

Hepatitis B care pathway in Jordan: current situation, gaps and recommended actions

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Abstract

Objectives: Hepatitis B virus (HBV) infection remains a worldwide public health problem. The last major review of the HBV care pathway in the Middle East was published in 2011. This article aims to assess the current situation of the HBV care pathway in Jordan, identify gaps and barriers and recommend initiatives that could be taken to improve disease management across all stages of the care pathway.

Methods: A Delphi process was used between February and October 2017, including a literature review (PubMed and Google Scholar) for published articles on HBV in Jordan, followed by individual interviews with various healthcare professionals and group discussions with leading Jordanian hepatologists and gastroenterologists to provide context to the results of the literature review.

Results and discussion: The national prevalence of HBV is estimated to be around 2.4% and has declined from 9.9% in the pre-vaccination era. There is limited data on the burden of HBV-related hepatocellular carcinoma in the country. Awareness of various aspects of the disease is considered low among the general population and medium among primary care providers. There are several mandated national screening structures, however, established protocols for those that test positive and subsequent linkage-to-care are not optimal. In conclusion, significant improvements have been made in the past 30 years in Jordan in terms of decline in HBV prevalence. However, efforts must be made by all key stakeholders to optimise screening and linkage-to-care of patients and reduce both morbidity and mortality in the country.

Keywords: hepatitis B, epidemiology, awareness, diagnosis, treatment, Jordan

Introduction

Hepatitis B virus (HBV) infection remains a worldwide public health problem with an estimated number of infections worldwide of 468 million cases in 2016 according to the Global Burden of Disease Study (GBD2016) [1]. The same study estimated the number of HBV-related liver cancer cases to be 599,000 in 2016 and of cirrhosis and other chronic liver diseases due to HBV to be 12 million [1]. Furthermore, globally 350,000 people died of HBV-related liver cancer in 2016 and 366,000 of cirrhosis and other chronic liver diseases due to HBV [2]. Unfortunately, only 22% of people living with HBV infection are aware of their diagnosis and among those only 8% received treatment [3].

The last major review of the HBV care pathway in the Middle East, including the assessment of the epidemiology and the management of the disease, was published in 2011 [4]. The authors observed a trend from ‘high-to-intermediate’ to ‘low-to-intermediate’ endemicity. Medical experts have considered it important to assess whether this trend continues and to assess the current ‘HBV care pathway’. In the World Health Organization Eastern Mediterranean Region, an estimated 3.3%, of the general population is HBV-infected [5].

At a population level, the ‘HBV care pathway’ encompasses services that the community and patients must receive to optimise

prevention and management of the disease. In their assessment the authors have considered the following key stages on the pathway:

- Stage 0 – epidemiology of the disease and awareness of different stakeholders about various aspects of the disease;
- Stage 1 – screening for the disease and diagnosis of patients presenting with symptoms, reporting of positive cases and linkage to care;
- Stage 2 – appropriate evaluation of the disease and treatment initiation if needed; and
- Stage 3 – compliance/adherence to treatment and periodic patient follow-up.

This article aims to assess the current situation of the HBV care pathway in Jordan, identify gaps and barriers and recommend initiatives that could be taken to improve disease management across all stages of the care pathway.

Materials and methods

In this study, a Delphi process was used over a period of about 9 months, between February 2017 and October 2017. It comprised a literature review in PubMed to identify HBV in Jordan using the key words ‘Jordan’, ‘hepatitis B or HBV or CHB’, ‘hepatocellular carcinoma or HCC’, ‘cirrhosis’, ‘prevalence’, ‘awareness’, ‘epidemiology’, ‘vaccination’, ‘diagnosis’, ‘screening’, ‘treatment’, ‘care pathway’ and ‘adherence’. The reference lists of articles found were scanned for any additional publications. In addition, a search was conducted on Google Scholar using similar key

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words to identify relevant published studies, reports, guidelines, conference abstracts, posters and presentations. To provide context to the results from the literature review as well as to collect diverse stakeholder perspectives on those areas for which no or limited evidence was found in the literature, individual interviews were held during March 2017 to April 2017 with various health-care professionals (HCPs), including general practitioners (GPs), gastroenterologists, hepatologists, regulators, payers (funding and procurement) and non-governmental organisations (NGOs). The final step of the process was to obtain input from leading hepatologists and gastroenterologists in Jordan via a working group meeting conducted in October 2017, to whom we will refer in this study as the ‘HBV Working Group’ [6]. The objective of this meeting was to gain insights into the current HBV burden, discuss unmet medical needs in the country and suggest recommendations to address emerging issues or gaps in the disease care pathway [6]. The results of the literature review, combined with the information gathered from individual interviews and the ‘HBV Working Group’ are described in this article.

Results and discussion

Prevalence of HBV infection

Historical prevalence of HBV in the general population in Jordan has been around 9.9% [7]. In 1995 the HBV vaccine was integrated into the childhood immunisation programme [8]. A four-fold decrease of the HBV prevalence has occurred in the last three decades, indicating a successful implementation of this programme [7,9]. The Polaris observatory has published a recent modelling study, showing an estimated HBV prevalence in Jordan in 2016 of 2.4% with an estimated number of HBsAg positive cases at 230,000 [9].

Six local studies were identified reporting on the HBV prevalence in Jordan (Table 1). Toukan *et al.* conducted a study in 1985 in a healthy population in selected areas of the country prior to the HBV immunisation programme and found a prevalence of 9.9% [7]. The remaining studies were performed in different types of populations, such as pregnant women and blood donors [8,10–13]. Surveys in more at-risk populations, such as patients with haemodialysis/end-stage renal disease, continue to show higher

prevalence rates [10]. One study in blood donors reported that out of all HBsAg+ HBV cases, the proportion of infected patients increased with increasing age groups (from 0% cases in those aged <20 years to 33.3% among those aged >50 years) [11]. In one study the prevalence among women was higher (2.6%) compared to that among men (1.3%), while another study found a higher incidence among men (8.4% vs. 3.0% in women) [14].

In addition, two studies looked at HBsAg positivity among haemodialysis patients and found rates of 4% in 2003 ($n=1711$) [12] and 5.9% in 2006 ($n=430$) [14]. Vaccine coverage among newborns is >95% [13], and the decrease in HBV prevalence among blood donors is probably due to the introduction of the HBV vaccine programme in the mid-1990s [7,8]. In 2001 Jordan also introduced a vaccination policy targeted at high-risk groups such as close household contacts of acute/chronic HBV-infected people, healthcare workers, injection drug users and haemodialysis patients. Available vaccination coverage data for dental staff was in the range of 14–95% of individuals [10,18–20].

Hepatitis B awareness

There was no information found in the literature on HBV awareness in the community. It was rated low to medium for general awareness and low for other aspects such as prevalence of disease, origin, transmission and high-risk groups by the ‘HBV Working Group’ [6].

Regarding the level of awareness about HBV among HCPs, in 2008 one study had assessed HBV knowledge among nursing students ($n=750$) [21]. Knowledge was found to be low, e.g. only 12% of participants knew that HBV and hepatitis C virus (HCV) could be transmitted by sharing razors and 18% were aware that it could be spread by sharing toothbrushes. Furthermore, two-thirds of healthcare workers ($n=339$ nurses and physicians) included in a study stated that they did not have adequate and up-to-date training in hepatitis infections, and 71% were interested in receiving information/training about HBV [22]. The ‘HBV Working Group’ members rated current HBV awareness among general practitioners to be medium for general awareness, prevalence of disease, origin, transmission and high-risk populations [6].

Burden of chronic HBV in Jordan

People with chronic HBV (CHB) have a lifetime risk of 15–40% of developing end-stage liver disease such as cirrhosis, liver failure and hepatocellular carcinoma (HCC) [23]. Health-related quality of life in patients with CHB tends to be impaired in later stages of liver disease [24–27].

In the Arab world, an estimated 6447 deaths occurred from HBV-associated HCC in 2010 and from 1990 to 2010, the burden of HBV-associated HCC deaths increased at a much faster rate (137% increase) compared to the rest of the world (62% increase) [28].

Jordan has seen a 10% reduction in the age-standardised death rate (ASDR) for HBV-associated HCC between 1990 and 2010 at 2.3/100,000 among men and 1.7/100,000 among women in 2010 [28]. According to the Jordan Cancer Registry there were 92 new cases of liver or biliary tree cancers (1.8% of all cancers) in 2012, however the number due to HBV was not known [29]. At King Hussein Medical Centre 17% of liver transplants are HBV-related [6]. Looking at the causes of liver cirrhosis observed at the Jordan University Hospital (JUH) in two analyses, one retrospective and one prospective, (Figure 1), it was found that HBV was one of the major causes, although in recent years HCV has become responsible for a similar proportion of cirrhosis [6].

Table 1. Prevalence of HBV in Jordan

Study year	Population type	n	HBV prevalence (HBsAg+) %	Reference
1985	Healthy population from selected areas	1115	9.9	Toukan <i>et al.</i> 1990 [7]
2001	Patients with hereditary haemolytic anaemia	143	3.5	Al-Sheyyab <i>et al.</i> 2001 [15]
2002	Pregnant women	1000	4.3	Bataneh and Bdour, 2002 [8]
2006–2009	Blood donors	8190	1.4	Al-Gani, 2011 [11]
2009–2010	Autopsies	242	2.1	Bakri <i>et al.</i> 2016 [16]
2015	Haemodialysis patients	712	7	Ghazzawi <i>et al.</i> 2015 [17]

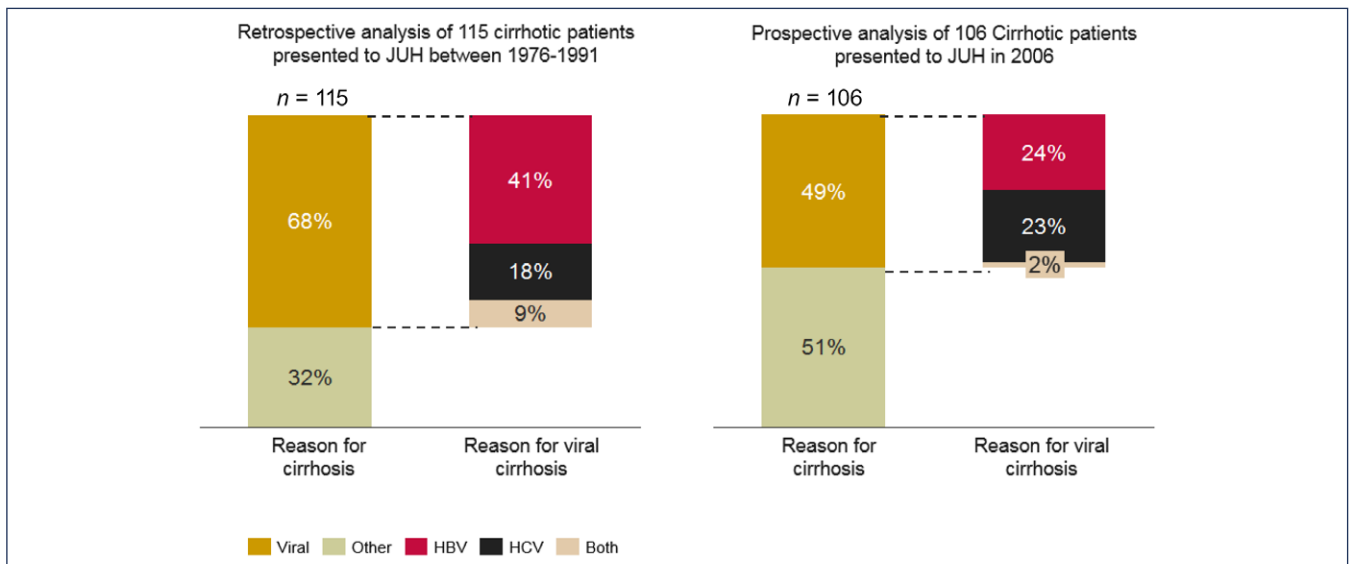


Figure 1. Causality of liver cirrhosis in Jordan University Hospital (JUH). Source: Jordan HBV Working Group Meeting [6]. HBV: hepatitis B virus; HCV: hepatitis C virus.

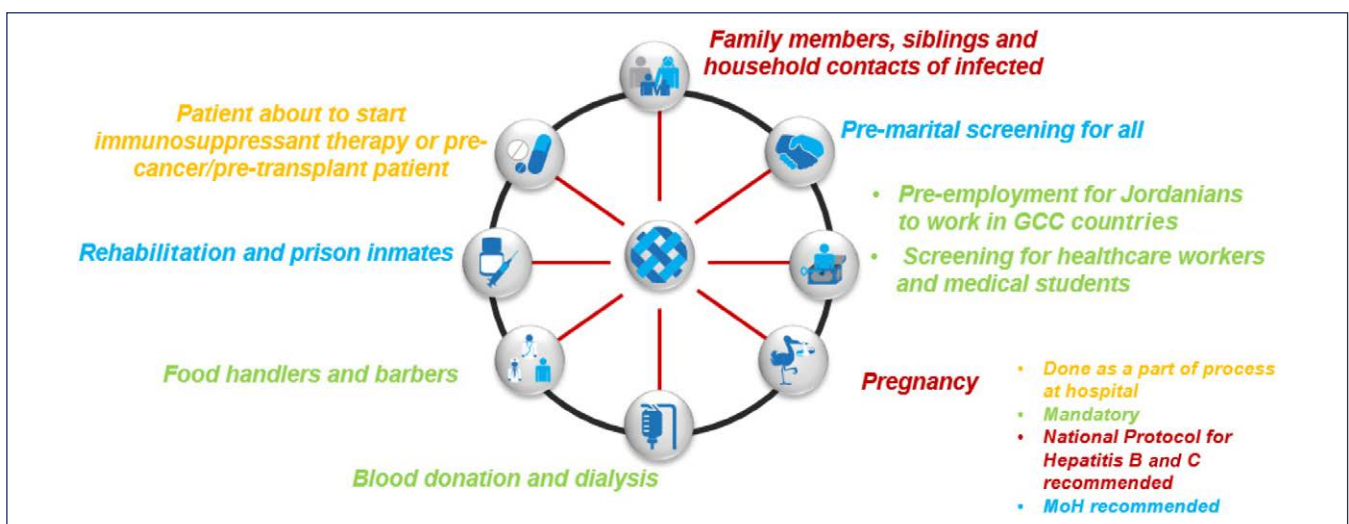


Figure 2. Potential HBV screening points in Jordan. MoH: Ministry of Health; GCC: Gulf Cooperation Council.

Immunisation has proven to be very effective in HBV prevention in adolescents and has led to a decrease in prevalence, however, it takes decades to observe its effect on the reduction in HCC in adults [28].

In a cross-sectional study conducted among 107 patients with CHB from different hospital departments in Jordan, genotype D was the only detected genotype [30]. Furthermore, 71.0% of participants were males with a mean age of 34.1 years, and among them only 17% were HBeAg positive. Another study including 491 blood samples from HBV patients also found 100% genotype D and 10.9% of HBeAg positivity [31]. These studies confirm that genotype D HBV is predominant in Jordan. This finding could be associated with a higher burden of the disease because this genotype has been significantly associated with more advanced stages of liver disease [32].

Presentation and screening/diagnosis

Hepatitis B is a reportable disease in Jordan [3,13]. There are a number of mandated screening structures (Figure 2) identifying patients through blood testing using HBV surface antigen test (HBsAg) and antibodies for blood donors. Screening is compulsory

for Jordanians who want to work in the Gulf countries, health-care workers (early in their careers, especially in haemodialysis units and blood banks) [3] and medical students, blood donors and dialysis patients, food handlers and those working in barber shops. Furthermore, the Ministry of Health (MoH) recommends pre-marital screening and testing for rehabilitation individuals and prison inmates. The National Protocol for Hepatitis B and C recommends screening for family members, siblings and household/sexual contacts of patients and pregnant women, so that newborns to HBV positive women can be provided with immunoglobulin and HBV vaccine [13]. Finally, screening is routinely performed in hospitals among patients starting immunosuppressant therapy, before cancer chemotherapy or organ transplantation [6].

The typical journey for an HBV patient in Jordan is illustrated in Figure 3 [6]. Besides screening, patients can be diagnosed by a GP or in a primary care facility, based on symptoms, signs and abnormal diagnostic tests (e.g. HBsAg, liver enzymes, alanine aminotransferase [ALT] levels to determine liver damage).

Once screened and diagnosed HBV positive, patients will be referred to a specialist for further investigations (e.g. liver function and activity, serology, molecular polymerase chain reaction,

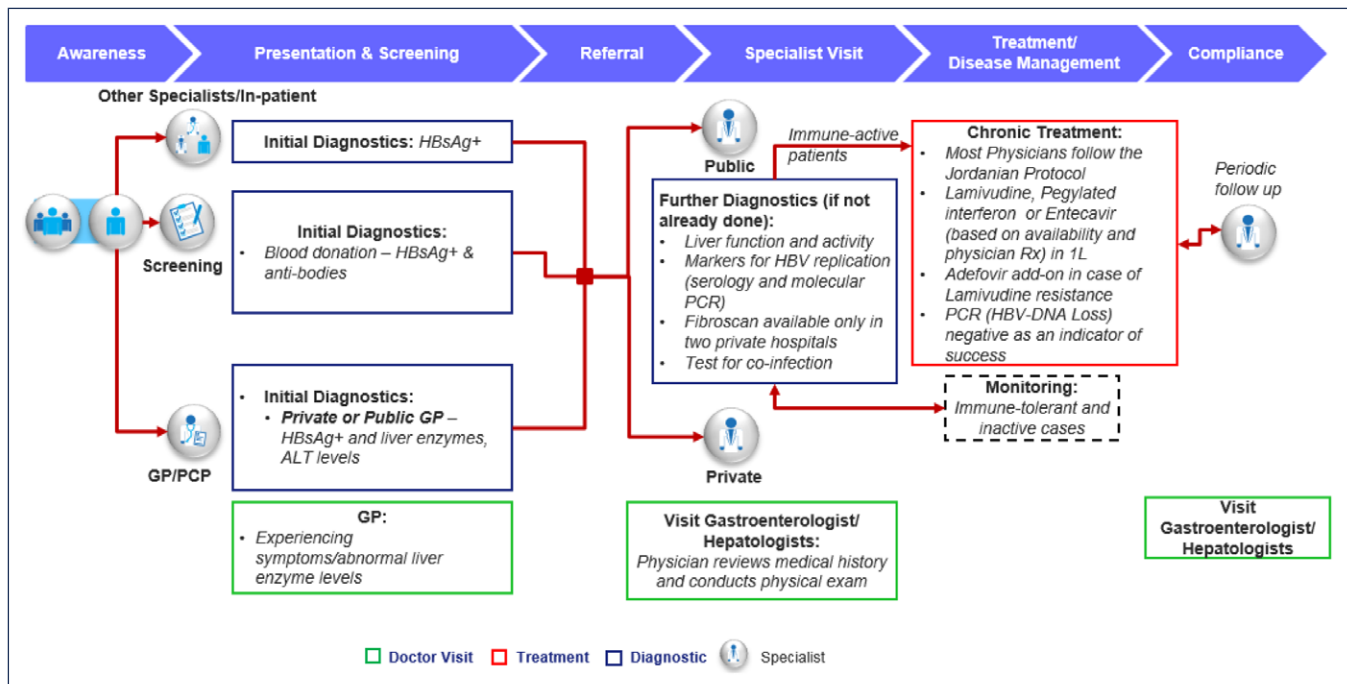


Figure 3. HBV patient journey in Jordan. ALT: alanine aminotransferase; HBV: hepatitis B virus.

test for co-infections) and treatment. It is estimated that 70–75% of referrals to specialist care originate from blood banks, although not all referred HBV cases are actually seen by a specialist and hence may not be linked to care [6]. The remainder of the cases (25–30%) are referred by GPs (public or private) and other specialists.

According to medical experts, occasionally some uncomplicated cases such as inactive carriers and/or immune-tolerant patients may be followed up by GPs owing to long waiting times for specialist appointment [6]. In a study among healthcare workers in 2008, 52.5% reported that they did not have standard protocols for hepatitis [33]. Protocols have been established since 2008, however, their overall use remains uncertain [6]. Stigma has been raised as an obstacle to optimal screening by the 'HBV Working Group'. As an example of this situation, a Jordanian study among staff of general dental practices found that only 45% of these practices were willing to provide care to an HBV-infected individual [34].

Treatment and disease management

In Jordan most treatment is delivered in the public sector tertiary hospitals of the MoH, Royal Medical Services and universities. Most patients are treated free-of-charge or for a minimal payment depending on the public-sector institution they approach. Few patients receive treatment in the private sector as this would depend on insurance coverage and out-of-pocket affordability.

Of the approximate 230,000 prevalent cases in the country, only 0.7–0.9% are estimated to be on treatment in 2017 [6]. This could be due to prevalent cases not having been diagnosed or reported as, currently, the main channel remains the blood banks [6]. It could also be that screened/diagnosed patients do not reach specialist care and hence are not linked to care owing to the lack of a monitoring infrastructure, tracking of patients and HCPs' follow-up, therefore leading to an interruption in the care continuum [6]. It is unknown how many of these people are aware of their HBV-positive status [6].

Public sector specialists are obliged to follow the National Protocol for Hepatitis B and C (last updated in 2017) [13], which is broadly consistent with the European Association for the Study of the Liver (EASL) [22] and the American Association for the Study of Liver Diseases (AASLD) [35] guidelines. The main goal of HBV therapy is to improve survival and quality of life by preventing disease progression and death. In terms of chronic treatment, antivirals registered and available in Jordan are lamivudine (LAM), pegylated interferon (Peg-IFN-2a), entecavir (ETV) and adefovir (ADV) while tenofovir disoproxil fumarate (TDF) is not registered in the country. LAM is mainly prescribed due to perceived lower costs. ADV is considered to have a high probability of renal toxicity, although research has only shown small differences in renal function among the different antivirals [36], and generally speaking treating physicians prefer to use ETV.

The main limitation of the currently available antivirals is that the long-term toxicity and side effects remain unknown when used lifelong. Furthermore, disease progression is likely to occur when the suppressive effect of nucleos(t)ide analogues (NAs) is removed; especially in cases of treatment cessation due to drug-related adverse events (AEs) or resistance [22]. There is an unmet need for an HBV cure. In its absence new effective treatment options with a higher barrier to resistance and fewer treatment-related AEs are needed. These should be suitable in a broad range of patients, including ageing ones, and should have favourable long-term tolerability profiles [6].

Compliance and adherence

It is recommended that all patients treated with NAs should be followed with periodical assessments [22]. Non-adherence with recommended follow-up visits is a significant barrier for completing treatment and consequently associated with unfavourable clinical outcomes. No quantitative information could be found on the chronic care and periodic patient follow-up among HBV patients in Jordan, however, the HBV Working Group rates the compliance/adherence to treatment as high as about 85–90% of patients who start treatment remain compliant [6]. Possible

Stage in HBV care pathway	Type of barrier affecting patient movement	Unmet needs	Impact on HBV care pathway
0 - Epidemiology and awareness	Awareness Related	<ul style="list-style-type: none"> Studies limited to certain pockets of patient population Urgency for a wider population based study to estimate the burden of HBV, especially with the current refugee influx Jordanian community's awareness is low to poor Need for better awareness related to HBV among primary care HCPs Limited data on HBV associated HCC 	<p>Community awareness is rated low to medium [6]</p> <ul style="list-style-type: none"> Under-diagnosis as main channel for detection is limited to blood banks [6] Unknown how many people know their HBV positive status [6] <p>Of the estimated prevalent number, only 0.7-0.9% may be currently on treatment [6]</p>
1 - Presentation and evaluation/diagnosis	Linkage to care and diagnosis related	<ul style="list-style-type: none"> Lack of a closed loop and limited follow-up post detection lead to leakage of patients Lack of registry and current reporting systems under-reporting Only one channel, blood banks, contributes majority (80%) of the patients GP/PC ability to interpret test results, make referrals, manage and follow-up of cases is questioned 	
2 - Treatment/disease management	Availability and affordability related	<ul style="list-style-type: none"> Cost conscious decision making often proves to be a deterrent for access to newer, more effective therapies Absence of data on the different steps in the care pathway Absence of a system to ensure patient follow-up throughout the care pathway 	
3 - Compliance/adherence	Adherence related	<ul style="list-style-type: none"> Drug availability in public sector hospitals and stocking could be of concern 	

Figure 4. Barriers affecting Jordan HBV patient care pathway. HBV: hepatitis B virus. HCP: healthcare professional. HCC: hepatocellular carcinoma. PC: primary care.

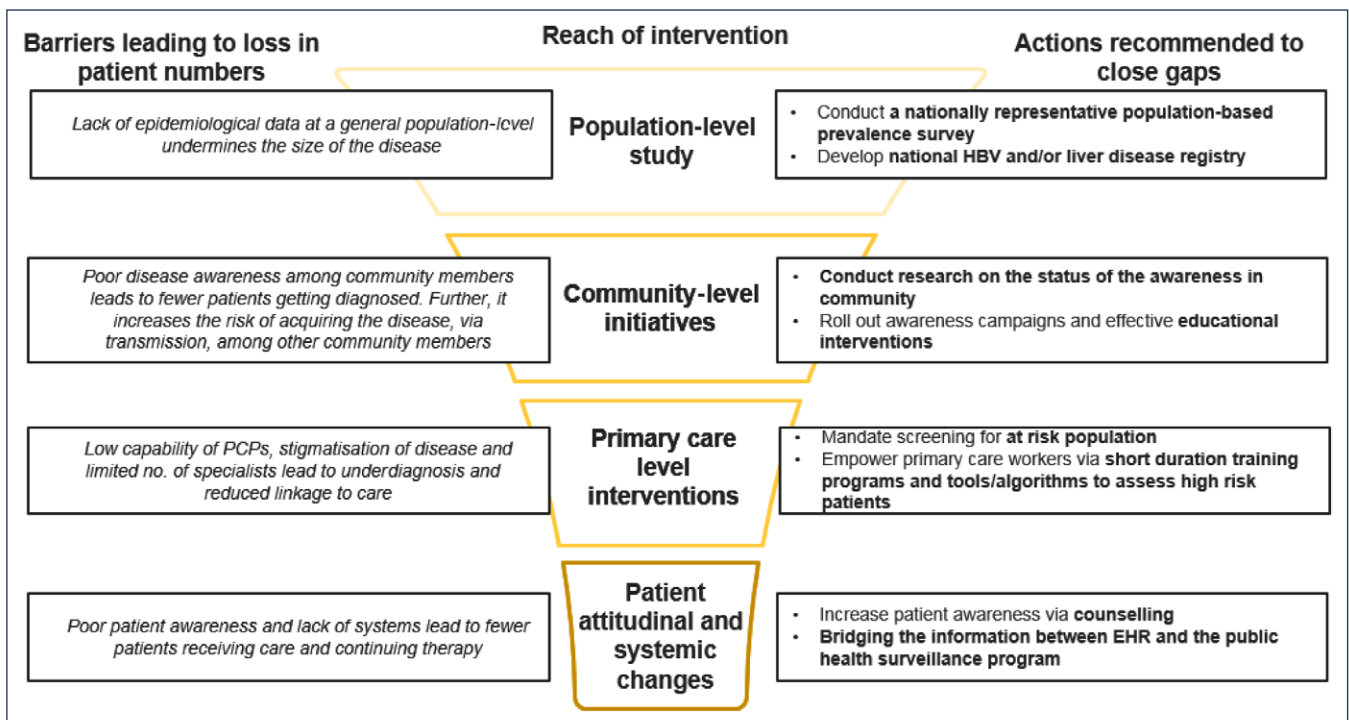


Figure 5. Actions recommended to address gaps in the HBV care pathway in Jordan. HBV: hepatitis B virus; EHR: electronic health record; PCP: primary care physician.

factors related to non-adherence may involve non-availability of certain drugs, patient forgetting to take medication while on holiday, and/or co-payment of up to 20% for some patients.

Recommendations

Four broad categories of gaps are present on the HBV patient care pathway in Jordan (Figure 4). The related recommendations (Figure 5) are discussed below.

In terms of HBV epidemiology, it is suggested to conduct a nationally representative (including rural areas) population-based

prevalence study of sufficient size, using HBsAg and core antigen screening. An accurate overall prevalence could then be estimated, with a possible epidemiological stratification by age (especially the population over 30 years old) and gender. This has already been recommended in the national protocol [13] and become more urgent due to the impact on the HBV burden from the refugee influx. Other considerations include sociodemographic characteristics, vaccination status and mode of transmission data to help inform prevention strategies. There is mandatory reporting for HBV cases (public health surveillance) but the data is not publicly available, and the cancer registry does not provide the cause of liver cancers. Therefore, there is a need for a unified

national and easily accessible HBV registry to inform treatment interventions [13].

More research should be conducted on the status of HBV awareness in the general population and high-risk groups, including medical staff. If needed, there should be regular awareness campaigns and effective educational interventions, based on a collaboration between the government, scientific societies, NGOs and the pharmaceutical industry.

The WHO advocacy brief ‘Combating hepatitis B and C to reach elimination by 2030’ highlights that certain prevention and diagnosis targets should be achieved to reach HBV elimination [37]. It is important that screening efforts are increased as currently the majority of cases originate from blood banks, which are not visited by the entire population. A national screening programme has been approved but funding has not been obtained yet. Screening should become mandatory for the following at-risk populations such as family members/close contacts/household contacts of infected patients, over 30-year-old population that was at high risk of exposure in the pre-vaccination era, premarital couples and pregnant women. Therefore, it is advised to provide screening free of charge or for a nominal fee to those who are not covered by public care and insurance.

Low cost and short training programmes must be conducted for healthcare workers. It is suggested that training programmes are evaluated regularly to ensure that information is current and meets the changing needs of workers and the workplace [33]. An electronic health record (EHR) system could be linked to hepatitis reporting systems in all hospitals in the country, producing alerts to ensure a patient treatment continuum. Furthermore, a systematic protocol should be established, leveraging on an EHR, to locate and screen family or close contacts of patients with their consent.

Conclusion

In conclusion, significant improvements have been made in Jordan over the past 30 years to reduce HBV prevalence. However, relevant challenges still remain in terms of CHB management. Efforts must be made by all key stakeholders at all stages of the HBV care pathway to optimise screening and linkage-to-care of newly tested/diagnosed patients and reduce both morbidity and mortality in the country.

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Conflicts of interest

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