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Review

Epidemiological update of hepatitis B, C and delta in Latin America

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Viral hepatitis B, C and delta still remain a serious problem in Latin America. Data from the 1980s indicated that HBV and HDV infection are the main causes of chronic hepatitis. However, the spread of HBV infection could be controlled through the implementation of immunization programmes. Different countries from Mexico to Argentina display marked differences in terms of HBV genotype distribution. HBV genotype F has been identified as the most frequent in most Latin America countries, except for Mexico and Brazil, where genotypes H and A are the most frequent, respectively. In Latin America, the overall prevalence of HCV antibody is estimated to be 1.5%. Latin American countries have been very proactive in screening their blood supplies, thus minimizing risk of HCV transmission through transfusion. The number of diagnosed and treated patients is still low, thereby increasing the burden of complications such as liver cirrhosis or hepatocellular carcinoma. The most prevalent HCV genotype is 1, which is the genotype with the greatest worldwide spread, but it is a different genotype from other regions like Africa and Asia. HDV is present worldwide but its distribution pattern is not uniform. HDV was recently detected in novel geographic regions, reinforcing that it is a very serious health threat in under-developed countries. The main prevalence areas are the Mediterranean basin, the Middle East, central and northern Asia, western and central Africa, the Amazonian basin (Brazil, Peru, Venezuela and Colombia) and the Pacific islands. Novel strategies to increase HBV immunization in the Latin American population are needed to warrant thorough coverage in the rural areas.

Introduction

Viral hepatitis is a major global health problem caused by five unrelated viruses, including HBV, HCV and HDV, the three major agents involved in chronic infections around the world. The consequences of these include acute and chronic infection, cirrhosis of the liver and hepatocellular carcinoma (HCC). Epidemiological profiles of these viral infections differ and have changed over time, revealing new prevention challenges and opportunities.

HBV

HBV is classified in the *Hepadnaviridae* family, *Orthohepadnavirus* genus [1]. The HBV genome is a partially double-stranded circular DNA with approximately 3,200 bp [1,2] and has four open reading frames [3,4]. The viral particle has a diameter of 42 nm and has envelope surface proteins comprising: large, medium and small (hepatitis B surface antigen [HBsAg]) [1]. HBV is transmitted through contact with infected body fluids. Although blood is the most important vehicle for the transmission, other fluids also are related to the infection, such as semen and saliva [5]. Currently, three transmission modes of HBV are recognized: vertical, sexual and parenteral. It is believed that other forms of transmission, such as horizontal, caused by close but non-sexual contact, must have a role to maintain high rates of infection in some populations [6].

HBV is classified into ten genotypes, from A to J, and genotypes F and H are the most common genotypes in Latin America. Genotype A is found mainly in northern and western Europe, North America and Africa [7]. Genotypes B and C are prevalent in southeast Asia and the Far East [8]. Genotype D has a worldwide distribution and is found predominantly in the Mediterranean region. Genotypes E and F are found in west Africa and in the Amerindian population, respectively [9]. More recently, genotype G has been reported in the USA and France [10], and

genotype H has been found in Central America [11]. Recently, genotype I was described in north-western China, Vietnam and Laos [12], and a novel genotype, J, was isolated from a Japanese man [13].

About 2 billion people worldwide are infected with HBV and about 350 million people are chronic carriers. HBV infection is associated with 0.5 to 1.2 million deaths each year, representing the tenth leading cause of death around the world [14]. The incidence of HCC is increasing in the world with a mortality rate of 300,000 to 500,000 people each year [15]. Vaccination against hepatitis B has been available since 1982 with more than 95% efficacy in preventing HBV infection. Demographic changes and expanded vaccination can create new epidemiological patterns of the virus with effects on region-specific endemicity levels [16]. In 2009, 177 countries reported that they had included hepatitis B vaccination in their national childhood immunization programmes. The percentage of children up to 1-year old who received three doses of the vaccine was around 70% in the world in 2009 and 86% in the Americas [17]. Approximately 45% of the world's population live in areas where chronic HBV infection is highly endemic (>8%), 43% live in areas of intermediate endemicity (2–7%) and 12% live in areas of low endemicity (<2%).

Epidemiological data suggest that 7 to 12 million Latin Americans are infected with HBV. The routes of transmission in Central and South America are highly variable [18]. The highest prevalence was reported for groups of people from 20 to 40 years old, supporting horizontal transmission in adults as the most common route of infection [18]. The regions with high prevalence (>8%) are found in the Amazon basin region, including northern Brazil, Colombia, Peru and Venezuela, where it is estimated that over 30% of patients in South America are located [19].

Recently, it was reported in Latin America strong evidence of a decrease in HBsAg prevalence [16]. The tropical Latin America region (Brazil and Paraguay) and Central Latin America demonstrated a strong decrease in HBsAg prevalence between 1990 and 2005 [16]. Tropical Latin America changed from an intermediate into a low endemicity region. Similarly, in Central Latin America and northern Latin America (Colombia, Panama and Venezuela) prevalence has halved in this period and most adult age groups shifted to a low endemicity level in 2005. Brazil, Colombia and Cuba pioneered the implementation of the universal HBV vaccination among Latin American countries, a programme still to be implemented in all South American nations.

Other Latin American regions such as Andean Latin America (Bolivia, Ecuador and Peru) and southern Latin America (Argentina, Chile and Uruguay) showed a decreasing prevalence by age but relatively constant intermediate endemicity levels [16]. A slight decrease in prevalence from 1990 to 2005 among Andean Latin Americans was paralleled by an increase in HBsAg prevalence in southern Latin America [16]. However, data on the prevalence of HBV infection in different regions of the Americas including Central and South America and the Caribbean are sparse, and mainly derive from blood bank reports and regional serological studies [20–22].

Injecting drug use is an important risk factor for transmission of viral hepatitis. Worldwide, we estimate 6.4 million injecting drug users (IDUs) are anti-hepatitis B core positive (range 2.3–9.7 million) and 1.2 million (range 0.3–2.7 million) are HBsAg-positive [23]. In Latin America, HBsAg prevalence among IDUs was reported as 8.6%, 2.3% and 4.5%, in Argentina, Brazil and Uruguay respectively [23]. These results showed that efforts to prevent, treat and reduce harm related to liver disease in IDUs are essential. Effective treatments for chronic HBV infection are accessible, which reduce the progression of liver disease and complications such as HCC. However, barriers to accessing treatment and care for chronic HBV infection result in reduced outcomes for those affected, and an ongoing spread to vulnerable contacts [23]. Thus, vaccination against hepatitis B must be prioritized in this risk group.

HCV

HCV is a positive-sense, single-stranded RNA virus with a genome of 9,400 bp. It contains a large open reading frame that encodes a precursor polyprotein of about 3,000 amino acids. HCV is classified in the family *Flaviviridae* [24], but is has some important differences to this family, specifically concerning the general genomic organization, and it is classified in the genus *Hepacivirus*. A total of six phylogenetically distinct genotypes are designated as HCV-1 to HCV-6, differing in 30–35% of their genome. Genotypes are further subdivided into subtypes identified by letters: there are more than 100 subtypes which differ from each other in 20 to 25% in their sequences [25,26].

Genotypes 1, 2 and 3 have a worldwide distribution, while genotypes 4, 5 and 6 are more frequent in some distinct areas [27]. Subtypes 1a, 1b, 2c and 3a are the most prevalent worldwide and are found in almost all regions of the world. Genotype 4 is predominant in Egypt, northern and central Africa and the Middle East, genotype 5 in Africa and genotype 6 in Indochina [27].

Currently, it is well-established that HCV infection is globally relevant, constituting a serious health problem that requires comprehensive and active measures for prevention and control. According to the WHO, over 170 million people worldwide are now infected with HCV, corresponding to 3% of the world's

population, substantially affecting public health all over the world [24].

Prospective studies have shown that 80% of cases of acute hepatitis C progress to chronic infection and 10 to 20% of these will develop complications of chronic liver disease such as cirrhosis and/or HCC. HCV prevalence tends to be higher in men than in women and in individuals over 40 years old. It is estimated that 6,800,000 to 8,900,000 adults are anti-HCV-positive in Latin America [28,29] with an overall distribution similar to other world regions [18]. The overall prevalence in Latin America of anti-HCV antibodies is estimated to be 1.5% [29]. It varies from 0.2–0.5% in Chile to 1.7–3.4% in north-east Brazil [30]. The main risk factor is injecting drug use, although in some countries blood transfusion remains as a risk factor for infection.

The largest populations of HCV-positive IDUs live in eastern Europe (2.3 million, range 1.2–3.9) and east and southeast Asia (2.6 million, 1.8–3.6) [23]. The three countries with the largest populations of IDUs living with HCV are China, Russia and the US. In Latin America, it was shown that among five countries (Argentina, Brazil, Mexico, Paraguay and Uruguay) there are 1,022,000 anti-HCV-positive IDUs (67% of IDU population) [23]. These results showed that injection drug use is not a large problem in Latin America as compared with the US, Europe and Asia. Nevertheless, policies and strategies in Latin American countries for viral hepatitis need to include IDUs, who are at increased HCV risk of transmission and frequently have poorer access to health services than the general population. The number of diagnosed and treated patients in this particular group is low, thereby increasing the burden of complications such as liver cirrhosis or HCC [28].

Finally, in Latin America the most prevalent HCV genotype is 1 (1a and 1b), although 1b is mostly found among older members of the population who have a history of blood transfusion [31]. Recently, results from our group showed that HCV genotype 1b, the most frequent in Colombia (as well as in most South American countries), exponentially spread up to 1992 in Bogotá, when its growth was controlled by HCV screening in blood banks [31]. Mandatory screening for HCV infection was gradually adopted in Latin America during the 1990s, leading to currently decreased blood transmission in most South American countries [18].

HDV

HDV was described in 1977 and is associated with coinfection or superinfection in HBV carriers [32]. HDV is associated with HBV, as a primary coinfection with HBV or a superinfection in an HBV carrier. HDV is a hepatotropic virus with a small RNA genome (1.7 kb), representing the genus *Deltavirus*, which encodes for two hepatitis D antigens (HDAg), a small 24-kDa HDAg and a large 27-kDa HDAg. The small HDAg accelerates HDV RNA synthesis, whereas the large HDAg inhibits HDV RNA replication and is necessary for virion formation [33]. HBsAg provides a lipid layer which surrounds the protein–RNA complex of HDV [33].

Genotypes of HDV are divided into eight distinct groups: genotype HDV/1 is the most common and is found in Europe, the Middle East, North America and north Africa [34,35]; HDV/2 prevails in Japan [33], Taiwan [34] and Russia [35]. HDV/3 prevails in the Amazon region of South America [36]; HDV/4 is found in Japan [37] and Taiwan [38] and genotypes HDV/5 to HDV/8 are found in Africa [39]. Genetic studies and sequencing of the HDV genome revealed a high heterogeneity of the virus, which resulted in a classification to the subgenotype level. HDV/2 has been divided into subtypes (2a and 2b). Each genotype of HDV has a different geographical distribution and association with different degrees of liver disease. HDV/3 is the most divergent and the most aggressive; often causing fulminant disease through a cytopathic non-inflammatory process of liver microsteatosis [22]. Little is known about the clinical course of the remaining HDV genotypes [36].

The prevalence of HDV varies widely depending on geographical region. In some regions of the Mediterranean, Africa and the Middle East more than 24% of HBV carriers have markers for HDV. However, this infection is uncommon in countries like the US, where this infection is largely confined to risk groups like drug users and haemophiliacs [40].

Latin America is an area of intermediate HBV endemicity [41], where HDV is not restricted to groups at risk, and has been associated with severe and fatal fulminant hepatitis. In Brazil, HDV has been reported in the western Amazon region, where a large number of cases of acute and chronic infections by this virus have been described [42]. In this region, the percentage of HBsAg carriers with anti-HDV is 32% [43]. Severe epidemics of HDV have been registered in this population, leading to fatality or rapid evolution towards cirrhosis. In Colombia, a few reports are available on HDV prevalence, most of them showed an association of HDV with fulminant hepatitis outbreaks. In the Amazon basin, high HDV antibody prevalence rates have been found among children younger than 4 years [22].

Epidemiological studies on HDV infection should consider the requirement of the presence of HBV. Indeed, HDV is mostly found in association with fulminant hepatitis epidemics in areas with high prevalence of HBV. Several studies performed in the 1980s showed the presence of HDV infection in South

America. HDV usually induces a severe disease but its clinical manifestations are very broad, ranging from asymptomatic cases to fulminant hepatitis [44]. The virus is found worldwide but is not uniformly distributed, as determined by seroprevalence studies of anti-HD in HBsAg-positive patients [45]. HDV/3 has been found to be almost segregated to the north of South America (the Amazon basin of Brazil, Peru, Colombia and Venezuela) [46]. For HDV/3, studies in the Amazon region on prevalence of HBV and HDV showed that family members are reservoirs for transmission of infection by HDV [47]. In this way, the chances of contamination from an extra-familial source are expressed by highly divergent isolates and the sequence similarity in most family units indicates a single source of infection providing evidence that HDV infection is probably mostly transmitted within the families [48]. Recently, it was determined that HDV/3 spread exponentially from the early 1950s to the 1970s in South America. It was suggested that the measures implemented to control HBV transmission resulted in the control of HDV/3 spreading in South America, especially after the important rise in this infection associated with huge mortality during the 1950s up to the 1970s [46]. Furthermore, in a recent study, it was reported that the presence of HDV/8-infected individuals in Brazil who have not been in Africa may reflect a close relation with HDV genotypes' geographic distribution and human migration [49]. Finally, it was reported that 1.2% of HIV–HBV-coinfected patients were found to be anti-HDV-positive in southeast Brazil indicating that this group is at potential risk for HDV infection [50].

HBV, HCV and HDV infections are detected throughout Latin America in frequency levels that would make some areas hyperendemic for HBV, especially those found in the Amazon region. Vaccination campaigns against HBV, systematic screening of blood and blood products, and improvement in socio-economic conditions would all be useful to control HBV and HDV circulation in endemic areas. In the absence of a specific vaccination, novel strategies to strengthen HCV surveillance in higher risk groups and careful selection and continuous screening of blood donors are needed.

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Disclosure statement

The authors declare no competing interests.

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