Review Article

Hepatitis B care pathway in Saudi Arabia: Current situation, gaps and actions

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Abstract

Hepatitis B virus (HBV) infection remains a public health problem worldwide. In this review, we aim to assess the current situation of the HBV care pathway in the Kingdom of Saudi Arabia (KSA), identify gaps/barriers therein, and recommend initiatives to be taken to improve the management of such patients. Towards this end, a literature search was conducted in PubMed and free Internet searches. Interviews with individuals and focus group discussions were held with HBV experts in KSA. Although significant improvements have been made in the past 30 years in KSA in terms of the decline in prevalence (currently estimated to be around 1.3%), the morbidity and mortality related to the disease have not shown a parallel decline. This makes HBV an important public health concern. Furthermore, poor disease awareness, low diagnosis rates, and nonadherence to therapy amplify the disease burden. There are several mandated national screening structures present; however, established protocols for those who test positive and subsequent linkage-to-care are inadequate. In the absence of a virologic cure, a concerted effort should be made to provide safe and effective lifelong treatment. This review provides recommendations to reduce the HBV disease burden in the Saudi population.

Keywords: Awareness, diagnosis, epidemiology, hepatitis B, Saudi Arabia, treatment

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INTRODUCTION

Hepatitis B virus (HBV) infection remains a public health problem worldwide with an estimated prevalence of 248 million cases in 2010 according to a systematic review.[1] In the World Health Organization (WHO) Eastern Mediterranean Region, an estimated 21 million people (3.3%) of the general population are infected.[2]

The last major review of the epidemiology and management of HBV in the Middle East was published in 2011.[3] The authors observed that the Middle East was in the past

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regarded as a region of high-to-intermediate epidemicity; however, infant vaccination programs have successfully lowered the prevalence of hepatitis B infection in most countries to that of low-to-intermediate endemicity. Leading hepatologists and gastroenterologists from the Kingdom of Saudi Arabia (KSA) considered it important to assess whether this trend continued, and therefore, the aim of this study was to assess the current situation of the HBV care pathway in KSA, identify gaps therein, and recommend comprehensive initiatives to improve the overall situation.

METHODS

To describe the current situation of the HBV care pathway (epidemiology and awareness; screening, diagnosis, linkage to care; treatment initiation; compliance/adherence) in KSA, a pragmatic literature search was conducted in PubMed, Web of Science, and Cochrane Reviews, using the keywords "Saudi Arabia or KSA," "hepatitis B or HBV or CHB," "hepatocellular carcinoma or HCC," "cirrhosis," "prevalence," "awareness," "epidemiology," "vaccination," "diagnosis," "screening," "treatment," "care pathway," "adherence," and so on. In addition, the reference lists of the articles found were scanned for any additional publications. Also, free Internet searches were conducted (Google Scholar) using similar keywords to identify relevant reports, guidelines, conference abstracts, posters, presentations, and so on.

To provide context to the results from the literature review and to collect diverse stakeholder perspectives on those areas for which no or limited evidence was found in the literature, discussions were held with various professionals: physicians (general and specialist), regulators, payers (funding and procurement), and staff at nongovernmental organizations. Finally, inputs were taken from a meeting with experts and key opinion leaders (KOLs) in the field of hepatology representing most public sectors and regions in Saudi Arabia.[4] There was one advisory group meeting to align on the first draft of the manuscript followed by individual consultations with these experts to finalize the content of the paper and to review specific points of data.

EPIDEMIOLOGY

A large number of studies have been conducted in KSA,[1,5-19] and a systematic review pooling data of 312,787 people from 36 studies published between 1965 and 2013 found a prevalence of 3.2% for the country which is slightly lower than the worldwide prevalence of 3.6%.[1] In this systematic review, a decrease in prevalence has been observed over time, and hence it is expected that the current prevalence rate in KSA would be lower than the average found.[1] The estimate of 3.2% is also based on studies including various populations, primarily conducted in HBV screening settings. The results from those studies including data from population surveys, hemodialysis patients, antenatal care attendees, blood donors, military personnel, premarital screening, and students are probably reasonably representative of the overall prevalence in the country. However, some surveys concentrated more on at-risk populations, such as heroin addicts and HIV-positive patients, where the prevalence of HBV infection is expected to be higher.

Among the more recent studies, a cross-sectional study including a large sample ($n = 74,662$) of premarital couples recruited from the general population in KSA found a prevalence rate of HBV of 1.3%,[20] which is considerably lower than the average found in the studies conducted from 1964 to 2013. Hepatology experts and KOLs agreed that this is the most reliable estimate currently available, clearly in accordance with the declining prevalence rate in the country.[4] With a Saudi population estimate of about 20 million in 2016, this proportion would give an estimated 260,000 HBV cases in the country.

Prevalence of chronic HBV (CHB) will be lower in the younger population (<30 years), compared with the older population, due to the impact of the vaccination program:

- The first large-scale community-based epidemiological study among Saudi children aged 1–12 years was published in 1988 and showed an HBV surface antigen (HBsAg) seroprevalence of approximately 7%.[21] The introduction of the HBV vaccine program in 1989 successfully reduced HBV endemicity in the country as reported in 2008, with a prevalence of 0% among 1,355 vaccinated school students age 16–18 years, from different endemic areas across the country.[10] A review article published in 2003 confirmed that the addition of the HBV vaccine, as well as the Ministry of Health (MoH) strategy for prevention of viral hepatitis infection, led to a decline in the prevalence among children.[11] The same article reported that the prevalence decreased from 4.7% in 1987 to 1.7% in 2000 among blood donors at a large center in Riyadh[11]
- For those born in the prevaccination era, the prevalence will be higher. This was seen in a cross-sectional study conducted among 10,234 persons in the Aseer Region, a southern province of KSA.[5] A seroprevalence of 0.8% was found among persons less than 15 years of age, 1.3% among persons 15–24 years of age, and 6.3% among those 25 years of age and older.

MoH blood donor results for HBV infection in the year 2000 showed a prevalence rate of 3.2% among persons between 18 and 44 years of age and 5.9% for persons more than 50 years of age (personal communication).[11] Another study rightfully points out that despite the optimism surrounding the low HBV infection rates in the younger Saudi populations, the prevalence in older generations has not been well-characterized and remains a source of concern[22]

- The vaccination program for newborns (and the catch-up program for children entering school between 1990 and 1996)[11] has reduced HBV prevalence in children due to effective implementation – 73% coverage of the third dose in the first year of implementation, 93% responders, and a protective efficacy of 99%,[23] with an 88% efficacy rate against HBsAg carriage 8 years after vaccination.[24] However, a catch-up vaccination program that supplemented the childhood program in 1990 to vaccinate healthcare workers (mandatory) and high-risk groups (voluntary)[11] might not have been optimally implemented. Two studies conducted among Saudi dental students and dentists found that 80%[25] and 80.5%[26] were vaccinated, respectively. Another study among medical students in a tertiary care academic hospital found that while 93.9% received the HBV vaccine upon entry to medical school, only 59.5% received all three doses.[27] Finally, a study among healthcare staff in a primary healthcare setting showed only 61% coverage of HBV vaccination (and of those, only 89% received the complete schedule).[28]

With respect to awareness about HBV in the community, in a cross-sectional study of 421 healthy individuals from Arar city, the majority (66.5%) had heard of HBV and were aware of the different modes of transmission (58.2%–78.9%), but only 27.6% knew the early symptoms.[29] Awareness regarding HBV and hepatitis C virus (HCV) was somewhat higher among first-year male and female students of medical sciences, at Jazan University ($n = 824$) in 2010.[30] The study showed that more than half of the students (64.4%) had basic awareness about HBV and HCV infection as well as about symptoms, and 57.1% had knowledge of the mode of transmission. In 2012, a cross-sectional survey of 180 primary care physicians revealed that the overall mean HBV knowledge level among the physicians was 62.9%.[31]

People with CHB have a lifetime risk of 15%–40% of developing end-stage liver disease including cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[32] Limited data on end-stage liver disease and related deaths due to HBV are available through the Systematic Observatory Liver Disease registry (SOLID)[33] which collects data from several centers in the country. A review study[34] found that about 35% of Saudi HCC patients were HBV-related. In two studies, it was found that for 29%[35] and 24.2%,[36] respectively, HBV was the underlying cause for HCC. In Arab countries, HBV-associated HCC deaths increased at a much faster rate (137% increase) compared with the rest of the world (62% increase) between 1990 and 2010.[37] Another recent study from the SOLID registry that analysed HBV-infected cohorts from the years 2010 and 2015 concluded that compared to 2010, the cohort from 2015 had not only aged significantly but was more likely to have liver disease sequelae such as HCC (1% vs. 12%) and cirrhosis (5% vs. 23%), and other comorbidities such as prevalence of coronary artery disease (4% vs. 10%).[38] This suggests that although the overall prevalence of HBV has decreased dramatically, the associated burden of end-stage liver disease secondary to CHB is likely to increase drastically in KSA in the next 20 years due to aging of the previously infected children.[39]

SCREENING AND DIAGNOSIS

There are a number of mandated screening structures present in the country aimed toward identifying patients through blood tests (HBsAg test, antibodies for blood donors) [Figure 1].[20,40-44]

The typical HBV patient journey in KSA is illustrated in Figure 2.[4] It is not known what proportion of the patients who are referred to specialists for further diagnosis come from GPs/primary care facilities or are referred by other specialties such as obstetrics/gynecology, surgery, and endoscopy.[4] Patients are often referred without having received the correct initial diagnostic testing. Diagnostic testing such as serology, molecular testing, liver enzyme tests, and transient elastography is at the specialist's disposal and is routinely conducted in the public sector.[4] Transient elastography may not always be available in all private or public facilities.

In KSA, any suspected or confirmed case of HBV should be reported to the MoH. In the past 10 years, the number of diagnosed cases has been fairly stable [Figure 3],[45] despite the declining prevalence. However, since prevalence is mainly declining in the younger populations due to the vaccination program, a lag in the trend of the diagnosed cases is to be expected.

LINKAGE TO CARE AND TREATMENT

Most patients with CHB infection are identified at the

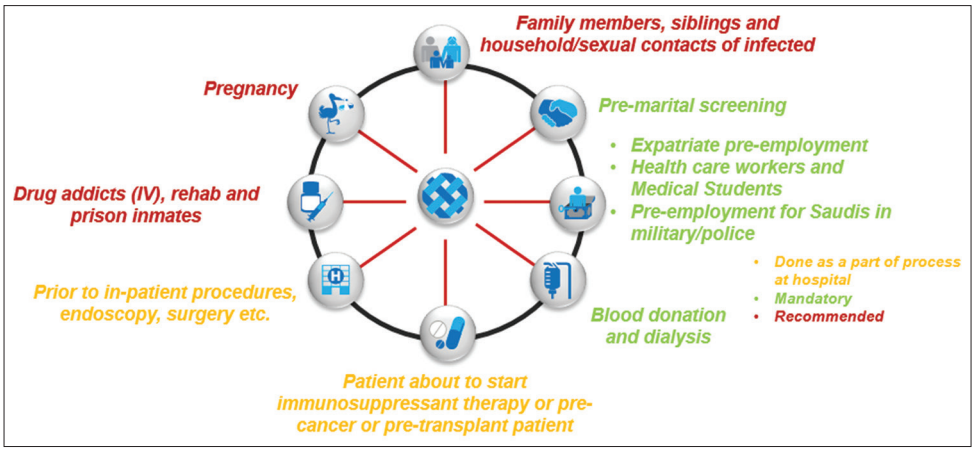

Figure 1: Potential HBV screening points in KSA

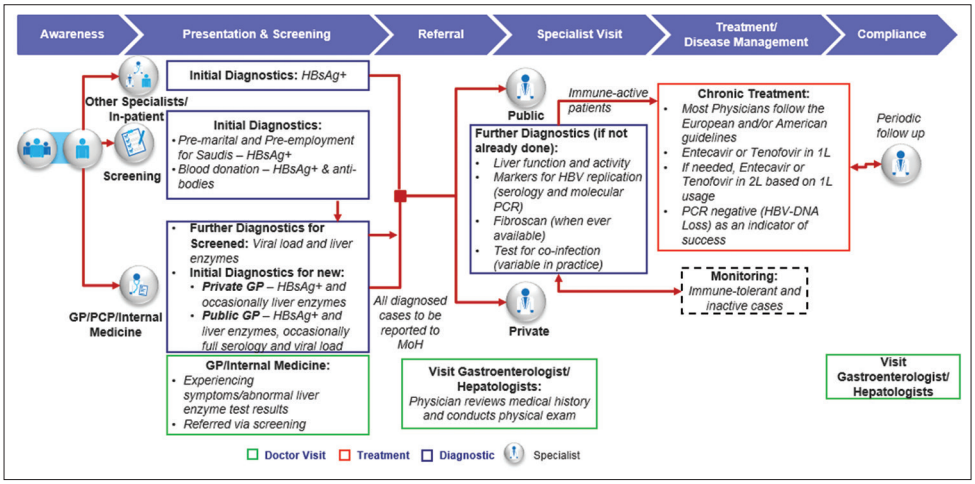

Figure 2: HBV patient journey in KSA

primary care level, and only those with chronic active HBV needing further evaluation and antiviral therapy would be referred to specialist care, although many centers also follow-up those with inactive carrier stage at specialist level. However, only 15.7% of physicians were of the opinion that primary healthcare facilities are suitable to manage patients with HBV.[24] In KSA, the majority of treatment is delivered in the public sector as it contributes to around 89% of the HBV medication market in the context of nucleos(t)ide analogs (NAs).[46] Private sector facilities are mainly located in metropolitans such as Riyadh and Jeddah.

Figure 4 displays the CHB care pathway cascade in KSA. Of the estimated 260,000 prevalent cases in the country, only 14% have been diagnosed in the past 10 years. It must be noted that this is possibly an underestimation of the actual number with knowledge of their HBV-positive status, but verifiable data on this are not available. Of those diagnosed in the past 10 years, only 14% were on treatment in the past year [5,330 on treatment/37,440 diagnosed – Figure 4].[46] These statistics may be an underestimation, as not all patients need long-term treatment. Therefore, there is no clear estimation of the actual linkage to care for diagnosed/screened patients.

The Saudi Association for the Study of Liver diseases and Transplantation (SASLT) has developed HBV practice guidelines which were published in 2014.[40] Although specialists also use the WHO,[47] European Association for the Study of the Liver,[48] and American Association for the Study of Liver Diseases[49] guidelines, implementation of these guidelines may differ across practitioners/hospitals. For chronic treatment, the recommended antiviral therapies for CHB treatment in the country are entecavir (ETV) and tenofovir disoproxil fumarate (TDF), although others – pegylated interferon (Peg-IFN-2a), lamivudine (LAM), telbivudine (TEL), adefovir (ADV) – have also been approved. In KSA, all these drugs have market authorization, but only ETV, TDF, and LAM are widely available in the public sector and freely reimbursable to Saudi patients when prescribed by a physician.[4]

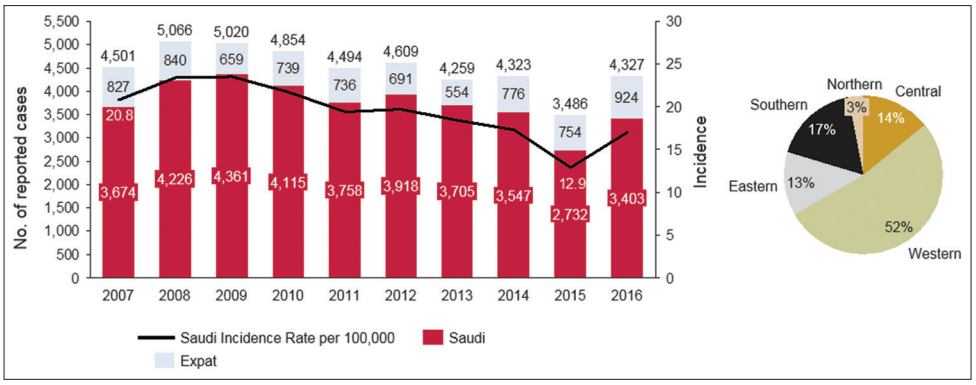

Figure 3: Cases of HBV reported to MoH.[45] Central: Riyadh and Qassem; Western: Makkah, Jeddah, Taif, Medinah, Tabuk, and Qunfudah; Eastern: Eastern Region, Al Ahsa, and Hafr Al Baten; Northern: Hail, Northern Borders, Al Jouf, and Qurayyat; Southern: Asir, Bishah, Jazan, Najran, and Al Baha

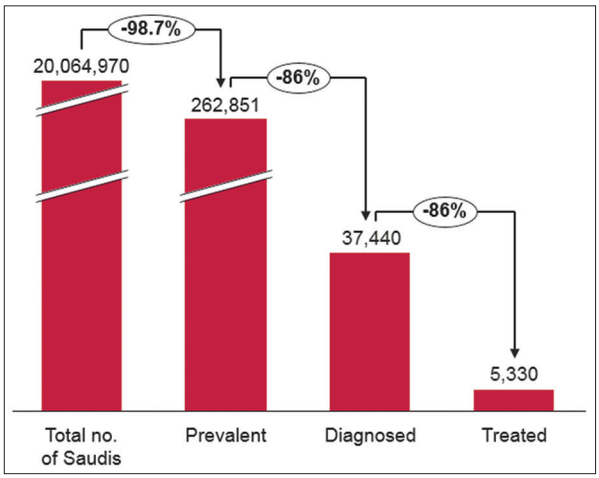

Figure 4: CHB care pathway cascade in KSA. Source: Total no. of Saudis from 2016 MoH Health Statistical Yearbook, Prevalence figure obtained by applying 1.31% on the population estimate, Treated[46]

There is the perception among some clinical practitioners and patients that current antiviral therapy may invoke long-term toxicity, and that health effects are unknown, while lifelong treatment might be needed. Disease progression is likely to occur when the suppressive effect of NAs is removed in cases of treatment cessation due to drug-related adverse events (AEs) or drug resistance in older publicly available medications.[48,49] The authors acknowledge, however, that newer effective medications may be available that do not carry such risks. There is an unmet need for a globally acknowledged and publicly available treatment that can cure HBV or at least present a higher barrier to resistance and fewer treatment-related AEs, than the currently available treatment options.

COMPLIANCE/ADHERENCE

It is recommended that all patients treated with NAs should be followed with periodical assessments.[40,48] Limited information could be found on chronic care and periodic patient follow-up among HBV patients in KSA.

A cross-sectional study collected data on 328 patients with viral hepatitis in a tertiary care setting;[50] 30% of patients were not compliant with follow-up visits. The loss to follow-up was higher among those who had been diagnosed with HBV compared with those diagnosed with HCV. The most important reasons for this included being unaware that a follow-up appointment was scheduled (69%), never being informed of the need for follow-up by healthcare provider (15%), personal belief that follow-up was not necessary (9%), logistical reasons (3%), and other reasons (5%).

Hepatology experts and KOLs also indicated that some patients defer therapy as it fails to provide a cure and they worry about the long-term effects of treatment as well as the risk of resistance.[4] This points to the need for enhanced patient education.

CONCLUSION AND ACTION POINTS

Four broad categories of gaps exist on the patient care pathway [Figure 5], and the related recommendations [Figure 6] are discussed below.

1. A task force should be established to assist with developing a national platform/patient registry that integrates data on the HBV care pathway of all patients with HBV. This could keep track of whether patients who are screened are correctly diagnosed; diagnosed patients are followed-up or referred, and referred patients are initiated and retained on treatment with regular follow-up visits. This would assist in establishing the correct overall prevalence of the burden of HBV by age, gender, and resident status. The need for such a platform corroborates the key priority indicator set by the National Transformation

Stage in HBV care pathway	Type of barrier affecting patient movement	Unmet needs	Impact on HBV care pathway
0 - Epidemiology & Awareness	Awareness Related	• *Studies focusing on sub-populations which may not truly represent the general population & older population* • *Lack of registry* • *Saudi community's awareness is rated poor and inversely related to age* • *Awareness and practices of GPs/HCPs at the primary care level need improvement*	In a cross-sectional study of healthy individuals, only 27.6% knew the early symptoms and 70.3% never went for any screening[38]
1 - Presentation & Evaluation/ Diagnosis	Linkage to care and diagnosis related	• *Lower PCP awareness related to diagnosis is leading to underdiagnoses* • *Stigmatization of HBV patients might lead to people being reluctant to go for testing* • *No clear data on the number of patients that are screened/diagnosed and actually linked to care* • *Below par care delivery and monitoring at primary care level*	Of the estimated prevalent, only 14% have been diagnosed [6,63]
2 - Treatment/ Disease Management	Availability and affordability related	• *Absence of systems that integrate patient care and maintain continuum* • *Need to update HBV practice guidelines published* • *Limited information is found on chronic care & periodic patient follow-up among HBV patients* • *Low awareness among patients about disease chronicity*	Of the diagnosed cases, only 14% is estimated to be currently on treatment[64]
3 - Compliance/ Adherence	Adherence related		

Figure 5: Barriers on the KSA HBV patient care pathway

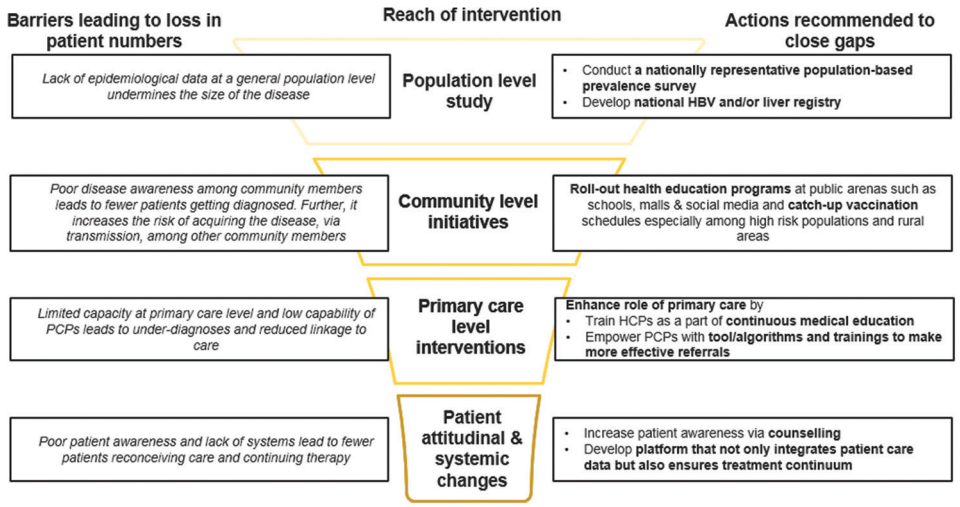

Figure 6: Action recommended to address gaps and optimize care pathway

Plan to increase the number of Saudi citizens who have a unified digital medical record[51]

2. Community-based educational interventions encompassing awareness about HBV, particularly the chronic nature of the disease, as well as the option of catch-up vaccination should be conducted. This is to increase knowledge in the general population and in high-risk groups (including medical staff).[43-46] Special attention should be paid to less developed areas to increase vaccination among high-risk populations and diagnosis of cases
3. Screening efforts should be increased (especially among those 30+ years and contacts of patients) to diagnose HBV-positive patients and link these to care
4. Training on HBV should be included as part of continued medical education activities organized by specialist associations such as the Saudi Gastroenterology Association and SASLT. Simple tools/algorithms and training for primary care physicians can empower them to make effective referrals for those patients in need. Also, those in primary care need to be educated on how to adequately follow-up those who do not need to be referred.

In conclusion, significant improvements have been made in KSA over the past 30 years to reduce HBV prevalence. However, challenges still remain concerning CHB management. Efforts must be made by all key stakeholders, including policy makers, in all phases of the HBV care pathway to reduce both morbidity and mortality in the KSA population.

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Conflicts of interest

Faisal M. Sanai is editor in chief of the Saudi Journal of Gastroenterology. There are no other conflicts of interest.

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