Epidemiology of viruses causing chronic hepatitis among populations from the Amazon Basin and related ecosystems

Epidemiología de las hepatitis crónicas con carácter vírico en las comunidades indígenas de la cuenca amazónica y de otros ecosistemas similares

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Abstract *On the last twenty years, viral hepatitis has emerged as a serious problem in almost all the Amerindian communities studied in the Amazon Basin and in other Amazon-related ecological systems from the North and Center of South America. Studies performed on communities from Bolivia, Brazil, Colombia, Peru and Venezuela have shown a high endemicity of the hepatitis B virus (HBV) infection all over the region, which is frequently associated to a high prevalence of infection by hepatitis D virus among the chronic HBV carriers. Circulation of both agents responds mainly to horizontal virus transmission during childhood through mechanisms that are not fully understood. By contrast, infection by hepatitis C virus (HCV), which is present in all the urban areas of South America, is still very uncommon among them. At the moment, there is not data enough to evaluate properly the true incidence that such endemicity may have on the health of the populations affected. Since viral transmission might be operated by mechanisms that could not be acting in other areas of the World, it seems essential to investigate such mechanisms and to prevent the introduction of HCV into these populations, which consequences for health could be very serious.*

Key words *Viral Hepatitis; Hepatitis; South American Indians; Amazonian Ecosystem*

Resumen *A lo largo de los últimos veinte años, las hepatitis víricas se han revelado como un importante problema para las comunidades indígenas de la cuenca amazónica y de otros ecosistemas similares del norte y centro de Sudamérica. Los estudios realizados en comunidades de Bolivia, Brasil, Colombia, Perú y Venezuela han demostrado una alta propensión endémica para la infección por el virus de la hepatitis B, que se asocia con frecuencia a una elevada prevalencia de coinfección con el virus de la hepatitis D entre los portadores crónicos. La circulación de ambos agentes responde a su transmisión horizontal durante la infancia, a través de mecanismos aún poco conocidos. Por el contrario, la infección por el virus de la hepatitis C es aún muy infrecuente entre los indígenas. No existen, por el momento, datos suficientes para evaluar el impacto real que esta endemia pueda tener sobre la salud de esas poblaciones. Considerando que la transmisión de estos agentes podría involucrar mecanismos que quizá no actúen en otras regiones, parece indispensable investigar dichos mecanismos y prevenir cuidadosamente la introducción del virus de la hepatitis C en esas comunidades, ya que las consecuencias para su salud podrían ser muy graves.*

Palabras-clave *Hepatitis Viral; Hepatitis; Indios Sudamericanos; Ecosistema Amazônico*

Introduction

Viral hepatitis is one of the main infectious health problems still existing in the world. Three of the five infectious agents, namely the hepatitis B, C, and D viruses (HBV, HCV, and HDV), can persist after acute infection and cause chronic infections that may lead to severe liver disease such as chronic hepatitis, hepatic cirrhosis, and primary liver cancer. Agents known as GB-C/hepatitis G virus and TT virus can also induce persistent infections and are present in the Amazon (Pujol et al., 1998; Tanaka et al., 1999), but their involvement in human diseases (whether hepatitis or others) has still not been convincingly demonstrated, so their public health relevance appears to be limited or nil.

HBV is spread worldwide, but with a non-uniform distribution. The Far East, Southeast Asia, and Sub-Saharan Africa are the main highly endemic areas. Introduction of HDV in populations with a high incidence of chronic HBV carriers may lead to epidemic outbreaks of severe liver disease, because of the ability of HDV super-infection to originate both acute fulminating hepatitis and chronic hepatitis evolving rapidly to cirrhosis. In East Asia, HBV endemicity is maintained principally through vertical viral transmission (either intrauterine or perinatal) and by sexual transmission. However, vertical transmission is much less frequent in endemic regions of Africa. In some rural areas of tropical Africa, HBV appears to be horizontally transmitted among children through unidentified mechanisms which may involve certain hematophagous arthropods (bedbugs, ticks) acting as passive virus vectors (Vall-Mayans et al., 1990). HDV involves nearly exclusive parenteral transmission infecting intravenous drug users (IVDUs) from many areas of the world. However, there are specific areas where the virus spreads widely among the general population. Phylogenetic studies suggest that both viruses may have originated in the tropical forests of South America, subsequently spreading to the rest of the world. HBV phenotype F and HDV genotype III, which predominate in South America and are characteristic of the continent's autochthonous populations, may represent the modern version of the ancestral strains of both viruses (Casey et al., 1996; Quintero et al., 2001).

Chronic HCV infection represents a health problem comparable to HBV. The virus is ubiquitous, and its global prevalence among the general population has been estimated at some 3% (WHO, 2000). In a developed country like Spain, HCV antibody prevalence among adults over 30 years of age is in fact higher (Consejería de Salud, Comunidad de Madrid, 1995). Viral transmission appears to be almost exclusively parenteral, but half of the seropositive individuals fail to identify any risk episode in their case histories. Vertical and sexual forms of HCV transmission do exist but are sporadic and epidemiologically irrelevant. In the role played by IVDU in the spread of the virus, other factors for parenteral exposure such as transfusion of contaminated blood and blood products, IM or IV administration of medicines using non-disposable needles, and other medical interventions are believed to have played an important role in the past and likely are still playing that role wherever adequate preventive measures are not yet taken. This was clearly demonstrated in Egypt (Frank et al., 2000) and has also been documented in developed countries, based on hospital outbreaks of HCV infection in various medical care contexts (Echevarría et al., 1996a; Esteban et al., 1996).

An important aspect of the epidemiological behavior of viruses causing chronic liver disease is the tendency to establish closed epidemiological cycles in isolated populations, due to geographical, social, or cultural factors. In addition to the well-known examples of IVDUs and institutions for the mentally handicapped, significant differences in the prevalence of these agents can be observed in relation to other specific behaviors that may increase the risk of transmission. This means that the overall statistics for a particular geographical area may simply result from the addition of many different realities, for which detailed knowledge is essential in order to design and improve specific prevention and control strategies. The Amazon and other ecologically related regions from the North and Center of South America exemplify such diversity.

Background of viral hepatitis in the Amazon

The earliest observations recognizing viral hepatitis as a serious health problem in the Amazon were in northwestern Colombia and the western Brazilian Amazon, leading to the definition of two endemic clinical entities, Santa Marta and Labrea hepatitis, respectively (Bensabath & Dias, 1987). Several years later, by the late 1960s, an outbreak of acute fulminating hepatitis occurred among the Yanomami from the upper Orinoco river basin. The epidemics extended for several years and reached severe proportions in 1975, with an attack rate of 320 cases per thousand inhabitants and several

deaths (Torres & Mondolfi, 1991). By the end of the 1970s, a similar outbreak occurred among the Yukpa Amerindians in the Perijá region in northwestern Venezuela. This new epidemic extended from 1979 to 1981 with an overall attack rate of 12.3 cases per thousand inhabitants, causing 149 cases and 34 deaths (Hadler et al., 1984).

An observation common to all these endemic or epidemic situations was the high frequency of cases with hemorrhagic manifestations, leading to the initial identification of the disease as an atypical form of yellow fever. However, this hypothesis was never confirmed by laboratory studies. In 1984, a team formed by North American and Venezuelan researchers demonstrated that the Yukpa epidemics corresponded to HDV super-infection among chronic HBV carriers in the context of high endemicity for the latter (Hadler et al., 1984). It was also demonstrated that both the Santa Marta and Labrea endemic forms of hepatitis and the outbreak affecting the Yanomami had the same etiology (Bensabath & Dias, 1987; Buitrago et al., 1986; Torres & Mondolfi, 1991). It was therefore realized that the forest areas in the North and Center of South America were highly endemic for both agents.

Regarding viral transmission mechanisms driving the endemic and the epidemic outbreaks, no clear conclusions could be drawn from these studies. Infection among children was observed frequently in all locations, thus excluding sexual transmission as a major explanation. Sharing instruments for performing ritual scarification was proposed as a major transmission mechanism in the outbreak among the Yukpa. However, cases among members of a Catholic mission were recorded during the Yanomami epidemics, and such individuals do not share any known risk practice with the Indians. Introduction of HDV into the Yanomami community by a European priest was suspected to be the origin of that outbreak. However, description of HDV genotype III as autochthonous and characteristic of the region (Casey et al., 1996; Quintero et al., 2001) and the recent demonstration of its direct involvement in the epidemics (Nakano et al., 2001) make such a hypothesis highly unlikely.

Finally, it is relevant for this brief review to cite the hepatitis D outbreak in a rural community in the Venezuelan State of Barinas in 1986-1987. Involvement of HDV was demonstrated by laboratory studies (Jaimes, 1987), but none of the risk factors commonly associated with HDV transmission could be found (Edgar Jaimes, personal communication).

HBV and HDV prevalence in the region

After obtaining the knowledge described above, investigators launched serological surveys to determine HBV and HDV prevalence in the region. The study by Ljunggren et al. (1985) in Sierra Nevada de Santa Marta (Colombia) demonstrated anti-HBc prevalence up to 93% in some communities, with an HBsAg incidence of over 20%. In one particular community, 60% of chronic HBV carriers were also infected with HDV.

Since 1994, several studies among communities in Brazil, Venezuela, and Bolivia have been published (Blitz-Dorfman et al., 1994, 1996; Coimbra Jr. et al., 1996; de Paula et al., 2001; León et al., 1999; Soares et al., 1994). Moreover, a wide, as yet unpublished study was performed in the Peruvian Amazon (Instituto Nacional de Salud, 1997). The main data are summarized in Table 1. As observed previously in the Sierra Nevada de Santa Marta, anti-HBc prevalence was high (66-96%) in most of the communities, both in the Amazon Basin (eastern and western Brazil, eastern Bolivia, and northeastern and southeastern Peru) and in other ecologically-related areas (Sierra de Perijá, Venezuela). However, the relative incidence of HBsAg carriers showed a wide variation and never reached the high level found in Colombia. Generally speaking, data corresponded to what can be expected from a wide dissemination of HBV as a result of horizontal viral transmission (HBsAg incidence from 5 to 15% for an anti-HBc prevalence ranging from 60 to 96%). The incidence of HBsAg carriers was, however, unusually low among some populations, like the Bolivian Yuki Indians (among whom anti-HBc prevalence was 74.8%, with no chronic HBsAg carriers found).

Anti-HDV prevalence among HBsAg carriers was high both in the areas already known as highly endemic (de Paula et al., 2001; Ljunggren et al., 1985) and among members of those communities that had experienced outbreaks in the past (Blitz-Dorfman et al., 1996), with a downward trend from North to South (Figure 1). In communities in the southern part of the region and those in the Amazon River estuary, anti-HDV prevalence was significantly lower (León et al., 1999; Soares et al., 1994).

Data to estimate age-specific anti-HBc prevalence figures were obtained in three of the studies cited above (León et al., 1999; Instituto Nacional de Salud, 1997; Soares et al., 1994) and are compared in Figure 2. HBV infection began occurring in the first two years of life, as observed both among the Yuki Indians (Bolivia)

Table 1

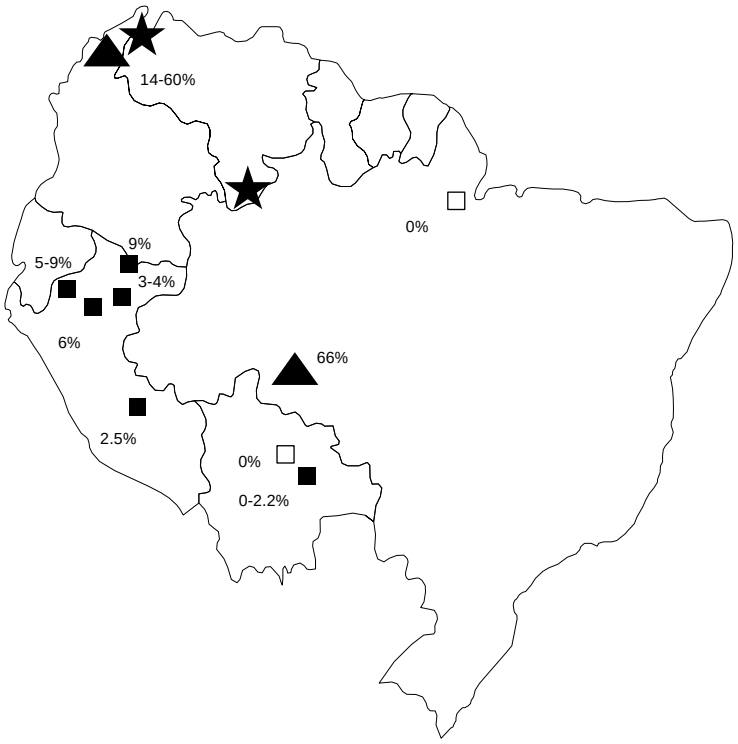
Prevalence of HBV and HDV infection among autochthonous populations in the Amazon and neighboring ecosystems.

Country	Area	% positive for		
		Anti-HBc	HBsAg	Anti-HDV*
Bolivia	Chapare, Santisima Trinidad	34-84	0-4.8	0-2.2
Brazil	Acre, Amazonas	66.1		66.6
	Pará	18-85	0-14.4	0
Colombia	Sierra de Santa Marta	35-93	1.8-23.0	Up to 60
Peru	Marañón, Madre de Dios	69-74	3.9-12.1	2.5-9.0
Venezuela	Sierra de Perijá	62-71	5.6-11.1	14.2-42.8

* Among HBsAg carriers.

Figure 1

Geographical distribution of HDV in the Amazon and neighboring ecosystems.



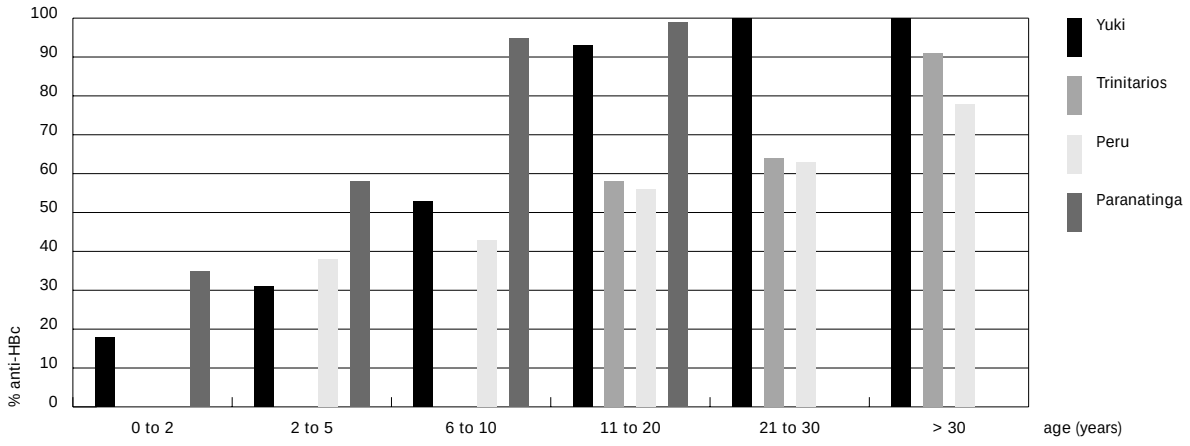
Legend: endemic areas for acute fulminating hepatitis (triangles); locations with outbreaks detected among isolated populations (stars); and communities with anti-HDV in chronic HBsAg carriers, but with no records of outbreaks (solid squares). White squares indicate populations with no record of anti-HDV in HBsAg carriers. Figures show anti-HDV prevalence in HBsAg carriers in each location.

and the Parakana from the village of Paranatinga (northeastern Brazil). Before the sixth year of life, almost 50% of children from these communities had developed anti-HBc. The prevalence then increased to nearly 100% by 20 years of age. Data recorded among communities from the Bolivian region of Santísima Trinidad and from the Peruvian Amazon were less complete, but confirmed that HVB infection occurs mainly among individuals younger than 20.

HBV and HDV prevalence rates in other ecological and cultural environments in the region (whether large cities or nearby rural communities) differ clearly from those described above (Table 2). Data obtained from such cities and rural areas in Bolivia, Peru, Venezuela, Colombia, and Brazil (Aguiar et al., 2001; Blitz-Dorfman et al., 1994; Cabezas et al., 1994; Castro, 2000; de Márquez et al., 1993; Figueiredo et al., 2000; León et al., 1999; Konomi et al., 1999; Ljunggren et al., 1985; Ponce et al., 1994; Pujol et al., 1994; Weir-Medina et al., 1987) show prevalence of HBV infection similar to what is commonly found in any region with low endemicity. In surveys performed among non-selected individuals from some large urban areas like Bogotá, Caracas, Maracaibo, or Cochabamba, anti-HBc prevalence was close to that recorded among the general population of Madrid (Consejería de Salud, Comunidad de Madrid, 1995). Such prevalence was indeed low among population segments that used to show figures higher than among the general population, as shown in Caracas (Ponce et al., 1994). Similar results were also obtained among rural communities from both the highlands of Bolivia (León et al., 1999) and the Brazilian States of Minas Gerais and Mato Grosso do Sul (Aguiar et al., 2002; Figueiredo et al., 2000). However,

Figure 2

Anti-HBc patterns among different Amerindian communities in the Amazon.



Summary of results from the Chapare (Yuki) and Santísima Trinidad (Trinitarios) regions, both in Bolivia (León et al., 1999), and from different ethnic groups in the Peruvian Amazon (Instituto Nacional de Salud, 1997) and Brazilian Amazon (Parakaná) (Soares et al., 1994).

the Peruvian transition valleys of Huanta and Abancay were a noteworthy exception (Cabezas et al., 1994). Such a phenomenon might be common to other valleys making the transition from the Amazon Plain to the Andean Highlands, and the observed HBV endemic could be driven by the same mechanisms as in viral transmission among the river-plain population. Other observations in southern Brazil suggest that HBV prevalence can display wide variations when specific populations from a single geographical area are studied (Aguilar et al., 2001; Castro, 2000).

Mechanisms of HBV and HDV transmission in the Amazon and clinical impact of the endemic

Since the study of the outbreaks among the Yukpa and Yanomami (Hadler et al., 1984; Torres & Mondolfi, 1991), few data have been added by subsequent investigation of the mechanisms driving HBV and HDV spread in the region and determining the epidemics. A recent study in western Brazil (Acre and Amazonas) (de Paula et al., 2001) found a significant correlation between anti-HBc infection and level of sexual activity. On the other hand, research in the Huanta and Abancay Valleys identified injected medication as the main factor in prior exposure to HBV (Cabezas et al., 1994). However, in a broad study of Amerindian communities in the Amazon region by the Peruvian National Institute of Health (Instituto Nacional de Salud, 1997), neither of these two risk factors was significantly associated with positive anti-HBc or anti-HDV. That study showed statistically significant associations ($p < 0.001$) between presence of anti-HBc and two novel factors: frequency of vampire bites (OR: 1.69; 95% CI: 1.21-2.35) and consumption of *masato* (OR: 4.98; 95% CI: 3.37-7.36), a drink made with fermented cassava and prepared by women chewing the tuber. Such an association with the intake of orally processed food has been also suggested from a study done in the Brazilian Amazon (Coimbra Jr. et al., 1996).

The association observed by the Peruvian research group between vampire bites and risk of HBV infection is especially interesting, because for the first time it suggests (based on experimental data) the involvement of an animal vector in HBV transmission in human populations of the Amazon. Such a possibility has been also suggested in relation to some species of arthropods (Echevarría et al., 1996b) and is indirectly supported by data from Africa. The role of bedbugs in the horizontal transmission of HBV among rural African children was drawn clearly from the results of an epidemiological study performed in Gambia (Vall-Mayans et al.,

Table 2

Prevalence of HBV and HDV infections among urban and rural populations from the transition Andean valleys and the highlands surrounding the Amazon.

Country	Area	% positive for		
		Anti-HBc	HBsAg	Anti-HDV*
Bolivia	Cochabamba (urban)	12	2.0	0
	Cochabamba (rural)	9-17	0-1.4	0
	Undefined		0.3	
Colombia	Bogotá	7	1.6	
Peru	Huanta, Abancay	82	16.0	17.9
Venezuela	Caracas	2-28	0-3.8	
	Maracaibo	6	1.2	

* Among HBsAg carriers.

1990). This conclusion also agreed with the detection of HBsAg in feces from wild African specimens of the bedbug species *Cimex hemipterus* Fabr., reported ten years earlier and later confirmed (Ogston & London, 1980; Wills et al., 1977). Moreover, other studies performed in the African tropics showed HBV antigen in wild populations of the tick species *Ornithodoros moubata* Murray (Joubert et al., 1985), as well as in mosquitoes from eight different species, including some from the world-ubiquitous genera *Culex* and *Aedes* (Dick et al., 1974; Prince et al., 1972), both present in the Amazon. At the moment, there is no news of any trial to detect HBV in hematophagous arthropod species captured in the Amazon, although the epidemiological pattern observed in the region and the data listed above would clearly justify such a study.

HDV super-infection of Amazon populations with a high incidence of HBV carriers leads to severe epidemic outbreaks of acute liver disease, with a marked trend to produce fatal cases of fulminating hepatitis that may resemble yellow fever because of the unusual hemorrhagic manifestations. Furthermore, no data have been obtained thus far to evaluate the impact that the HBV/HDV endemicity observed in the region may have on the health of communities with no previously reported outbreaks of acute disease. Incidence of acute and chronic viral hepatitis, liver cirrhosis, and primary liver cancer among the Amerindian communities of the Amazon is unknown, and studies designed to generate such data must be conducted in order to obtain a better understanding of viral hepatitis in the region. At any rate, the lack of data is surprising, considering that such populations show one of the highest endemic situations for these two viral agents anywhere in the world. The main mechanisms driving the spread of HBV in the Amazon have not been totally identified and may involve factors that are highly specific to the region. Thus, one cannot rule out that viral transmission through such unusual mechanisms may lead to characteristics of the infection that differ from those observed in other areas. The surprisingly low relative incidence of HBsAg carriers in some of these communities (León et al., 1999) suggests a viral persistency rate considerably lower than normal after horizontal transmission of HBV (5-10%), which would lead to an incidence of chronic liver disease much lower than expected from the high anti-HBc prevalence observed. A full understanding of hepatitis B and D problems in the Amazon depends on the clarification of all these issues.

Epidemiology of HCV infection

HCV is not autochthonous to the Americas, and its penetration into the Amazonian populations still appears quite limited (Table 3). In the large urban areas, anti-HCV prevalence is similar to that of other regions of the Americas and southern Europe, with the same risk factors as other regions of the world (Barham et al., 1994; Blitz-Dorfman et al., 1994; de Márquez et al., 1993; León et al., 1999; Ponce et al., 1994; Pujol et al., 1994; Silva et al., 1995). In contrast, the infection is almost absent from all the Amerindian communities studied in both the Amazon Plain and the Andean Highlands, as shown by studies in Venezuela, Bolivia, French Guiana, and Brazil (Blitz-Dorfman et al., 1994, 1996; de Paula et al., 2001; León et al., 1999; Soares et al., 1994; Talarmin et al., 1997).

However, anti-HCV prevalence ranging from 0.5 to 2.5% has been found among Amerindians in Colombia (Robinson et al., 1996), three remote areas of Brazil (Aguiar et al., 2002; de Paula et al., 2001; Soares et al., 1994), and the Orinoco Basin (Aguilar et al., 2001), meaning that the introduction of HCV into remote Amazonian communities is already occurring. The resulting impact on health in the future is difficult to predict.

Considering that iatrogenicity is believed to have played an important role in the spread of HCV in the human population, health services coming to remote, isolated, previously HCV-free communities are likely to pose a considerable risk of introducing the virus, and this risk must be dealt with seriously. Although some mechanisms in HBV transmission (i.e., sexual and vertical) do not spread HCV efficiently, one cannot exclude the possibility that mechanisms responsible for HBV transmission in the Amazon may by equally efficient in transmitting HCV. More than 70% of HCV-positive individuals develop a persistent infection that may lead to chronic liver disease, whereas persistent infection occurs in only 5-10% of post-natal HBV cases. Therefore, if the introduction of HCV into Amazonian communities reached a similar prevalence to that of HBV, it would generate a health problem seven to eight-fold that currently associated with HBV infection, a problem that could not be attenuated through an effective vaccine. Egypt's serious episode with HCV, spread through a program for schistosomiasis prevention (Frank et al., 2000), provides an important lesson for those involved in health programs in the Amazon.

Table 3

Anti-HCV prevalence among populations from different areas of the Amazon region.

Country	Area	% positive for anti-HCV
Bolivia	Chapare, Santisima Trinidad	0
	Cochabamba (rural)	0
	Cochabamba (urban)	0.5
	Undefined	0
Brazil	Acre, Amazonas	1,7
Colombia	Several	0.6-0.7
French Guiana	Several	0
Peru	Lima	1,6
Venezuela	Caracas	0.4-4.8
	Maracaibo	4,6
	Rural	0.8
	Western Amerindians	0
	Southern Amerindians	1.8
	Eastern Amerindians	2.5

Conclusions

Infections caused by two of the three known etiologic agents for chronic viral hepatitis and primary liver cancer are widespread among the most vulnerable human populations in the Amazon Basin. Control of HBV infection is an immediate target that can be achieved through immunization programs, which will also be effective in controlling HDV. Concomitantly, the identification of specific mechanisms driving the transmission of both viruses could aid additional preventive measures that could also be effective in controlling the spread of HCV. Health programs in the region should take especial care to prevent the introduction of HCV into Amerindian communities, which could lead to a novel endemic of unpredictable proportions. All these measures would improve quality of life for inhabitants of the Amazon and contribute to the conservation of what can be considered not only the most beautiful ecosystem on the planet, but also the most important for the future of life on Earth.

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