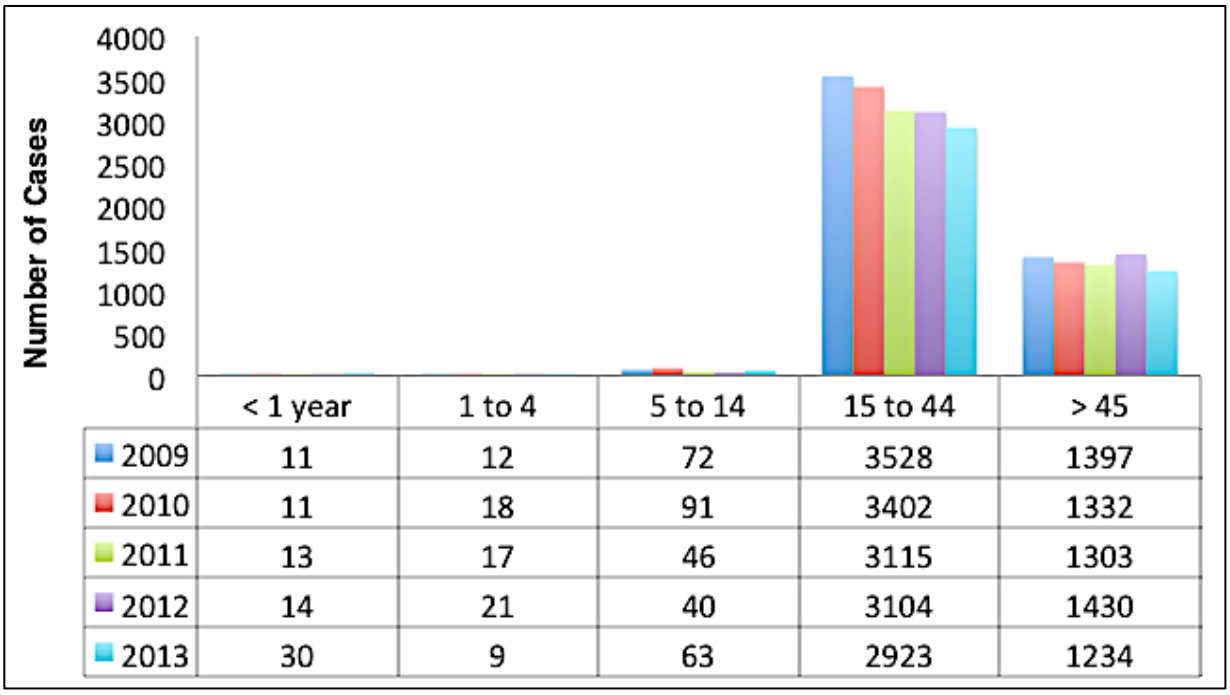


Figure 1. Incidence Rates of Reported Cases of Hepatitis B Virus Infection, by Year and Region, Kingdom of Saudi Arabia, 2009 – 2013

By age group, those in the 15-44 year old age range had the majority of hepatitis B cases over the 5-year study period. There were a total of 16,072 hepatitis B cases among this group, representing about 70% of cases in all age groups. In the over-45 age group, there were 6,696 cases; among those aged 5-14 years, there were 312 cases; among those aged 1-4 years, there were 77 cases; and among those under one-year old, there were 79 cases (Figure 5).



	< 1 year	1 to 4	5 to 14	15 to 44	> 45
2009	11	12	72	3528	1397
2010	11	18	91	3402	1332
2011	13	17	46	3115	1303
2012	14	21	40	3104	1430
2013	30	9	63	2923	1234

Figure 2. Reported Cases of Hepatitis B Virus Infection, by Year and Age Category, Kingdom of Saudi Arabia, 2009 – 2013

DISCUSSION

The current study aims to analyze changes in hepatitis B IR during 5 years of surveillance from 2009 to 2013. In addition, it aims to study the distribution of these IR according to gender, nationality, and region. The number of cases by age group is also examined.

The IR showed a gradual decrease during the five years of surveillance, dropping to

fewer than 15 per 100,000 people in 2013. The incidence rates among males and females were equal during the first three years of surveillance; however, males had a higher IR during the last 2 years. Saudi citizens had a two- to three-times higher IR than non-Saudis during the entire 5-year surveillance period. There were also huge differences in the IR among the 13 administrative regions. By age, those in the 15 – 45 year old age group had the highest number of cases, followed by those in the over-45 age group. There were low numbers of cases among the other age groups.

The decline in the overall IR can be explained by the various preventive measures that have been carried out by the MoH; these include the introduction of a hepatitis B vaccine as part of the Expanded Program on Immunization (49), investigation of blood donations, maternal screening, pre-marital screening, and health education efforts. Moreover, the MoH has begun implementing an electronic surveillance system, using the internet to monitor and manage diseases and epidemics and provide healthcare workers and decision-makers accurate information that enables them to offer a high level of health services (50). This system enables better notification of infectious diseases and prevents data duplication through the use of a specific identification number for each patient.

The difference in the IR between males and females can be explained by the fact that males are prone to engage in riskier behavior, such as the use of injection drugs and unsterilized equipment. To a lesser extent, females are also predisposed to other types of risky behavior.

Non-Saudi workers have to undergo medical examinations in their countries of origin at accredited centers prior to their arrival in any Gulf Cooperation Council (GCC) country and are reexamined when they enter the country (51). This may explain the lower IRs among the non-

Saudi population. However, the lower rate could also be attributed to underreporting; many non-Saudis may choose not to seek medical advice if they suspect they are infected due to fear of having their employment contracts terminated and being sent back to their countries of origin.

The lack of adult hepatitis vaccination programs, the greater number of years of potential exposure, and a lack of awareness concerning the HBV infection in earlier decades could explain the higher number of cases among the 15-44 and over-45 age groups as compared to the younger age groups.

The strength of the current study is that it involves data from the entire kingdom compared to other studies that were conducted only in specific regions or specific health facilities. Moreover, this study includes the most current data obtained from the surveillance system; therefore, it is a suitable tool for policymakers. However, this study has some limitations. First, the population data for 2009 was based on census estimates from a baseline KSA census taken in 2007, and the population data for 2010, 2011, 2012, and 2013 were based on census estimates from a baseline KSA census taken in 2010. In 2009, there were no calculations of growth rate across regions. Therefore, there was an overestimation of the IR across the regions (less than 5%) compared to the IR in the total population. In 2010, 2011, 2012, and 2013 the total population and regional population figures were in alignment. However, these estimates were not as precise as those that would have been derived from an annual census. Second, we examined confirmed cases reported to the MOH according to the WHO definition of a confirmed case. A stronger surveillance program is necessary to detect every suspected case and test the confirmation of these cases; without that, we may underestimate the incidence rate. Third, the hepatitis B screening program only includes blood donors, couples registering for

marriage, and high-risk groups. Including the entire population would provide an accurate estimate of the incidence rate.

In conclusion, hepatitis B has significant consequences, including mortality, morbidity, negative impact on health-related quality of life, and increased healthcare expenditures (52). The status of HBV in KSA should be a source of concern to all sectors involved in public health, particularly those involved in strategic planning and decision-making. In view of this, we recommend continuous monitoring and evaluation of surveillance and prevention strategies, implementation of a range of strategies and preventive measures to control the HBV infection, and the launch of well-designed research programs by the MOH and various regions of the Kingdom to improve planning and define priorities. Furthermore, we recommend further studies to examine the hypotheses generated by the current study, such as those concerning the differences in incidence rates between males and females and between Saudis and non-Saudis, as well as those pertaining to the huge variations in incidence rates among different regions of KSA.

Chapter IV: CONCLUSION AND RECOMMENDATIONS

The burden associated with hepatitis B is significant and entails mortality, morbidity, impact on health-related quality of life, and healthcare expenditures (52). The status of HBV in KSA should be a source of concern to all sectors involved in public health, particularly to people who are involved in strategic planning and decision-making. The control and prevention of HBV infections requires continuous monitoring and evaluation of surveillance and prevention strategies. Various strategies and preventive measures should be implemented to control HBV infection. These measures include vaccination, maternal screening, and additional preventive measures.

Vaccination

In KSA, the administration of the HBV vaccine is a part of the WHO-recommended Expanded Program on Immunization. KSA was the first Arab country to mandate the hepatitis B vaccination (53), which is administered at birth and at 2, 4, 6 and 18 months of age. However, KSA needs to start a comprehensive vaccination program to prevent virus transmission among all age groups (newborns, children, adolescents and high-risk adults). This vaccination program will lead to the prevention of acute and chronic symptomatic infections and to the reduction of healthcare costs in the short- and medium-term. Additionally, in the long-term, it will prevent the development of HBV complications such as cirrhosis and HCC that carry significant morbidity and mortality (54).

Maternal Screening

The practice in KSA is that all pregnant women are screened for chronic infection with

HBV, which is defined as testing positive for HBsAg (54). To improve this practice, it is recommended that all pregnant women be tested for HBsAg during each pregnancy, preferably in the first trimester, and re-tested at the time of admission for delivery if the HBsAg test result is not available or if the mother was at risk for infection during pregnancy. To prevent perinatal transmission, infants of HBsAg-positive mothers and mothers of unknown HBsAg status should receive vaccination and postexposure immunoprophylaxis (55).

Other Preventive Measures

The public health department of the MoH and other sectors involved in public health should implement continuous prevention strategies that include well-planned educational programs that inform people of the risk of HBV both at the community and health institution levels; the implementation of international and national guidelines regarding the prevention of HBV, especially in special hospital settings such as blood banks and haemodialysis units, and for high-risk groups in the community; strict adherence to guidelines and regular monitoring and evaluation of HBV control measures; and the introduction of specific patient-care practices (52).

Moreover, special-setting prevention programs should be strengthened in hemodialysis units and laboratories. In hemodialysis units, there should be HBV screening programs for blood and blood products, strict adherence to the nosocomial prevention program, and routine reviews of practices to confirm consistency and their strict adherence to recommendations (56). In laboratories, testing and sterilization should be improved, with regular adjustments and quality control, injections should be safer, and there should be less exposure to blood products (52).

Regarding the long-term preventive strategies, the surveillance program currently in place should be strengthened. This surveillance program must be able to report any problems concerning HBV, allowing for early intervention and access to the latest knowledge and

technology. This program should devise the prevention strategies to minimize the progression of the HBV infection and establish guidelines for the elimination of widely-used, dangerous medical procedures. The surveillance program for HBV also should enact special long-term preventive strategies for high-risk populations, for example injection drug users, HIV–HBV co-infected patients, and prisoners (55).

Finally, well-designed research programs should be initiated at the MOH and in different regions of the kingdom to improve planning and to define the priorities. These research programs could include population-based surveillance studies to learn more about the distribution and determinants of HBV. These could be used to conduct further evaluation of the iatrogenic causes of HBV transmission and the safety and efficacy of antiviral therapy for HBV (52) .

References

1. Gasim GI. Hepatitis B virus in the Arab world: Where do we stand? Arab Journal of Gastroenterology. 2013;14(2):35-43.
2. Tong S, Kim K-H, Chante C, Wands J, Li J. Hepatitis B virus e antigen variants. Int J Med Sci. 2005;2(1):2-7.
3. Williams R, Taylor-Robinson SD. Clinical Dilemmas in Primary Liver Cancer: John Wiley & Sons; 2011.
4. Ott J, Stevens G, Groeger J, Wiersma S. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012;30(12):2212-9.
5. Organization WH. International travel and health: situation as on 1 January 2010: World Health Organization; 2010.
6. Cooper GM. The cancer book: a guide to understanding the causes, prevention, and treatment of cancer: Jones & Bartlett Learning; 1993.
7. Al Jadid M. A retrospective study on traumatic spinal cord injury in an inpatient rehabilitation unit in central Saudi Arabia. Saudi medical journal. 2013;34(2):161-5.
8. Harpaz R, Von Seidlein L, Averhoff FM, Tormey MP, Sinha SD, Kotsopoulou K, et al. Transmission of hepatitis B virus to multiple patients from a surgeon without evidence of inadequate infection control. New England Journal of Medicine. 1996;334(9):549-54.
9. Abu-Raddad LJ, Hilmi N, Mumtaz G, Benkirane M, Akala FA, Riedner G, et al. Epidemiology of HIV infection in the Middle East and North Africa. AIDS. 2010;24:S5-S23.
10. Blumberg BS. Hepatitis B: The hunt for a killer virus: Princeton University Press; 2002.
11. Shetty K, Wu G. Chronic viral hepatitis: Diagnosis and Therapeutics: Springer; 2009.
12. AI-Faleh FZ, AI-Jeffri M, Ramia S, AI-Rashed R, Arif M, Rezeig M, et al. Seroepidemiology of hepatitis B virus infection in Saudi children 8 years after a mass hepatitis B vaccination programme. Journal of infection. 1999;38(3):167-70.
13. Cassidy A, Mossman S, Olivieri A, Ridder MD, Leroux-Roels G. Hepatitis B vaccine effectiveness in the face of global HBV genotype diversity. 2011.
14. Poynard T. Hepatitis B and C: management and treatment: CRC Press; 2004.
15. Willis AP. Hepatitis B Research Advances: Nova Publishers; 2007.
16. Pawlotsky J-M. EASL Clinical Practice Guidelines: management of chronic hepatitis B. J Hepatol. 2009;50(2):227-42.
17. Organization WH. Global policy report on the prevention and control of viral hepatitis in WHO Member States: World Health Organization; 2013.
18. Yuen MF, Wong DKH, Fung J, Ip P, But D, Hung I, et al. HBsAg Seroclearance in chronic hepatitis B in Asian patients: replicative level and risk of hepatocellular carcinoma. Gastroenterology. 2008;135(4):1192-9.
19. Heiberg IL, Hoegh M, Ladelund S, Niesters HG, Hogh B. Hepatitis B virus DNA in saliva from children with chronic hepatitis B infection: implications for saliva as a potential mode of horizontal transmission. The Pediatric infectious disease journal. 2010;29(5):465-7.
20. Control CfD, Prevention. Updated CDC recommendations for the management of hepatitis B virus-infected health-care providers and students. MMWR Recommendations and reports: Morbidity and mortality weekly report Recommendations and reports/Centers for Disease Control. 2012;61(RR-3):1.
21. Tong MJ, Hsu L, Chang PW, Blatt LM. Evaluation of current treatment recommendations for chronic hepatitis B: a 2011 update. Journal of gastroenterology and hepatology. 2011;26(5):829-35.
22. Yu X, Jin L, Jih J, Shih C, Zhou ZH. 3.5 Å cryoEM Structure of Hepatitis B Virus Core Assembled from Full-Length Core Protein. PloS one. 2013;8(9):e69729.
23. Bajunaid HA. Genetic variability of Hepatitis B virus: University of Nottingham; 2013.
24. Jayalakshmi M, Kalyanaraman N, Pitchappan R. Hepatitis B Virus Genetic Diversity: Disease Pathogenesis. VIRAL REPLICATION. 2013:69.

25. Alshabanat AA, Albacker RB, Basalama AA, Salamah AAB, SalehAlfrayh A. Profile of viral hepatits in Saudi Arabia. Biomedical Research. 2013;24(3):396-9.
26. McMahon BJ, editor. Epidemiology and natural history of hepatitis B. Seminars in Liver Disease; 2005: Published in 2005 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
27. WHO. Global policy report on the prevention and control of viral hepatitis. 1-20. Retrieved from http://www.who.int/csr/disease/hepatitis/GHP_framework.pdf.1-20.
28. Alswaidi FM, O'Brien S. Is there a need to include HIV, HBV and HCV viruses in the Saudi premarital screening program on the basis of their prevalence and transmission risk factors? Journal of epidemiology and community health. 2010;64(11):989-97.
29. El Beltagy KE, Al Balawi IA, Almuneef M, Memish ZA. Prevalence of hepatitis B virus markers among blood donors in a tertiary hospital in Tabuk, northwestern Saudi Arabia. International Journal of Infectious Diseases. 2008;12(5):495-9.
30. Madani TA. Trend in incidence of hepatitis B virus infection during a decade of universal childhood hepatitis B vaccination in Saudi Arabia. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2007;101(3):278-83.
31. Abdo AA, Sanai FM, Al-Faleh FZ. Epidemiology of viral hepatitis in Saudi Arabia: Are we off the hook? Saudi journal of gastroenterology: official journal of the Saudi Gastroenterology Association. 2012;18(6):349.
32. Memish ZA, Knawy BA, El-Saed A. Incidence trends of viral hepatitis A, B, and C seropositivity over eight years of surveillance in Saudi Arabia. International Journal of Infectious Diseases. 2010;14(2):e115-e20.
33. Aljarbou AN. Current Prevalence of HBV and HCV Seropositivity: The Initiative for Attentiveness and Deterrence of Viral Hepatitis in the Qassim Region of Saudi Arabia. J Antivir Antiretrovir. 2012;4:075-9.
34. Alghonaim M. Prevelance of Viral Hepatitis Among Population of Al-Quwayiah Governorate, Saudi Arabia. World Journal of Pharmaceutical research. 2012;1(1):10. Epub September

2012.
35. Al-Ajlan A. Prevalence of hepatitis B and C among students of health colleges in Saudi Arabia. Eastern Mediterranean Health Journal. 2011;17(10).
36. Vincent H. Hepatitis B in Pregnancy: Specific Issues and Considerations. Journal of Antivirals & Antiretrovirals. 2012.
37. Bani I, Mahfouz MS, Maki E, Gaffar A, Elhassan I, Yassin AO, et al. Prevalence and Risk Factors of Hepatitis B Virus among Pregnant Women in Jazan Region-Kingdom of Saudi Arabia. Journal of Biology, Agriculture and Healthcare. 2012;2(7):39-43.
38. Dwivedi M, Misra SP, Misra V, Pandey A, Pant S, Singh R, et al. Seroprevalence of hepatitis B infection during pregnancy and risk of perinatal transmission. Indian Journal of Gastroenterology. 2011;30(2):66-71.
39. Abdo AA, Al-Jarallah BM, Sanai FM, Hersi AS, Al-Swat K, Azzam NA, et al. Hepatitis B genotypes: relation to clinical outcome in patients with chronic hepatitis B in Saudi Arabia. World J Gastroenterol. 2006;12(43):7019-24.
40. Al-Suliman. Prevalence of hepatitis B and C in adult sickle cell disease patients in the eastern province of Saudi Arabia. 2012:1-4.
41. Al-Thaqafy MS, Balkhy HH, Memish Z, Makhdom YM, Ibrahim A, Al-Amri A, et al. Improvement of the low knowledge, attitude and practice of hepatitis B virus infection among Saudi national guard personnel after educational intervention. BMC research notes. 2012;5(1):597.
42. Paul T, Maktabi A, Almas K, Saeed S. Hepatitis B awareness and attitudes amongst dental health care workers in Riyadh, Saudi Arabia. TROPICAL DENTAL JOURNAL. 1999:9-12.

43. Alshehri A. Hepatitis B and C Viruses incidence, the Risk Factors of Hepatocellular Carcinoma, is low in Aseer Region, Saudi Arabia.
44. Ayoola AE, Tobaigy MS, Gadour MO, Ahmad BS, Hamza MK, Ageel AM. The decline of hepatitis B viral infection in South-Western Saudi Arabia. Saudi medical journal. 2003;24(9):991-5.
45. Gasim GI. Hepatitis B virus in the Arab world: where do we stand? Arab J Gastroenterol. 2013;14(2):35-43. Epub 2013/07/04.
46. Central department of statistics and information, kingdom of saudi arabia. (2014, February). Retrieved from http://www.cdsi.gov.sa/english/index.php.
47. WHO. Hepatitis B fact sheet (July, 2013) Retrieved from http://www.who.int/mediacentre/factsheets/fs204/en/.
48. Administrative regions of the kingdom. (2014, February). Retrieved from http://www.saudinf.com/main/a7.htm.
49. Al-Faleh F, Ayoola E, Al-Jeffry M, Arif M, Al-Rashed R, Ramia S. Integration of hepatitis B vaccine into the expanded program on immunization: The Saudi Arabian experience. Annals of Saudi medicine. 1993;13(3):231-6.
50. MOH. Deputy Minister for Public Health (2014) Retrieved from http://www.moh.gov.sa/en/Ministry/Structure/Agents/PublicHealth/Pages/default.aspx.
51. Alswaidi F, Memish Z, Al-Hakeem R, Atlam S. Saudi Arabian expatriate worker fitness-screening programme: a review of 14 years of data. Eastern Mediterranean Health Journal. 2013;19(7).
52. Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection: Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention; 2008.
53. East SPoCHBitM. A review of chronic hepatitis B epidemiology and management issues in selected countries in the Middle East. Journal of viral hepatitis. 2012;19(1):9.
54. André F. Hepatitis B epidemiology in Asia, the middle East and Africa. Vaccine. 2000;18:S20-S2.
55. Mast EE, Margolis HS, Fiore AE, Brink EW, Goldstein ST, Wang SA, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States. MMWR. 2005;54(16):1-32.
56. Alter MJ, Lyerla R, Tokars J, Miller ER, Arduino M. Recommendations for preventing transmission of infections among chronic hemodialysis patients. Atlanta, GA, Centers for Disease Control and Prevention. 2001:1-43.