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TOPIC HIGHLIGHT

2015 Advances in Hepatitis B virus

Hepatitis B virus burden in developing countries

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Abstract

Hepatitis B virus (HBV) infection has shown an intermediate or high endemicity level in low-income countries over the last five decades. In recent years, however, the incidence of acute hepatitis B and the prevalence of hepatitis B surface antigen chronic carriers have decreased in several countries because of the HBV universal vaccination programs started in the nineties. Some countries, however, are still unable to implement these programs, particularly in their hyperendemic rural areas. The diffusion of HBV infection is still wide in several low-income countries where the prevention, management and treatment of HBV infection are a heavy burden for the governments and healthcare authorities. Of note, the information on the HBV epidemiology is scanty in numerous eastern European and Latin-American countries. The studies on molecular epidemiology performed in some countries provide an important contribution for a more comprehensive knowledge of HBV epidemiology, and phylogenetic studies provide information on the impact of recent and older migratory flows.

Key words: Hepatitis B virus; Molecular epidemiology; Prevention; Developing countries; Chronic hepatitis

Core tip: Hepatitis B virus (HBV) infection is a heavy burden in most developing countries because of its wide spread, particularly in rural areas, and the high cost of

prevention, management, and treatment. Therefore, a greater effort should be made towards implementing universal vaccination programs as they have been demonstrated to be effective in reducing the incidence of acute hepatitis B and the prevalence of hepatitis B surface antigen chronic carriers. In several low-income countries, an improvement in the current knowledge of HBV epidemiology, molecular epidemiology, HBV replication and co-infection with other viruses such as hepatitis C virus and human immunodeficiency virus is strongly desired.

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INTRODUCTION

Nearly 240 million people worldwide carry hepatitis B virus (HBV) infection[1], associated in nearly half of the cases with a chronic liver illness. The progression of liver disease to the more severe forms and the development and complications of hepatocellular carcinoma (HCC) entail a heavy burden for low-income countries. Also political and socio-economic problems make it difficult, at times impossible, to deal with the prevention, management and treatment of HBV infection and associated diseases. This review article focuses on the epidemiology and prevention of HBV infection in low-income countries with an intermediate or high endemicity level.

AFRICA (EPIDEMIOLOGY, MOLECULAR BIOLOGY, PREVENTION)

Epidemiology

Africa is on the whole considered to have a high HBV endemicity. HBV infection is hyperendemic [> 8% of hepatitis B surface antigen (HBsAg) chronic carriers in the general population] only in some sub-Saharan countries such as Nigeria, Namibia, Gabon, Cameroon, Burkina Faso. Other countries like Kenya, Zambia, The Ivory Coast, Liberia, Sierra Leone and Senegal are considered areas of intermediate endemicity (2%-8%), while Egypt, Tunisia, Algeria and Morocco, located in the north of the continent, show a low endemicity level (< 2%)[2]. The prevalences of HBV carriers and genotype distribution in some African countries are listed in Table 1.

The endemicity level varies also in different districts and in different target groups in the same country, *e.g.*, in Burkina Faso, one of the African countries with a high endemicity[3], the HBV overall prevalence is estimated at around 14.5%[4], some authors having reported a level of 12.1% in the health district of Nanoro[5], 18% in blood donors of Nouna, 11% in blood donors and 9.3% in pregnant women in the district of Ouagadougou[6,7]. In Nigeria, HBsAg seropositivity is estimated at around 13.6%, but higher rates have been found in surgeons (25.7%)[8], voluntary blood donors (23.4%)[9] and infants (16.3%)[10]. In Cameroon, recent studies reported an HBV prevalence of 10.1% and 12.1% in blood donors referring to two hospital blood banks[11,12] and of nearly 8% in pregnant women[13-15].

HBsAg-positive age-specific rates were estimated on a global level for 1990 and 2005 using an empirical Bayesian hierarchical model. A 12% prevalence was observed in 1990 in children and adolescents aged up to 19 years in western sub-Saharan African countries, the highest rate documented in the world in this age class, and only slightly decreasing in 2005. In southern sub-Saharan Africa, chronic HBV infection among younger age groups (0-14 years) had increased in 2005, with a prevalence of 8%-9% in females. Also in eastern sub-Saharan African countries, the HBsAg positivity rate had increased in the younger ages over time, whereas no significant changes were detected in the older age groups. An evident decrease in the HBV endemicity was observed in central sub-Saharan Africa, from a high endemicity in the aged 0-34 in 1990 to intermediate values in all ages in 2005. Also in northern Africa and the Middle East regions, the HBV prevalence decreased from 1990 to 2005, particularly among males aged up to 34 years[16].

Of note, the epidemiology in Africa is characterized by a much higher HBsAg prevalence in rural than in urban areas[17,18] and by a greater risk for males of becoming HBV chronic carriers, with a male to female ratio ranging from 1.1:1 to 3:1 and increasing with the increase in age[19-31]. The higher percentage of HBsAg-positive males harboring HBV chronic infection may be the result of differences in tribal and sexual behaviors between males and females[32].

Compared with the adult HBsAg chronic carriers from Southeast Asia, another hyperendemic area, those from Africa show a lower rate of HBeAg positivity. In African countries, 20%-30% of subjects infected by HBV in their early childhood become chronic carriers and only 10% of them remain HBeAg-positive during adolescence. The majority of HBeAg-positive subjects lose HBeAg quickly, at an annual rate of 14%-16%[33]. As is the case in Euro-Mediterranean countries, also in Africa a large majority (> 85%) of patients with a biochemically and histologically active disease are HBeAg-negative[34,35]. In addition, the rate of HBeAg-positive cases found in HBsAg-positive pregnant women was < 1% in Ethiopia, 1.16% in Ghana[36], 1.39% in Nigeria[37], 3.3% in Zimbabwe[38], 4.6% in South Africa[39], 9.5% in Senegal[40], 16.1% in Zambia[41], and 24% in southern Tanzania[42]. The low

Table 1 Prevalence of hepatitis B virus infection and genotype distribution in some African countries

Countries	HBsAg-positive prevalence[4,11]	HBV genotype distribution[66,68-73,75,77]
Burkina Faso	14.5%	A: A1 southern and eastern Africa
Cameroon	10.1%	A2 South Africa
Gabon	9.5%	D: D1 and D7 northern Africa
Ghana	13.8%	E: western and central Africa
Mali	15.5%	Recombinant A/D and A/E
Mauritania	10.9%	
Nigeria	13.6%	
Senegal	13.8%	
Zambia	6.5%	
Zimbabwe	25.0%	

HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

rate of HBeAg positivity in HBsAg-positive pregnant women in most African countries correlates with the low rate of perinatal transmission observed in Africa[43].

The data from 18 African countries showed a median HBsAg-positive prevalence of 12.1% in human immunodeficiency virus (HIV)-infected individuals (range 3.9%-70.3%)[44]. In sub-Saharan Africa, the prevalence of patients with HIV/HBV co-infection varies from 0% to 28.4% in different studies[45-49], with a median rate of 3.8% (0%-13%) in pregnant women and 7.4% (1.2%-7.8%) in children and young adults aged from 18 mo to 17 years. Western African countries seem to have the highest co-infection rates (median: 11.5%) in the continent, southern African countries the second highest (median 5.4%), and eastern African countries the lowest (median 4.1%), with a wide variation in single countries[50]. Also the prevalence of cases with occult HBV infection in HIV-infected patients varies largely across the continent, the available information, mostly from southern and western Africa, stating rates from 10% to 33%[51-56].

In African countries, children are at a high risk of acquiring HBV infection. The annual seroconversion rates to HBV markers varied from 10.2%-60.5% in children aged 1-10 years in Somalia, with the highest rate in those with a lower socio-economic condition[23]. The highest rate of children with HBV infection was 15.7% in children aged 5 and 6 years in a study from South Africa[57]. Children acquire HBV infection most frequently by parenteral horizontal transmission[58] from parents or siblings, as clearly demonstrated by phylogenetic analysis in Gambian families where HBV transmission occurred in at least two-thirds of the families investigated[59]. Unsafe sharing in the daily practices of toiletries and sharpening, cutting, scraping or scratching objects accounts for such a high horizontal transmission. In addition, cultural practices like scarification and tattooing and promiscuous sexual activity greatly increase the risk of HBV infection[29,60-63].

HBV transmission through the transfusion of blood or blood products still occurs[58] and is believed to have an epidemiological impact in some areas in sub-Saharan Africa[64]. Over the last decade, the United States President's Emergency Plan for AIDS Relief and the Global Fund have supported blood safety programs in 38 sub-Saharan African countries. The median percentage of HBV markers in blood donations was 7.1% in 2000/2004 and 4.4% in 2010/2011. From 2000/2004 to 2010/2011, 28 (82%) of the 34 reporting countries described a statistically significant decrease in HBsAg marker-reactive donations. Overall, the combined data from the 34 countries showed a 37% decrease in the HBsAg-reactive donations[65].

Molecular epidemiology

Five HBV genotypes are more frequently detected In Africa, A, B, C, D and E (Table 1)[2]. Despite the limited number of studies, a trend in their distribution is emerging. Genotype A predominates in southern and eastern Africa, genotype D in northern Africa[2] and genotype E in the vast region from Senegal to Namibia and eastward to the Central African Republic. HBV/E is the most frequent genotype found in the Central African Republic, the Democratic Republic of the Congo, Benin, Togo and Nigeria[2,66,67]. Recombinants of HBV genotypes have also been detected, an A and E recombinant in Cameroon[66] and western Africa[67] and an A and D recombinant in healthy black African adults positive for hepatitis B surface antibody alone[68].

Most of genotype A sequenced in Africa belongs to subgenotype A1, which is mainly found in southern and eastern Africa, including South Africa, Malawi, Tanzania, Uganda, the Democratic Republic of the Congo and Somalia. This subgenotype has been frequently detected also in southern Asia (India, The Philippines, Bangladesh, Nepal), supporting the hypothesis that this subgenotype was introduced to Asia through the intensive trade and frequent travels from eastern Africa[69-73].

Subgenotype A2, mainly isolated in South Africa, resembles some European isolates and the hypothesis that Portuguese sailors probably introduced this subgenotype to Europe in the 16th and 17th century has been formulated[73]. Genotype E prevails in native populations of western and central Africa[2]. All genotype E strains have the same characteristic, an in-frame deletion of three nucleotides in the 5' pre-S1 region, a signature pattern of amino acids in the pre-S1 region and a serological subtype formulated as *ayw4*. The low genetic diversity over large geographical areas suggests that HBV/E may have a short evolutionary history and a recent introduction to African countries[2,74].

HBV genotype D is the most prevalent in northern Africa, particularly subgenotypes D1[75,76] and D7[76,77], but it is also diffuse worldwide. A recent comprehensive reconstruction of the phylogeography of HBV genotype D in the European Mediterranean basin indicates that it originated in the second half of the 19th century in

India[78,79].

Prevention

Vaccination is essential to control HBV infection. Thanks to the Expanded Programme on Immunization started in 1995 in some African countries, such as South Africa, the monovalent anti-HBV vaccine continues to be administered at 6, 10, and 14 wk of age and the rate of HBV infection and HCC in children shows a clear tendency to decrease[80].

HBV vaccination in HIV-positive African populations provides a moderately lower response rate than in the general African populations, but, as in other countries, revaccination of non-responders increases the response rate to 95%[81].

ASIA (EPIDEMIOLOGY, MOLECULAR BIOLOGY, PREVENTION)

Epidemiology

Southwestern Asia, also known as the Arabian region, accounts for 10% of the Asian territory. The Arabian peninsula, including Saudi Arabia, Yemen, Oman, Bahrain, the United Arab Emirates (UAE) and Kuwait[82-84], shows an HBsAg-positive prevalence ranging from 1.5% to over 8%[16]. In particular, this prevalence ranges from 1.5% to 2.6% in Saudi Arabia, is reported to be 5.1% in blood donors in Yemen, the poorest country of the Arabian peninsula, 3.5% in volunteer blood donors in Kuwait and to range between 2% and 7% in the general population in UAE[85-88]. The Levant (Sham) Arabian region comprises Syria, Iraq, Lebanon, Jordan and the Gaza Strip. The HBsAg-positive prevalence is 0.6% in the general population in Iraq[89], 1.6% in volunteer blood donors in Lebanon[90] and 1.4 % in blood donors in Jordan[91]. No data are available for Syria at present, apart from its classification as a geographical area with an intermediate endemicity in the report by Lavanchy[86]. The HBsAg-positive prevalence in the Gaza Strip is 3.5% in the general population and 3.8% in blood donors[92]. Arab countries have implemented the WHO-recommended Expanded Programme on Immunization, and HBV vaccination programs started in these countries have now covered a large proportion of their population, successfully reducing the HBV endemicity. In Saudi Arabia, the first Arab country to adopt an HBV vaccination program[93], a steady decline in the HBsAg-positive prevalence has been observed in children aged 1-12 years, from 7% in 1989, to 0.31% in 1997 and 0% in 2008[94,95].

In Cambodia, one of the western Pacific countries, the HBV prevalence was 4.6% in the adult population[96] and 6.3% in blood donors (Ministry of Health in Cambodia, 2013, unpublished. data). In this country, high anti-HBc rates have been reported, 58.6% and 72.4% in different studies[97,98], suggesting a principal role played in the past by horizontal transmission in childhood and adulthood.

The HBsAg-positive prevalence was 3.6% in subjects aged 18-79 years in Singapore in 2010, and HBeAg was detected in 4.2% of the HBsAg-positive cases. The national childhood HBV vaccination program adopted in this country has shown a great impact in reducing the spread of HBV infection[99].

In China, thanks to the universal HBV immunization program of newborn babies initiated in 1992, the prevalence of HBsAg carriers decreased from 9.8% observed in 1992 to 7.18% registered in 2006[100]. Of note, the vaccination coverage rate at the end of 2005 was 20% lower in rural areas than in the urban areas, a difference that has steadily decreased in recent years. Despite the suboptimal coverage, the prevalence of anti-HBs was higher in fully immunized children (63.2%-74.3%) than in non-immunized subjects (21.1%-34.8%)[101]. As a result of the universal HBV vaccination campaign, China has gone from a high to an intermediate endemicity level in a short period of time[102]. At present, however, the HBV prevalence in some high-risk groups is very high, *e.g.*, 11.9% in hemodialysis patients[103] and 12.5% in HIV-positive subjects[104].

In South Korea the HBsAg-positive seroprevalence is 4%, slightly higher in the southern than in the central provinces. In the last decade, however, the universal vaccination program has brought about an impressive reduction in HBsAg positivity documented in the younger population, from 2.2% to 0.12%[105,106].

In Kazakhstan, an HBV seroprevalence of 3.8% has been documented, with a peak in the adult population aged 30-49 (6.3%) and lower rates in the aged 10-29 (2.5%) and in subjects over 50 (1.7%)[107].

In India, the estimated HBsAg-positive prevalence is 3.1% in the non-tribal population and 11.85% in tribal populations[108], with wide geographical variations within this subcontinent due to differences in socioeconomic status, religion, culture and tribal practices.

The prevalences of HBV infection and genotype distribution in some Asian countries are shown in Table 2.

Molecular epidemiology

In the Arabian countries HBV genotype D predominates, particularly, subgenotypes D1 and D3[109]. Patients living on the northern coast of the Persian Gulf are infected mainly with HBV subgenotype D1, spread widely by ancient migrations from Iran, Syria, and Turkey[110].

In China, HBV genotypes B and C, and in particular subgenotypes B2 and C2, predominate, with some geographical differences. Genotype B is more frequent in southern China and genotype C in the north of the country. In some regions of northern China subgenotype C2 is predominant, whereas subgenotype C1 is more frequent than C2 in southern China. Recombinant C/D1 and C/D2 have been found

Table 2 Prevalence of hepatitis B virus infection and genotype distribution in some Asian countries

Countries	HBsAg-positive prevalence[16,85-92,96,99,105-108]	HBV genotype distribution[109-118,121,123,125]
Cambodia	4.6%	A: India A1 India B: China
China	7.18%	B2 southern China
Gaza Strip	3.5%	C: China
India	3.7%	C1 southern China, India
Iraq	0.6%	C2 northern China
Jordan	1.4%	D: Arabian countries and India
Kazakhstan	3.8%	D1 Persian Gulf (Iran, Syria,
Kuwait	3.5%	Turkey), India, Pakistan
Saudi Arabia	1.5%-2.6%	D2, D3, D4, D9 India
Singapore	3.6%	C/D1-CD2 western China
South Korea	4.0%	
United Arab Emirates	2%-7%	
Yemen	5.1%	

HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

Table 3 Prevalence of hepatitis B virus infection and genotype distribution in some eastern European countries

Countries	HBsAg prevalence[133-138,142-145,147,148]	HBV genotype distribution[150-156,160,161]
Albania	> 9%	A: Eastern Europe (Poland, Czech Republic, Bulgaria, Hungary[1]) A2 Bulgaria D: Southeastern Europe (Russia, the Baltic region, Belarus, Romania, Hungary, Serbia, Croatia, Lithuania, Romania, Bulgaria)[1] D1 Bulgaria D2 Albania, Russia, Estonia, the Siberian and eastern part of the former USSR
Bulgaria	3.80%	D3 Serbia
Croatia	1.7%-15.8%	[D: prevalent genotype
Poland	3.91/100000[1]	(70%-80%)]
Romania	5.59%	1A,D: equal distribution
Russia	7.6/100000	
Serbia	4.4%-13%	

[1]Incidence/year. HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

to be predominant in the Qinghai-Tibet Plateau and in western China, indicating that the spread of these two recombinants may have an ethnic origin[111-118]. Other HBV subgenotypes, such as C5 and C7, possibly introduced from the southeastern Asian countries, have been infrequently detected in China[119]. Compared with HBV subgenotype B, subgenotype C shows a lower replicative activity in young patients and harbours higher frequencies of HCC-associated mutations[120].

In Pakistan HBV genotype D predominates, particularly subgenotypes D1 and D3 and a B/D recombinant plays a marginal role, being responsible for 3.5% of the cases. It has been suggested that genotype D achieved its wide distribution in ancient times associated with the ancient history of the civilizations in this region[121].

Taking into consideration the HBV-host co-evolution, the diverse Indian population provides an excellent opportunity for further studies to investigate some underpinnings of the HBV diversity. Of the three HBV genotypes found in India, namely D, A and C, genotype D is predominant, whereas all the HBV/A and HBV/C isolates discovered in India belong to subgenotype A1 and C1, respectively; the genotype D strains are divergent and classified into 5 distinct subgenotypes, D1, D2, D3, D5 and D9, with a different geographical distribution[122-125].

Prevention

The WHO estimates that Asia is the continent with the highest rate of HBsAg carriers in the world, with an overall prevalence in the adult population of over 8%. In order to prevent HBV infection and its associated diseases, several Asian countries have started vaccination programs[126]. An extensive program (China GAVI Hepatitis B Immunization Project) was started in China in 2002 in all the Chinese provinces to prevent HBV transmission to newborn babies in order to decrease over time the circulation of HBV in the country and reduce the heavy burden of liver cirrhosis and HCC. Although the program has not yet reached some rural areas, HBV vaccination covers more than 75% of newborn babies and the rate of HBsAg positivity has decreased from 10% to 1%[127]. This project has certainly required a strong political, social and economic commitment, but the results obtained to date are truly impressive.

EASTERN EUROPE (EPIDEMIOLOGY, MOLECULAR BIOLOGY, PREVENTION)

Epidemiology

The low number of epidemiological studies on HBV infection performed in eastern Europe does not allow conclusive statements to be made on the spread of HBV infection and on the level of application of universal vaccination in this large geographical area. The available data from eastern European countries show higher HBsAg-positive prevalences than in western Europe[128-131] (Table 3), but the ongoing universal HBV vaccination campaign in rural and urban areas of the single countries will reduce this gap in the near future. In fact, in a recent study from Bulgaria, the HBsAg-positive prevalence in individuals aged 19 or less, targeted by HBV vaccination, was significantly lower than that found in non-vaccinated individuals aged over 20 (1% *vs* 4.8%)[132]. The HBsAg-positive seroprevalence in the general population was 3.8% in studies performed in Bulgaria[133,134], 5.6% in

Table 4 Prevalence of hepatitis B virus infection and genotype distribution in some Latin American countries

Countries	HBsAg prevalence[166-169]	HBV genotype distribution[177,178]
Mexico, Honduras, Nicaragua, Costa Rica, Panama, Uruguay, Chile, Argentina, Peru, northern Colombia	Low prevalence (< 2%)	F: F1 Central America eastern South-America F2 Venezuela, Brazil F3 Central (Panama) and northern (Colombia and Venezuela) Latin America F4 Bolivia and Argentina (F genotype: prevalent) H: Amerindians and Mestizios in Mexico A, D: Gualalajara, Jalisco, Mexico, Argentina
Central America: Guatemala, El Salvador, Honduras, Haiti, Dominican Republic, Puerto Rico South America: Ecuador, French Guyana, Suriname, south Brazil	Intermediate prevalence (> 2%, < 8%)	
Northern Brazil, southern Colombia, Peru, northern Bolivia	High prevalence (> 8%)	B, C: dispersed among Latin America populations (due to Asian immigrants)

HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

Romania[135] and from 4.4%-13% in different studies in Serbia[136-138], with wide variations within single countries that reflect the different socio-economic conditions between rural and urban areas[135]. In these studies, males showed higher rates of HBsAg positivity than females.

Although introduced in 1995, HBV vaccination has not as yet significantly reduced the high HBV endemicity level in Albania[139-141], where HBsAg positivity in the general population is over 9% and the overall risk of becoming infected exceeds 60%[142-145]. In Poland, an incidence of acute hepatitis B of almost 4 cases per 100000 inhabitants was registered both in 2011 and 2012, suggesting a stable spread of HBV infection in this country[146]. In the adult population in Croatia, HBV seropositivity increased with the increase in age, from 1.7% to 15.8%, and was higher in subjects from rural areas than from urban areas (10.7% *vs* 6.1%)[147]. The incidence of acute hepatitis B in Russia was 7.6 per 100000 inhabitants in 2009, with wide variations across the country[148].

Molecular epidemiology

HBV genotypes A and D are those most frequently detected in eastern Europe (Table 3)[149], genotype D being responsible for 70%-80% of the HBV infections occurring in the northern and central areas and in eastern Mediterranean countries[128,150-153]. In fact, HBV genotype D predominates in Romania (67%), Lithuania (54%), Serbia (82%), Croatia (80%), Albania (92%) and Russia (93%), whereas genotype A predominates in Poland (77%) and in the Czech Republic (67%), two countries with similar ethnic backgrounds and a small proportion of immigrants (3%-4%)[79,128,152,154,155].

HBV genotype A and D, and subgenotypes D1 and A2 in particular, are those more frequently detected in Bulgaria[156]. Using a phylodynamic approach, the beginning of the spread of D1 in this country dated back to the early 1980s[78,156], whereas the strains analyzed of subgenotype A2 dated back to 1996. HBV genotype A is frequent in central and northern Europe, where the HBV spread is mainly sustained by sexual transmission[157-159], and in Bulgaria, which has a crossroads position between western and eastern Europe favoring the introduction of new subgenotypes[156].

More than 70% of Albanian HBsAg carriers are infected with HBV D2 subgenotype, suggesting an epidemiological relationship between Albania and northeastern European countries of the former USSR, rather than from other Mediterranean countries, where HBV subgenotypes D1 and D3 predominate[79,160,161].

Hungary shows an almost equal distribution of HBV genotypes A and D, probably due to its central position between western and eastern Europe[152].

Prevention

In 2009, Nardone *et al*[162] published a report on the HBV epidemiology in 10 European countries in relation to the application of the vaccination policies. At the time of publication of this report, HBV universal vaccination programs recommended by the WHO were in progress in different countries of eastern Europe (the Czech Republic, Romania and Slovakia), but coverage differed between countries, most probably reflecting the difficulty to reach people living in rural areas in some countries (Romania, Slovakia).

In Poland, HBV vaccination of newborn babies is active and no new HBV cases in childhood and adolescence have been registered, whereas non-vaccinated subjects aged 45-49 years still show a high rate of acute HBV infection[163].

LATIN AMERICA (EPIDEMIOLOGY, MOLECULAR BIOLOGY, PREVENTION)

Epidemiology

The information on the HBV epidemiology in Latin American countries is scanty and fragmentary, but it has been estimated that 7-12 million Latin Americans carry HBV chronic infection[164,165]. The rate of HBsAg-positive subjects varies between countries (Table 4)[166], the highest values being detected in the 20-40 age class as a possible consequence of a major role played by horizontal transmission[163].

More recently, some tropical Latin American areas such as Panama, Colombia and Venezuela shifted from an intermediate to a low endemicity level[166-169]. In

addition, countries with a low HBV endemicity show a high rate of anti-HBc positivity in HBsAg-negative subjects, a clue to the more extensive exposure to HBV in the past[170,171]. A slight decline in the HBsAg-positive prevalence was observed from 1990 to 2005 in Andean Latin American countries, whereas a slight increase was reported in southern Latin America in the same period[16].

Molecular epidemiology

HBV genotypes F and H predominate in indigenous populations of Latin America, whereas genotypes A and D have been introduced from European and African populations[172,173]. Four subgenotypes of HBV genotype F (F1-F4) have been identified, predominating in Central America and frequent in Amerindians in all countries of South America[174-176] (Table 4), and HBV genotype H in Amerindians and in Mestizos in Mexico[177,178]. Genotypes F and H show a close phylogenetic relationship, suggesting an introduction of F/H ancestral strains before European colonization[174].

Introduced by European colonization, HBV genotypes D and A have been detected in nearly 35% and 5% of HBsAg-positive subjects of the urban population of Guadalajara and Jalisco (Mexico), respectively, while in various cities of Argentina they have been documented with frequencies ranging from 22% and 45%, respectively[177-179].

Genotypes B and C, introduced by Asian immigrants, are sporadically detected[180,181].

Worthy of note is that liver cirrhosis and hepatocellular carcinoma are rare in Mexicans, indicating that the immune response and course of liver disease in the Mexican native population may differ from that described in other geographical areas worldwide[182,183].

Prevention

Unfortunately, the universal vaccination programs remain unaffordable for most South American countries[184,185]. Where applied, however, they have achieved important epidemiological results, *e.g.*, in the Colombian Amazon, where the rate of HBsAg positivity dropped from 9% to 2% in children after eight years of application[186].

FINAL COMMENTS

Although of reduced impact in several countries due to the HBV universal vaccination programs started in the nineties', HBV infection still entails a heavy socio-economic burden in several developing countries.

Vaccination programs should be extended without delay to cover rural areas of the countries where HBV vaccination is showing its efficacy in reducing the spread of HBV infection. Countries still unable to adopt a universal immunization program for newborn babies should receive support from international health organizations to implement this.

At present, the high cost of effective nucleo(t)side analogues, namely entecavir and tenofovir, to treat HBV infection and its correlated diseases is a strong handicap for most developing countries where numerous patients await treatment.

In addition, the information on the HBV epidemiology is scanty in several low-income countries and needs to be extended to cover information on HBV replication, co-infection with HCV and HIV, molecular epidemiology, phylogenies and clinical aspects.

In Africa, co-infection with HIV is a further problem that requires a therapeutic approach with the most appropriate combination therapies.

In Asia, a high viral load and a high prevalence of HBeAg-positive patients characterize HBV infection, and make the achievement of viral suppression more complex.

In Eastern Europe and South America, more epidemiological, virological and phylogenetic information is needed and further implementation of the vaccination programs to cover all the rural territories.

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