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Hepatitis B virus infection in immigrant populations

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Abstract

Hepatitis B virus (HBV) is the most common cause of hepatitis worldwide, with nearly 350 million people chronically infected and 600000 deaths per year due to acute liver failure occurring during acute hepatitis or, more frequently, in HBV-related liver cirrhosis or hepatocellular carcinoma. Ongoing immigration from countries with a high HBV endemicity to those with a low HBV endemicity warrants particular attention to prevent the spread of HBV infection to the native population. This review article analyzes the epidemiology and virological and clinical characteristics of HBV infection in immigrant populations and in their host countries, and suggests prophylactic measures to prevent the spread of this infection. Among the immigrants from different geographical areas, those from South East Asia and sub-Saharan Africa show the highest prevalences of hepatitis B surface antigen (HBsAg) carriers, in accordance with the high endemicity of the countries of origin. The molecular characteristics of HBV infection in immigrants reflect those of the geographical areas of origin: HBV genotype A and D predominate in immigrants from Eastern Europe, B and C in those from Asia and genotype E in those from Africa. The literature data on the clinical course and treatment of HBsAg-positive immigrants are scanty. The management of HBV infection in immigrant populations is difficult and requires expert personnel and dedicated structures for their assistance. The social services, voluntary operators and cultural mediators are essential to achieve optimized psychological and clinical intervention.

Key words: Hepatitis B virus infection; Chronic hepatitis B; Immigration; Immigrants; Developing countries

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Core tip: Extensive immigration from countries with a high hepatitis B virus (HBV) endemicity to those with a low HBV diffusion warrants particular attention to prevent the spread of HBV infection to the native population. This review article analyzes: (1) the prevalence of subjects with hepatitis B in screened immigrants; (2) the distribution of the HBV genotypes; (3) the cost effectiveness of screening immigrants for hepatitis B; and (4) the clinical and therapeutic approach.

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INTRODUCTION

Due to numerous socio-economic and political crises that have occurred in Africa, Eastern Europe, Asia and South and Central America in recent decades, Western countries have become lands of immigration for citizens of these sub-continent. Immigrants are frequently poor, out of work, carry on the cultural and religious traditions of their country of origin and do not speak the language of the host country. One of the most important forces driving young and middle-aged adults to emigrate to a western country in search of work is the low income in their countries of origin. Consequently, the typical immigrant is a healthy young male who leaves his country in the hope of new opportunities to improve his living conditions^[1]. This phenomenon is called "healthy migrant effect", a kind of self-selection whereby only those subjects in good physical condition who are young and with enough initiative and psychological stability emigrate. For these subjects their good health is the only certainty to invest in their own future and in that of their family. Although in good clinical conditions, these subjects may carry asymptomatic chronic infections, such as those related to hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV), all widespread in low-income countries. In addition, political reasons often favor the flow of immigrants, such as dictatorships, persecution, war and genocide, all of which induce numerous families to seek freedom outside their country.

The immigrant populations frequently move from geographical areas with intermediate or high HBV, HCV and HIV endemicity to countries where these infections have a low endemicity level. The high or intermediate endemicity in low-income countries is most frequently a consequence of scanty knowledge of the routes of transmission of these infections, due to a low level of schooling and difficulty obtaining information from

the media^[2]. In addition, tribal rituals may favor the parenteral spread of these infections in some countries. Concluding on this point, immigration from developing countries may influence the epidemiology of these infections in western countries, which can be controlled by improving the immigrants standard of life and by taking prophylactic measures in the host countries^[3].

This review article analyzes the epidemiology of HBV infection in immigrant populations and in their host countries and suggests prophylactic measures to prevent the spread of this infection in western countries.

WORLDWIDE EPIDEMIOLOGY OF HBV INFECTION

HBV is the most common cause of hepatitis worldwide, with nearly 350 million people chronically infected^[4] and 600000 deaths per year due to acute liver failure occurring during acute hepatitis or, more frequently, in HBV-related liver cirrhosis or hepatocellular carcinoma^[5-7]. HBV is mainly transmitted at birth from an infected mother to the newborn baby, by parenteral route mainly in adults (intravenous drug use, surgery, dialysis, tattooing and piercing) or by unsafe sexual intercourse. The spread of chronic HBV infection differs widely from one geographical area to another, and the prevalences of hepatitis B surface antigen (HBsAg) chronic carriers classify the level of endemicity as low (< 2%), intermediate (2%-7%) and high (> 8%) in different countries^[7]. HBV endemicity is high in Asia, sub-Saharan Africa and Alaska, but enclaves with high rates of HBsAg chronic carriers have been discovered in Southern and Eastern Europe and South and Central America. The prevalence of the HBV chronic infection varies in European countries from 0.1% to 8.0%. In Italy, the HBsAg seroprevalence is around 1% and the incidence of acute hepatitis B registered in 2013 is one case per 100000 inhabitants, the new cases almost exclusively involving non-vaccinated adults infected by sexual route^[8]. In the United States and Australia the prevalence of HBsAg chronic carriers is lower than 0.5%.

In geographical areas with a high prevalence of HBsAg chronic carriers, HBV infection is frequently transmitted at birth or during early childhood^[4], while in areas with a low prevalence it is typically acquired during adulthood by percutaneous or sexual transmission^[9].

HBV INFECTION IN IMMIGRANT POPULATIONS

This review was prepared in accordance with the PRISMA guidelines. PubMed searches considered papers published between March 1974 and January 2015, and combined "Country" with the free-text search terms "hepatitis B, HBsAg" and "epidemiologic studies, prevalence, and seroprevalence" and "immigrants, foreigners and refugees".

The studies included in this review reported original

Table 1 Studies and immigrants screened, according to the geographical area of origin

Region	No. of studies	No. of immigrants investigated
Eastern Europe	8	4163402
Africa	13	959046
Latin America	5	130003914
Asia	17	8468256

data on the HBsAg seroprevalence in immigrants. The data on the immigrants' status was classified in the following categories: Immigrants, refugees, asylum seekers. We excluded studies on acute hepatitis B in immigrants.

The data on the study design, decade of study, immigrant status, immigrants' region of origin, mean or median age, gender distribution, co-morbidities, method of participant identification for the study, and serological testing method used were also extracted. The method of participant selection was categorized as occurring in reception centers at the time of arrival, in the context of a clinic or hospital visit, screening or others situations (*i.e.* screening studies in general host populations that included a subset of immigrants or studies which invited certain immigrant groups to be screened).

A total of 273 citations were identified in the electronic search. After screening the titles and abstracts, 245 were excluded because they were considered irrelevant and 5 were duplicated. A total of 23 articles were assessed with the predefined eligibility criteria and included in this review.

In these studies we evaluated: (1) the prevalence of subjects with hepatitis B in screened immigrants; (2) the distribution of the HBV genotypes; (3) the cost effectiveness of screening immigrants for hepatitis B; and (4) the clinical and therapeutic approach.

Prevalence of HBV infection in immigrants

The 23 selected articles involved 27948420 immigrants from several geographical regions (Table 1). All studies but two were prospective and evaluated the demographic, epidemiological and clinical data from immigrant screening programs performed in countries with a low HBV endemicity.

Among immigrants from different geographical areas, those from South East Asia (0%-27.3%) and sub-Saharan Africa (0%-15%) showed the highest prevalences of HBsAg carriers, in accordance with the high endemicity of the countries of origin (Table 2).

McCarthy *et al.*^[10] observed 15421 immigrants at 41 GeoSentinel clinics and found that 17% of the cases were HBV chronic.

Studies performed in Western Europe: The HBsAg seroprevalence in sub-Saharan immigrants ranged from 7.4% to 13.9% in four Italian studies^[11-14] and was 8% and 15% in two studies from Spain^[15,16], but another Italian study showed a prevalence of 3.7%^[17].

Italy is a land of immigration also from Eastern Europe, and immigrants from this subcontinent living in Italy showed HBsAg-positivity rates ranging from 6.94% to 36.7%^[11,14,17]. High prevalences were also observed in Albanian refugees in two Greek studies, 11.7% and 15.3%, respectively^[18,19]. In Germany the Turkish community accounts for about 20% of the whole population, with an HBsAg prevalence of 5%^[20]. In studies carried out in England and Holland the Chinese immigrants showed a percentage of HBV chronic carriers of 8.5% and 8.7%, respectively^[21,22].

Studies performed in North America: Several American studies screened subjects from Asia (China, Pakistan, Afghanistan, Vietnam, Cambodia, Laos)^[23-29]. The study by Mitchell *et al.*^[25] is an impressive retrospective investigation that tested for the HBsAg prevalence the immigrants to the United States from 1974 to 2008 (Table 2). Nearly 27 million immigrants from 225 countries were examined. The largest geographical subgroup came from Latin American countries (13 million cases) and the smallest from African countries (940000 cases). The percentage of HBsAg-positive immigrants was 1.6% in those from Latin America, 11.1% in those from South Africa, 5% in those from the Mediterranean countries, 2.9% from Europe, 4% from South East Asia and 11% from The Pacific countries.

Studies performed in Australia: At present, immigrant populations come to Australia prevalently from countries of South-East Asia. Caruana *et al.*^[30] screened 95 Laotian and 236 Cambodian immigrants, of whom 9.5% of the Laotians and 8% of the Cambodians were HBV chronic carriers. Most of the HBsAg-positive subjects were unaware of their HBV status. Further studies are needed to extend the knowledge of the impact of immigration on the HBV endemicity in Australia.

HBV Genotypes in immigrants

The molecular characteristics of HBV infection in immigrants reflect those of their geographical areas of origin. HBV genotyping in immigrants was investigated only in small studies (Table 3). Mixson-Hayden *et al.*^[23] studied immigrants from Asia and Somalia and detected HBV genotypes B and C in 90% of subjects with chronic hepatitis B. Rivas *et al.*^[15] studied 34 HBV viremic patients from Equatorial Guinea and other sub-Saharan countries and found HBV genotype A in 22, genotype E in 10, and genotype D in 2. El-Hamad *et al.*^[17] investigated 45 immigrants and found that HBV genotype D predominated in those from Eastern Europe, HBV genotypes B and C in those from Asia, genotype A in those from India and genotype E in those from West Africa. Scotto *et al.*^[11] evaluated 144 HBV-DNA-positive immigrants, prevalently from Africa, and identified 65 (45.1%) with HBV genotype E, 26 (18.1%) with D, 22 (15.3%) with B, 19 (13.2%) with C and 12 (8.3%) with A.

Table 2 Prevalence of hepatitis B virus infection in immigrant populations

Ref.	Country	Type of study	No. of patients ¹	Area of origin and percentage (%)	HBsAg positive (%)
Roussos <i>et al</i> ^[18]	Greece	Prospective	130	Eastern Europe: 86 Asia: 8.5 Africa: 6.2	15.3 ³ 27.3 0
Caruana <i>et al</i> ^[30]	Australia	Prospective	329	South east Asia (Laos and Cambodia)	Laos 9.5 Cambodia 8
Toro <i>et al</i> ^[16]	Spain	Prospective	1303	Latin America: 46 Sub-Saharan Africa: 23.7 Eastern Europe: 9.4 Northern Africa: 9.2 Asia: 4.9	0 15 0 3.2 Unknown
Hislop <i>et al</i> ^[29]	Canada	Prospective	504	China: 100	6
Majori <i>et al</i> ^[13]	Italy	Prospective	182	Sub-Saharan Africa: 100	9.3
Museru <i>et al</i> ^[24]	United States	Retrospective	9570	Asia: 24 Africa: 71 Eastern Europe: 4	10.7 ²
Tafari <i>et al</i> ^[12]	Italy	Prospective	529	Africa: 96.4 Asia: 3.6	8.3 0
Milionis <i>et al</i> ^[19]	Greece	Prospective	504	Albania: 100	11.7
Lee <i>et al</i> ^[27]	United States	Prospective	567	Asia: 100	6
Levy <i>et al</i> ^[26]	United States	Prospective	684	South America: 96.4 Asia: 7.7	0.3 3.8
Mitchell <i>et al</i> ^[25]	United States	Retrospective	1502 27900000	Latin America: 46.6 Africa: 3.36 Mediterranean countries: 6 Europe: 14.3 South East Asia: 6.6 Pacific Countries: 23.7	1.6 11.1 5 2.9 4 11
Kallman <i>et al</i> ^[28]	United States	Prospective	322	Vietnam: 100	9.3
Veldhuijzen <i>et al</i> ^[22]	Holland	Prospective	1090	China: 100	8.5
Rivas <i>et al</i> ^[15]	Spain	Retrospective	1493	Sub-Saharan Africa: 100	8.4
McCarthy <i>et al</i> ^[10]	Canada, Europe, United States, Australia, New Zeland	Retrospective	15421	Africa: 41 Asia: 35.8 South America: 16.1 Eastern Europe: 4	12.5 11.7 2 0
Vedio <i>et al</i> ^[21]	United Kingdom	Prospective	229	China: 100	8.7
Zuure <i>et al</i> ^[38]	The Netherlands	Prospective	465	Egypt: 100	1.1
Richter <i>et al</i> ^[39]	The Netherlands	Prospective	959	Eastern Asia: 100	2.2
Burgazli <i>et al</i> ^[20]	Germany	Prospective	1287	Turkey: 100	5
Mixson-Hayden <i>et al</i> ^[23]	United States	Prospective	4890	Somalia: 14.5 Asia: 86.5	5.5 ⁴ 6.8 ⁴
El-Hamad <i>et al</i> ^[17]	Italy	Prospective	3728	North Africa: 12.4 Eastern Europe: 44 Sub-Saharan Africa: 21.4 Asia: 16.8 (37 China) Central-South America: 5.4	2.8 6.9 3.7 3.4 3.3
Coppola <i>et al</i> ^[14]	Italy	Prospective	882	Northern Africa: 9 Sub-Saharan Africa: 50.3 Eastern Europe: 22 India-Pakistan Area: 14.3	2.5 13.9 6.2 3.2

¹Estimated cases; ²It is not possible to differentiate for geographical area of origin; ³Albania 22.4%; ⁴HBV-DNA-positive. HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

Table 3 Prevalence of hepatitis B virus genotype in immigrant populations *n* (%)

Ref.	No. of HBV-DNA-positive patients (%)	HBV genotype A	HBV genotype B	HBV genotype C	HBV genotype D	HBV genotype E	HBV genotype F	HBV genotype G
Toro <i>et al</i> ^[16]	43 (81)	15 (34.9)	-	-	16 (37.2)	10 (23.2)	-	1 (2.3)
Scotto <i>et al</i> ^[11]	144 (75.4)	12 (8.3) ¹	22 (15.3)	19 (13.2)	26 (18.1)	65 (45.13)	-	-
Rivas <i>et al</i> ^[15]	40 (52.6) ²	22 (64.7) ³	-	-	2 (5)	10 (25)	-	-
Zuure <i>et al</i> ^[38]	5 (100)	-	-	-	5 (100)	-	-	-
Mixson-Hayden <i>et al</i> ^[23]	331 (12.1) ¹	9 (2.7)	164 (49.5)	137 (41.4)	-	-	-	1 (0.3)
El-Hamad <i>et al</i> ^[17]	45 (27)	8 (18)	5 (11)	5 (11)	27 (60)	-	-	-

¹Twenty specimens could not be genotyped; ²Six specimens could not be genotyped; ³Five subjects presented mixed genotypes (A/D); ⁴Four subjects presented mixed genotypes (2 A/D; 2 A/F). HBV: Hepatitis B virus.

The flow of immigrants may modify the distribution of HBV genotype in host countries with a low endemicity, since the immigrants frequently come from countries with a high or intermediate HBV endemicity. An example of this has occurred in Italy, where HBV genotype D was responsible for acute hepatitis B in 95% of cases observed until two decades ago, whereas in recent years HBV genotypes non-D has been found to be responsible for 60% of the cases^[31]. This phenomenon is of clinical value, since some studies reported that the natural history and the response to antiviral treatment of HBV infection may differ in relation to the HBV genotypes^[32].

Clinical and therapeutic approach in relation to the legal status of the immigrants

The literature data on the clinical course and treatment of HBsAg-positive immigrants are scanty. Interesting information, however, comes from a study performed on a Chinese community in Rotterdam in the Netherlands^[22] where 1090 Chinese immigrants were tested for HBsAg and 92 (8.5%) were found positive. Of these 92, the 35 (38%) with chronic hepatitis were referred to a specialist and 15 of them started antiviral treatment, whereas the 57 (62%) HBsAg asymptomatic carriers were referred to general practitioners for a long-term follow-up. The good clinical practice applied in this study is a good example to imitate in host countries. Instead, in most host countries the management of HBV infection in the immigrant population is a complex issue, due to bureaucratic difficulties and to the numerous language, economic, social, religious and cultural barriers the immigrants finding a foreign country.

Risk for host countries and cost effectiveness of screening immigrants for hepatitis B

Extensive immigration from countries with a high HBV endemicity to those with a low HBV endemicity requires vigilance to prevent the risk of spreading HBV infection to the native population. In fact, in most western countries, apart from the vaccination of subjects with a greater risk of acquiring HBV infection, universal vaccination now regards only newborn babies and, consequently, the majority of middle-aged adults and the elderly lack immunological protection against HBV. Extensive screening programs should be implemented to identify the HBsAg-positive immigrants and acquaint them with the correct information on HBV, its routes of transmission and prevention. HBV vaccination should be offered free of charge to the household members of HBsAg carriers.

Veldhuijzen *et al.*^[22] in Holland used an interesting screening strategy. In a 3-mo campaign targeting the Chinese community in Rotterdam with free HBV-testing at an outdoor location, 49% of 1090 immigrants had positive serology for a past or current HBV infection. The Chinese community organizations gave their support to the campaign, which started at the time of celebrations for the Chinese New Year. Ninety-two HBsAg-positive subjects were invited by telephone in their native

language for clinical consultation and counseling.

In an Italian prospective study, 926 illegal or refugee immigrants were observed for a clinical consultation at a first-level clinical center with the help of cultural mediators^[14]. During the clinical consultation, screening for HBV, HCV and HIV infections offered to all immigrants was accepted by 95% of them. The 81 subjects found to be HBsAg-positive were referred to a 3rd level clinic of infectious diseases to complete the diagnostic procedures and be considered for a clinical or therapeutic follow-up.

A particular screening strategy, based on a peer-to-peer communication, was applied in nine Italian prisons, where more than one third of the prisoners were immigrants. Briefly, a former prisoner acquainted with the correct information on HBV, HCV and HIV infections and correlated diseases and treatments acted as a peer educator for the inmates in the nine prisons. The sampling, performed on a voluntary basis, improved the percentages of screened prisoners from 25%-30% of the previous year to 65%. Active HBV infection was diagnosed in 15.2% of the immigrant inmates^[33].

Of 1970 immigrant pregnant women recently screened in an Italian study, 143 (7.3%) were found to be HBsAg-positive and screening for HBsAg was offered also to their family members. All immigrants found to be HBsAg-positive in this study were referred to a unit of infectious diseases to complete the diagnostic procedures and be considered for a clinical and therapeutic follow-up (unpublished data).

CONCLUSION

People fleeing from cruel wars and/or extreme need are often destitute, but the current social and economic crises in some western countries do not favor their integration in the host country^[34]. Correct management of the healthcare problems of immigrants requires expert personnel, funds and dedicated structures for their assistance. The experience of personnel on HBV infection is essential, also considering the suggestion of literature; in fact, recently in a survey on the knowledge on HBV infection in physicians in various stages of their training in Santa Clara, California, United States, Chao *et al.*^[35] demonstrated that both medical school and residency training had no adequately prepared physicians on the management of HBV infection.

Moreover, the assistance of the social services, voluntary operators and cultural mediators is essential to obtain an optimized psychological and clinical approach^[36,37]. The first-level clinical centers that usually have the initial clinical contact with immigrants should have proven experience in the clinical, psychological and legal management of vulnerable groups, since HBV infection is only part of a global social and clinical problem. The role of the cultural mediators during clinical consultations is of great importance, since they can reassure the immigrants in their own language and be of help to a skilled physician in explaining to them

the importance of screening, diagnostic tests, clinical follow-up and treatment. Only if trust is established, will the immigrants listen and follow the suggestions put forward. The cultural mediators can also act as tutors to help the immigrants deal with the bureaucratic requirements to be carried out.

Information to immigrants is a key point. As regards HBV infection, they should improve their knowledge on the infection and related diseases, risk factors of transmission, methods for prevention including vaccination programs and available treatments. This information could be more easily delivered in illustrative brochures and informative cartoons prepared in different languages and with educational videos uploaded on the social networks (facebook, twitter, *etc.*). It is of great importance to stress the practical measures to prevent the acquisition and transmission of HBV and other infectious agents. The importance of condom use in preventing HBV transmission during sexual intercourse should always be stressed.

Healthcare operators offering the immigrants HBV screening free of charge, and hopefully for HCV and HIV infection, should act in accordance with the local laws of privacy. Adhesion to the screening and a signed informed consent, written in the immigrant's native language, should be obtained on a voluntary basis. Patients should be asked about their geographical origin, time of immigration, level of education, religion, family history, cohabitation conditions, sexual habits, history of previous surgery, dental care, tattooing, piercing, drug addiction, blood transfusion and tribal rituals, and for females previous abortions. These data should be recorded in a pre-coded questionnaire.

A skilled physician should discuss the result of the screening with the help of a cultural mediator, and the HBsAg-positive subjects should be referred to a 3rd level liver unit to complete the diagnostic course, clinical evaluation, monitoring and treatment if necessary. Each HBsAg-positive subject should be assisted by a cultural mediator at the 3rd level clinical center throughout the monitoring or treatment period. Vaccination against HBV should be considered for each HBsAg-negative subject exposed to HBV infection.

In conclusion, the integration of immigrants in the host country where they will start a new life should be a major objective of governments and those working in dedicated associations. Good quality medical care and improved quality of life are the first steps to ensuring integration.

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