

Immigration and viral hepatitis

Suraj Sharma¹, Manuel Carballo², Jordan J. Feld¹, Harry L.A. Janssen^{1,3,*}

¹Toronto Centre for Liver Disease, University Health Network, University of Toronto, Toronto, Canada; ²International Centre for Migration, Health and Development, Geneva, Switzerland; ³Department of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

Summary

WHO estimates reveal that the global prevalence of viral hepatitis may be as high as 500 million, with an annual mortality rate of up to 1.3 million individuals. The majority of this global burden of disease is borne by nations of the developing world with high rates of vertical and iatrogenic transmission of HBV and HCV, as well as poor access to healthcare.

In 2013, 3.2% of the global population (231 million individuals) migrated into a new host nation. Migrants predominantly originate from the developing countries of the south, into the developed economies of North America and Western Europe. This mass migration of individuals from areas of high-prevalence of viral hepatitis poses a unique challenge to the healthcare systems of the host nations. Due to a lack of universal standards for screening, vaccination and treatment of viral hepatitis, the burden of chronic liver disease and hepatocellular carcinoma continues to increase among migrant populations globally. Efforts to increase case identification and treatment among migrants have largely been limited to small outreach programs in urban centers, such that the majority of migrants with viral hepatitis continue to remain unaware of their infection.

This review summarizes the data on prevalence of viral hepatitis and burden of chronic liver disease among migrants, current standards for screening and treatment of immigrants and refugees, and efforts to improve the identification and treatment of viral hepatitis among migrants.

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Introduction

Hepatitis B (HBV) and Hepatitis C (HCV) viruses are leading causes of chronic liver disease and associated morbidity and

mortality globally [1]. According to WHO estimates, an estimated 500 million (1 in 12 people) are living with chronic viral hepatitis, making HBV and HCV one of the top 10 infectious disease killers globally [1]. At least 1.3 million deaths annually can be attributed to chronic liver disease caused by HBV and HCV [2]. In addition, viral hepatitis is also largely responsible for the global increase in liver cancer. Liver cancer is now the fifth most common cancer among men globally (ninth among women) with an annual mortality of at least 750,000 patients [1,3]. Since the majority of people living with chronic viral hepatitis are asymptomatic until the late stages of disease, estimates suggest that 40–80% of people with chronic viral hepatitis are unaware of the infection [2]. The largest burden of morbidity and mortality from chronic liver disease continues to be in nations of the developing world. For example, 5–10% of the adult population in East Asia and sub-Saharan Africa are estimated to have chronic HBV infection [4]. These countries are also the source of a steady influx of migrants into North America and the European Union (EU), posing unique challenges to the public health and immigration systems in the host nations.

This review will focus on immigration in the context of the global viral hepatitis epidemic, outlining the data on prevalence of viral hepatitis among migrants, current standards for identification and treatment of infected individuals, and the evidence supporting targeted screening of immigrants and refugees.

How common is viral hepatitis globally?

Hepatitis B

The global prevalence of HBV is estimated to be about 350–400 million people [2]. An estimated 15–40% of chronically infected patients will go on to develop liver cirrhosis, cancer or liver failure [3]. HBV is responsible for up to 1.2 million deaths annually, making it the 10th leading cause of mortality globally [2]. Chronic HBV infection is also responsible for 60–80% of the global burden of liver cancer, with an estimated annual mortality of 350,000 [3].

HBV is highly prevalent (>8%) in East Asia, Pacific nations and sub-Saharan Africa (Fig. 1) [4]. 45% of the global population live in areas of high HBV prevalence, while another 40% live in regions of intermediate prevalence [5]. The most common route of acquiring infection in these countries is perinatal transmission, or

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* Corresponding author. Address: Toronto Center for Liver Disease, University Health Network, University of Toronto, 6B-Fell Pavilion, 399 Bathurst Street, Toronto, Ontario M5T 2S8, Canada.

Abbreviations: HCC, Hepatocellular carcinoma; HBV, Hepatitis B virus; HBSAg, Hepatitis B surface antigen; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus.



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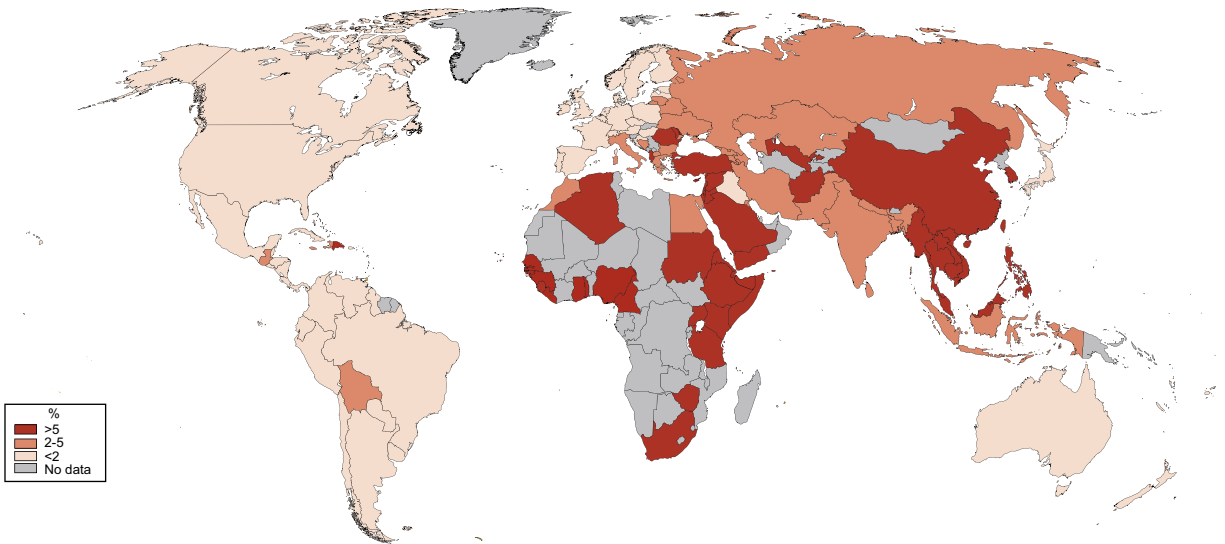


Fig. 1. Global HBV Prevalence [1,2,87].

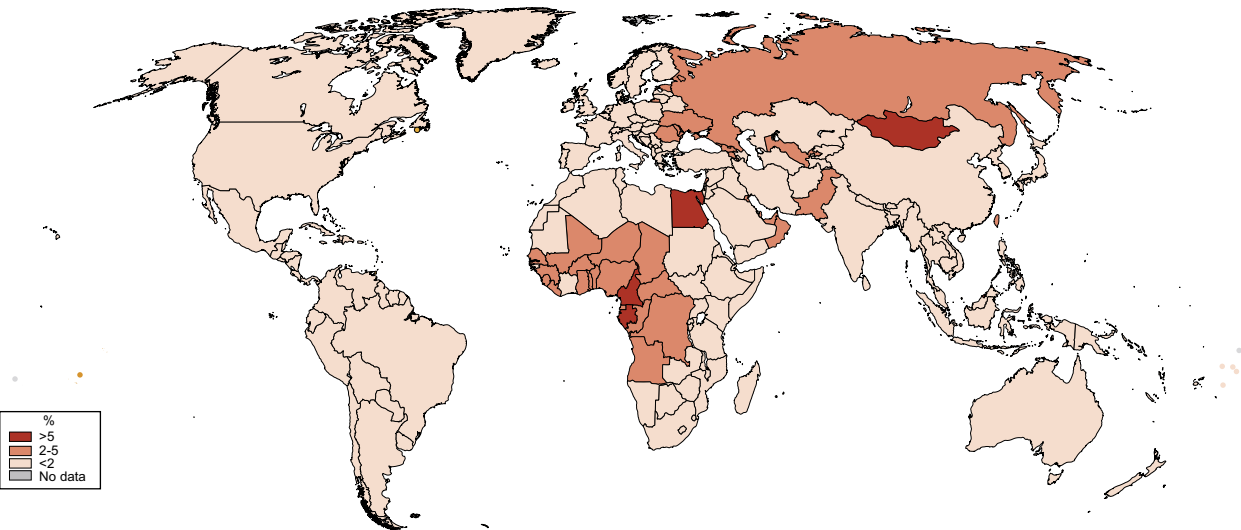


Fig. 2. Global HCV Prevalence [12,42,87].

during preschool years [2]. HBV is present in blood, saliva, semen and vaginal secretions, as well as in breast milk of infected persons. HBV exposure can also occur through contaminated needles and other medical equipment in developing countries. HBV is more infectious through blood-borne exposure than both HCV and human immunodeficiency virus (HIV). Contaminated needles alone are thought to be responsible for 8–16 million HBV infections per year [6].

Areas of intermediate prevalence (2–7%) include parts of Central and Eastern Europe, the Middle East, Latin America as well as the Indian subcontinent [4]. Once again, perinatal or horizontal transmission is most common in these regions.

In contrast, HBV is lower in prevalence (<2%) in North America and Western Europe [4]. In these countries, infection is usually spread through sexual contact or IV drug use. The risk of HBV transmission through blood transfusion has decreased

dramatically in most Western nations with the institution of routine screening of blood products, as well as universal vaccination programs [7]. For example, the incidence of HBV in the US has declined by 80% from 1987 to 2004 [7]. Healthcare workers continue to be an at risk population, through exposure to infected blood or contaminated medical equipment [8].

The route of exposure, and the age of acquisition of the infection are important determinants of the long-term sequelae of HBV. Vaccination is a safe and effective way of decreasing the risk of neonatal HBV infection, and is especially relevant to the nations with high HBV prevalence [9]. The WHO recommends universal HBV vaccination at birth in countries with high prevalence (>8%) [10]. However, as of 2006, only 38 of 81 (44%) high prevalence countries reported adopting birth-dose vaccination as part of the national immunization schedule. WHO estimates show that in 2006, birth-dose coverage was only 36% among

the 62 million infants born in high prevalence nations [9]. Thus, while vaccination is an effective preventive strategy, its full implementation has been lacking in nations most at risk.

Hepatitis C

The global burden of HCV is estimated to be 185 million people in 2005 (prevalence 2.8%), with up to 350,000 deaths annually [11,12]. Importantly, robust population level data is not available in most regions with high HCV prevalence, and the available estimates rely on small studies, which are prone to bias. The highest reported prevalence of chronic HCV is in Central Asia and the Middle East. Globally, Egypt has the highest prevalence of HCV, with some studies reporting HCV antibody positive rates of up to 15%, with an estimated 10% with chronic viremia (Fig. 2) [13,14]. This high prevalence is partly due to treatment programs for schistosomiasis with unsterilized needles, which led to high rates of transmission of HCV [14]. As a result of iatrogenic exposure, and improperly sterilized medical equipment, the incidence of HCV in Egypt continues to be high [15]. One study estimated the incidence of new infections to be approximately 7/1000 patient-years, leading to approximately 500,000 new infections per year [16]. Intra-familial spread of HCV is also common in this region, however the specific practices leading to transmission are not well understood [17].

The largest population of HCV patients worldwide resides in East Asia and the Indian subcontinent, with at least 100 million HCV positive individuals in this region [15,18]. HCV prevalence rates in South and East Asia range from 0.6% in China to 4.9% in Pakistan [19,20]. Iatrogenic exposure, through infected blood products or medical procedures with contaminated needles, continues to be the major mechanism of transmission of HCV in these countries [19]. However, injection drug use (IDU) is becoming an increasingly important route of transmission [21].

The prevalence of HCV in North America and Western Europe is comparatively lower. HCV transmission in Europe and North America is predominantly through IDU [22,23]. At least 7.3 million people (1.1%) are estimated to be living with HCV in Europe [24,25]. Estimates suggest that 5.2 million people are anti-HCV positive in the United States [26]. These figures likely underestimate the true prevalence in both regions [26]. The implementation of blood product screening and proper disposal and sterilization of medical waste has led to a decline in the incidence of HCV in both regions [27]. In the USA, HCV incidence dropped from an estimated 7.4/100,000 people in 1982–89 to 0.7/100,000 in 1994–2006. In contrast with the developing world, iatrogenic outbreaks in North America and Western Europe are uncommon, and are typically confined to individual clinics using improper sterilization technique [28].

These data reveal large differences in the prevalence of these chronic liver diseases among migrant groups and the host nations. In an era of increasing migration, these differences in HBV and HCV prevalence between regions have important implications for public health agencies in host nations.

Global migration statistics, countries of origin and destination

With the growing ease of air travel, and the globalization of the world economy, mass migration has been on the upswing in the last half of the 20th century. According to UN estimates, the

total number of international migrants in 2013 was 231.5 million, making this group larger than the 5th most populous nation [29]. In 1990, 154 million people, or 2.9% of the global population were migrants, whereas the corresponding figure for 2013 was 3.2% [30]. These numbers do not include undocumented migrants or trafficked persons, and therefore likely underestimate the global migrant population. Many of these migrants move into and remain part of ethnic minority groups where traditional social and cultural behaviors that may have adverse implications for exposure to HBV and HCV are reinforced and persist.

In 2013, the United States, Canada and four EU states (Germany, UK, France and Spain) were among the top 10 destinations for international migrants [30]. The EU was home to 72 million foreign-born migrants in 2013, while the US alone was home to 45 million migrants. Refugees accounted for 7% (15.7 million) of the global migrant stock in 2013 [29].

Migration to EU and North America occurs mainly from countries with high prevalence of viral hepatitis. For example, China, India and Philippines are among the top-10 countries of origin to both North America as well as the EU [30]. The US is also home to a substantial population of Mexican immigrants, and the EU hosts large migrant populations from Turkey and Morocco [31,32].

Prevalence of viral hepatitis among migrants

The National Health and Nutritional Examination (NHANES) survey estimated that 0.3% of American residents, or about 800,000 individuals were positive for HBsAg [33]. This survey likely under-represents the true prevalence of HBV in the US, since it excludes high-risk populations such as migrants, incarcerated persons, homeless and veterans [7]. Currently, data on the HBV seroprevalence among migrants is not recorded systematically in the US. However, the prevalence of HBV among migrants tends to reflect the prevalence in their country of origin. Surveys performed in migrant populations show very high HBV seroprevalence rates. For example, a survey of over 4300 Asian immigrants to New York City showed that 13% of this cohort was HBsAg positive [34]. Similarly, a study of Somali immigrants in Minnesota showed HBV prevalence rates of ten times the baseline population [35]. Given these data, the true prevalence of HBV in the US has been estimated to be as high as 2.2 million individuals, with up to 1.3 million foreign-born HBV positive individuals [36].

Data from the EU reveal a similar pattern, with regional variations. HBV prevalence is higher in Eastern European nations such as Turkey (8%), Romania (6%) and Bulgaria (4%), when compared to Western European nations such as Netherlands (<0.5%), Italy (1%) and Germany (1%) [37]. HBV and HCV seroprevalence data is now being collected by the European Centre of Disease Prevention and Control [37], although reporting has been poor from many member countries [38]. Pooled estimates of chronic HBV prevalence data from ECDC surveys indicate that 53% of HBV carriers were born outside the EU. In the Netherlands, where robust population level data has been available, 77% of chronic HBV infections are estimated to originate from outside the EU, predominantly from high and intermediate prevalence regions [39]. Studies from at least seven EU nations have shown that the prevalence of HBV is higher in the immigrant population than in the indigenous population. A meta-analysis on HBV prevalence among immigrants found that prevalence rates among migrant

Table 1. Current guidelines for testing and treatment of immigrants and refugees at risk for viral hepatitis.

	Immigrants	Refugees and Undocumented Migrants
USA	No routine HBV and HCV testing HBV vaccination for children <18 years Positive screen does not meet inadmissibility criteria	HBsAg testing if HBV prevalence >2% in country of origin HBsAg testing if HBV prevalence <2% and risk factors (eg., IDU, household contact of HBV positive person) HCV screening if 1945-65 cohort or risk factors for HCV (eg., IDU) Positive screen does not meet inadmissibility criteria
Canada	History and physical to screen for risk factors, history of liver disease, HIV, tuberculosis or syphilis - testing if any of these present Positive screen does not meet inadmissibility criteria	Same as for immigrants Positive screen does not meet inadmissibility criteria
European Union	HCV and HBV screening guidelines are country-specific Mandatory HBV/HCV testing is not required as a condition of entry 24 EU countries have universal HBV vaccination targeted at infants and adolescents Six countries (Denmark, Finland, Iceland, Norway, Sweden and United Kingdom) have targeted vaccination of high-risk groups only Some countries with low HBV prevalence screen immigrant mothers from high-prevalence regions and offer newborn vaccination	

populations mirror the prevalence in the country of origin, with particularly high prevalence (>10%) among migrants from East Asia and sub-Saharan Africa [40].

The prevalence of HCV antibody in the US may be at least 5.2 million according to one estimate, when high-risk groups such as incarcerated and homeless individuals are taken into account [26]. However, this estimate did not include immigrants with HCV, so that the true prevalence of HCV in the US is likely even higher. Data on the prevalence of HCV among US immigrants and refugees is sparse. However, small studies of migrant communities have found very high HCV seropositivity rates. For example, a hepatitis screening program enrolled 283 New Yorkers from the former Soviet Union, 28.3% of whom were anti-HCV positive. In Canada, immigrants are estimated to account for at least 20% of all cases of HCV, with an estimated prevalence of 3% in this group (general population prevalence estimated at 0.8%) [41]. The prevalence in some groups, such as immigrants from Egypt is reported to be as high as 18%.

HCV prevalence among EU member states is estimated to be 1% overall [42]. However, some regional differences do exist. Anti-HCV prevalence is lowest in the Scandinavian countries (<0.5%), but higher in Italy, Greece and Romania (>3%) [37]. ECDC data on the prevalence of HCV among migrants is limited due to incomplete records from many member states. However, studies in individual countries do suggest that immigrants may constitute a high-risk group. For example, a modeling study from the Netherlands estimated the 50% of the HCV burden in the Netherlands occurred in immigrants, with prevalence 10-fold higher than the native population (2% vs. 0.2%) [43]. Data from the UK show that HCV prevalence among South Asians, and especially among migrants from Pakistan may be as high as 2.7%, while 0.5% of the general population is estimated to have chronic HCV [44].

In summary, migrant populations have higher rates of chronic viral hepatitis than the local population in both North America and the EU. These data have prompted various national and regional guidelines for screening of migrants at high-risk for HBV and HCV, especially in host nations that attract the largest numbers of immigrants globally. The European, Canadian and American guidelines for HBV and HCV screening will be summarized below.

Current standards for screening of immigrants and refugees

The American immigration medical exam does not include routine testing for viral hepatitis [45]. Importantly, HBV or HCV positive serology does not meet grounds for inadmissibility to the US. Under the current regulations, medical assessment includes a review of prior medical history, drug and alcohol use as well as a physical examination (Table 1). However, routine HBV and HCV testing is not required as part of the immigration medical exam. Age-appropriate vaccination recommendations do include routine HBV vaccination for children below 18 years of age [46].

On the other hand, the examination of refugees on arrival to the US includes assessment for the risk of viral hepatitis [47]. Current guidelines recommend HBsAg testing for all refugees arriving from countries with an HBV prevalence of 2% or higher. In addition, refugees arriving from countries with HBV prevalence less than 2% are also screened if they have risk factors (such as homosexual men, IDU, household contacts of known carriers). HBV vaccination is recommended in non-immune adults. Recommendations for HCV testing are similar to the US population, and include universal testing of the 1945–1965 birth cohort, as well as testing of individuals with risk factors (such as IDU, HIV positive individuals, and recipients of blood products). Patients found to be positive for HBV or HCV are referred to a physician with expertise in management of viral hepatitis.

Similar to the US immigration medical exam, universal testing for viral hepatitis is not mandated in Canada, even in patients originating from countries with high prevalence [48]. Rather than screening of immigrants based on country of origin, the immigration medical exam requires identification of risk factors for viral hepatitis and evidence of liver disease on history and physical examination. Patients with positive risk factors, history of liver disease, HIV, tuberculosis or syphilis require mandatory HBV and HCV testing. Refugee claimants are also mandated to undergo an immigration medical examination with the same standards. A positive HBV or HCV test does not meet grounds for inadmissibility into Canada.

Immigration medical screening policies in the EU region are country-specific. However, hepatitis screening is currently not required as a condition of entry into the EU region. According to ECDC statistics, 24 out of 30 EU/EFTA countries have adopted

universal HBV vaccination targeted at infants, adolescents or both [38]. Six countries (Denmark, Finland, Iceland, Norway, Sweden and United Kingdom) have targeted vaccination of high-risk groups [37]. Targeted screening and vaccination of immigrants is not performed universally in the EU, but some countries with low-prevalence of HBV have developed programs to screen pregnant mothers from high prevalence regions and vaccinate their newborns [49,50]. The optimal vaccination strategy continues to be debated [49], but the success of these programs depends on identification of at-risk individuals and broad implementation of vaccination. With high rates of HBV prevalence among immigrants, horizontal transmission to uninfected and unvaccinated individuals remains a concern, in addition to high rates of vertical transmission.

Burden of chronic liver disease among migrants

Studies show that the awareness of chronic HBV or HCV in most populations is low but that among migrants it tends to be even lower [51]. This is likely due to a combination of factors, including poor knowledge of the diseases, their risk factors and symptoms, lack of access to healthcare and health information, stigma associated with disease, as well as the lack of symptoms from the early stages of liver disease such as viral hepatitis [52,53]. Estimates from Canadian studies show that immigrants and refugees are 2–5 times more likely to die from liver disease than the baseline population [54]. A study from Ontario, Canada showed that Hepatitis B and C were both among the top five infectious causes of health-adjusted life years lost (HALY's) in the province, responsible for 18% of the total HALYs lost [55]. While the incidence of both acute HBV and HCV infection in Canada has dropped, the prevalence of chronic viral hepatitis has remained stable, owing mainly to the ongoing influx of migrants from high prevalence nations [56].

Migrants are also more likely to develop hepatocellular carcinoma (HCC). Studies from both Canada and the US show that the incidence of HCC in migrant cohorts is at least 2–3 fold higher than the baseline population [57,58]. In addition, mortality from HCC is also higher in immigrant cohorts than their native-born counterparts [54,59]. Among immigrants with HBV, the onset of HCC tends to occur at a younger age than in the baseline population, and especially so among patients with a family history of HCC [60].

Thus, migrants are disproportionately afflicted with both increased mortality and morbidity from chronic viral hepatitis, and this trend is expected to continue over the next decade with implications for costs to the healthcare system [2]. In the US, where migrants constitute the majority of people with HBV, outpatient and inpatient visits for HBV have increased 4-fold over the last two decades [7]. During this period, direct healthcare costs for HBV have risen from \$350 million in 1990 to over \$1.5 billion in 2003. Costs for HBV antivirals have also increased at 50% per year, and were estimated at \$82 million annually in 2008.

Improving case identification and treatment among migrants

Studies have identified patient factors such as lack of knowledge, late presentation and poor adherence to follow-up and fear of the side effects of treatment as major barriers for

effective treatment of viral hepatitis [61,62]. In addition, limited knowledge of natural history, treatment options and fear of side effects remain barriers among primary care providers treating patients with viral hepatitis [63]. Identification of barriers to treatment is critical since studies show that improving sustained virological response (SVR) rates is not enough to improve HCV eradication rates without a concurrent increase in treatment uptake [64].

In response to these barriers, various outreach programs have been developed in order to educate, screen, vaccinate and offer treatment to migrants at risk for viral hepatitis [34,65–70]. Successful campaigns, such as the BFreeNYC project, have combined education and awareness initiatives with screening events in order to both educate and identify migrant populations most at risk of viral hepatitis [71]. Over four years, this program reached one million people, educated 11,000 and screened 9000 Asian migrants living in New York City. Other initiatives have aimed at educating primary care providers, in order to improve their knowledge and comfort with managing viral hepatitis and its complications [72,73]. In order to be successful, outreach programs require buy-in from the target community, ongoing efforts to raise awareness, and a linkage to care for screen-positive individuals [74]. Different approaches are usually needed for participants with different ethnic background. For example, outreach programs targeting South Asians migrants for viral hepatitis screening have enlisted the support of local religious organizations and community leaders in order to raise awareness in the community [75]. Unfortunately, many outreach programs are hampered by the high cost of screening, and lack of funding for antiviral treatment, especially for uninsured individuals. Estimates suggest that 31 US outreach programs active in 2008 screened only 21,000 individuals [74]. Studies on viral hepatitis treatment rates and efficacy among immigrants are limited [76–78]. One Italian study showed that immigrants were significantly less likely than Italian-born patients to receive HBV antiviral therapy [76]. However, other studies have shown no difference in treatment uptake rates among immigrants [79]. Lack of insurance coverage [34] and lack of access to specialist physicians [78] were felt to be barriers to treatment in some studies. Therefore, a concerted system-wide approach is required to identify and treat a significant proportion of migrants with viral hepatitis, in order to reduce the burden of chronic liver disease in this population.

Universal screening of migrants for viral hepatitis has been evaluated by several modeling and cost-effectiveness studies [37,41,59,80,81]. These studies have shown that screening immigrants from intermediate or high prevalence nations for HBV is likely to be cost effective, and may reduce liver-related mortality and morbidity [59,80]. Estimates for the cost per quality adjusted life year (QALY) range from €9000 in a Dutch study proposing one time screening for immigrants, to \$39,000 in an American study proposing screening, treatment and vaccination of contacts among Asian migrants [59,80]. Based on these data, experts have made recommendations for the implementation of screening programs for HBV targeting immigrants and refugees [37,47,59]. However, these recommendations have not yet been adopted by government agencies.

The cost-effectiveness of universal screening of migrants for HCV is not as clearly established, since HCV prevalence varies widely among host nations and migrant groups. Studies on cost-effectiveness of HCV screening have focused on high-risk

Public Health

groups such as IDU patients, or specific birth-cohorts, such as the 1945–65 US birth cohort [82–84]. These studies suggest targeted screening of high-risk groups is likely to be cost effective, even with the added costs of the new DAAs. The cost-effectiveness of screening for HCV among migrants is likely to depend on the expected HCV prevalence in the particular cohort, treatment uptake rates, and expected SVR [85]. Younossi *et al.* have estimated that screening in the US would be cost effective at a threshold prevalence of 3% if 50% of the patients started treatment [86]. Based on this data, experts in Canada have recommended screening among migrant populations with HCV prevalence above 3% [41]. With the development of several interferon-free treatment regimens for HCV, treatment options have expanded, and expected SVR rates have improved. Thus, more studies are needed to assess the cost-effectiveness of HCV screening in immigrant populations with the currently available treatment options.

Conclusion

Viral hepatitis is a common and growing public health problem worldwide. Liver cirrhosis and HCC caused by chronic HBV and HCV infection are responsible for more than one million deaths annually. While the majority of this burden of illness is experienced in the developing world, the migration of large numbers of people from high prevalence countries is changing disease burden profiles in Europe and North America. The implications of this for the planning and management of national viral hepatitis prevention, diagnosis and treatment are considerable and call for action. A large proportion of the burden of chronic liver disease in developed countries is now being borne by migrants who may not have good access to the type of services they need and could use. Thus despite improved vaccination for HBV in many (but not all) European countries and better hygiene measures, the incidence of new cases of both HBV and HCV is increasing in the context of migration. Unfortunately, routine screening of migrants for viral hepatitis is not being performed in the majority of host nations despite the fact that multiple studies suggest that targeted screening of migrants is likely to be cost-effective, especially in the case of HBV. Efforts to alter the course of the viral hepatitis epidemic must take up the case of migration from countries where HBV and HCV are common. National programs to deal with the challenge will have to address the linguistic, cultural, social and medical insurance barriers that are faced by migrants with viral hepatitis.

Conflict of interest

The authors report no conflict of interest with the topics discussed in this review.

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