Hepatitis B and hepatitis delta virus infection in South America

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Abstract

About 100,000 cases of acute hepatitis B virus (HBV) infection occur annually in South America. The overall prevalence of HBV infection in low risk populations ranges from 6.7% to 41%, while hepatitis B surface antigen (HBsAg) rates range from 0.4% to 13%. In high endemicity aboriginal or rural populations, perinatal transmission may play a major part in the spread of HBV. In urban populations, however, horizontal transmission, probably by sexual contact, is the predominant mode of spread, with higher rates of HBV positivity in lower socioeconomic groups. High risk populations such as health care workers and haemodialysis patients show higher rates of HBV infection than comparable populations elsewhere. The risk of post-transfusion hepatitis B remains high in some areas. Concomitant HBV infection may accelerate the chronic liver disease seen in decompensated hepatosplenic schistosomiasis. In the north, the prevalence of hepatitis delta virus (HDV) infection ranks among the highest in the world. In the south, the problem appears negligible although it is increasing within high risk urban communities. HDV superinfection has been the cause of large outbreaks of fulminant hepatitis. The cost of comprehensive or mass vaccination programmes remains unaffordable for most South American countries. Less expensive alternatives such as low dose intradermal schedules of immunisation have been used with success in selected adult subjects.

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Viral hepatitis remains an important cause of morbidity and mortality in many Latin American countries, where hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis delta virus (HDV) and, to a lesser degree, hepatitis E virus, have all been reported as aetiological agents of both major regional outbreaks and isolated cases. Among these, HBV, HCV, and HDV are the key agents responsible for chronic infection and liver disease.

In common with other developing regions of the world with high rates of viral hepatitis, most South American countries display socioeconomic conditions that favour the occurrence of hepatitis B and other related infections. Such conditions are characterised, among other factors, by a deteriorating public health and educational infrastructure, overcrowding of populations crammed into a few large cities, resulting from uncontrolled internal and external influxes of population, as well as persistent and extreme poverty.

While it is certain that both HBV and HDV infections are highly prevalent in South America, pronounced regional differences in infection and carrier rates do exist, not only among different nations within the area but also – because of racial, geographical, socioeconomic, and other related factors – within individual countries. Thus, in terms of morbidity and mortality, a complex regional mosaic of epidemiological patterns and pathologies emerges.

Data limitations

Information on HBV prevalence in different areas of South America remains partial and scarce, at best. Most available data are inherently biased as they originate from blood bank reports, and blood donors are often selected from healthy adult populations. Furthermore, blood banks that perform routine HBV serological screening are mostly located in urban settings, and important differences in testing methodology exist.

Although National Hepatitis Committees have been established to facilitate the accumulation of valuable local data, only limited information exists from any single country with regard to HBV prevalence according to race, age, socioeconomic level or urban/rural status. As most cases of HDV infection occur precisely in rather remote locations, such as the Amazon Basin, where the prevalence of HBV infection is highest, epidemiological information is especially hard to collect. Moreover, the true prevalence of HDV can be difficult to estimate because it increases the severity of chronic liver disease and is also found more frequently in people with chronic HBV liver disease than in asymptomatic HBV carriers. Therefore, to clarify the level of endemicity and the predominant regional patterns of HDV spread, more reliable figures are required on HDV prevalence, both in known HBV carriers and in those people with chronic liver disease.

The shortcomings of analysing limited epidemiological data are illustrated by two recent surveys of different Peruvian towns. One such survey showed that the prevalence of antibodies to hepatitis B surface antigen (anti-HBs) in coastal towns was very similar to that reported in the main cities, reaching a high of 16%. In contrast, towns located closest to...
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HBV continues to spread throughout South America with very variable frequencies between one region and another. Available surveillance data on partially classified hepatitis cases have shown morbidity rates that range from 25 to 150 cases per 100,000 population per year. A significant proportion of such cases – mostly those seen in the adult population – can be attributed to HBV infection. Accumulated data also suggest that HBV is the cause of 25–67% of all cases of chronic hepatitis in Latin America and is also probably responsible for 10–70% of all cases of primary liver carcinoma.

Acute hepatitis B

HBV as a cause of acute hepatitis has only been investigated in a few countries, where it has been shown to be the causative agent in up to 50% of patients screened. In general, it has been estimated that 140,000 to 400,000 new cases of acute hepatitis B may be occurring annually in the entire Latin American region – two thirds of them in South America alone – including 440 to 1000 cases of fulminant hepatitis. Higher rates of fulminant hepatitis are seen in areas where concurrent HBV and HDV infections are common.

Chronic hepatitis B

Currently available information on the epidemiology of chronic hepatitis B infection in the region is largely derived from seroprevalence studies in blood donors. According to such studies, the seroprevalence of HBsAg ranges from 0.4% in some areas of Chile up to 13% in northern Brazil, demonstrating a wide spectrum of HBsAg prevalence, not only within the region, but also between different populations of a particular geographical area (Table I). However, it should be emphasised that calculations of HBV seroprevalence based only on HBsAg determination in blood donors probably underestimate the actual level of HBV infection in a particular country. Larger population screening studies incorporating additional HBV serological markers, such as anti-HBc and anti-HBs, will provide a more accurate picture. Data such as these are available for only half of all South American nations, as shown in Table II, but serve to demonstrate the importance of this disease as a serious public health problem regionally.

Precise numbers of chronic HBV carriers in Latin America are hard to obtain. However, most of the analyses estimate that between 6/6 and 12 million Latin Americans – more than 65% of them living in South America alone – are infected with HBV.

Sequela of chronic hepatitis B

Additional longitudinal studies are required to clarify the actual impact of chronic HBV infection on the occurrence of long-term sequelae such as chronic active hepatitis and liver...
TABLE 1 Geographical distribution of HBsAg in South America according to seroprevalence level\(^2\) 6 7 9 11 20 21 27 29

<table>
<thead>
<tr>
<th>Low prevalence</th>
<th>Intermediate prevalence</th>
<th>High prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2% (0-3-2%)</td>
<td>2-10% (2-2-8%)</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>Brazil (north), Colombia, Peru, Suriname</td>
<td>Amazon Basin (Brazil, Colombia, Peru, Venezuela)</td>
<td></td>
</tr>
</tbody>
</table>

Argentina, Bolivia, Brazil (south), Chile, Ecuador, Paraguay, Uruguay

cirrhosis in South America. Nevertheless, both complications are known to occur extensively in the Amazon Basin, as well as in other areas of high HBV endemicity.\(^6\) 7 13 31-33

Based on the lowest annual estimate of 140 000 acute HBV infections in Latin America, it can be anticipated that there will be at least 8000 to 15 000 new chronic carriers of HBV, more than 4000 cases of chronic active hepatitis and a variable number of cases of cirrhosis every year. It has been estimated that up to 60 000 cases of cirrhosis and 3000 cases of liver carcinoma annually could be related to HBV infection.\(^6\) 7 9 13 20 30

Contrary to reports from hyperendemic areas in other parts of the world, serum \(\alpha\) fetoprotein values do not seem to be a reliable indicator of the risk of HCC or severe chronic liver disease due to HBV or HCV infection in some South American countries.\(^34\) Serum values of \(\alpha\) fetoprotein remain either normal or only slightly increased in most urban patients with confirmed chronic liver disease, in accordance with the lower enzymatic inflammatory activity and negative HBeAg pattern already reported in the region.\(^18\) 35 However, among 232 Amerindians of all ages from an isolated Venezuelan Yanomami community, with overall positivity rates of 7-8% for HBsAg and 12% for anti-HCV (RIBA), abnormally increased serum \(\alpha\) fetoprotein values were seen in up to 12-4% of the 121 subjects over 30 years of age. Within this age subgroup, 7% were positive for HBsAg and 16% for anti-HCV (J R Torres, C Botto, unpublished data).

ROUTES OF TRANSMISSION

Perinatal transmission

Most HBV seroprevalence studies carried out in pregnant women have failed to show clearly a perinatal pattern of HBV transmission in South American urban areas. HBsAg positivity rates in these women have been found to resemble those reported in low risk populations and blood donors.\(^5\) 13 20 29 Recent seroepidemiological surveys in Caracas have shown that, as in the general population, low income pregnant women exhibit higher anti-HBC and HBsAg positivity rates compared with women from higher income brackets.\(^18\) 27 30 Moreover, in contrast with findings in Asiatic populations, hepatitis B e antigen (HBeAg) positivity is seen only infrequently in HBsAg carrier women and HBV-DNA is also negative as determined by nested-PCR techniques, suggesting a low rate of perinatal transmission in this population.\(^18\) 27 30 Nevertheless, in 1985, it was estimated that HBV induced liver deaths among Latin American babies could be expected to reach over 33 000 per 13-5 million births.\(^6\) 7 9 It is likely that, in areas of high HBV endemicity such as the Amazon Basin, the perinatal route may play a major part in the propagation of the disease. Initial studies in isolated Yanomamo communities of the Upper Orinoco Basin, for example, have shown that 75% of all HBsAg carriers – all of whom are also HBeAg positive – are women of childbearing age.\(^12\) 33 Furthermore, the prevalence of anti-HBc among children aged 1-4 years reached an astounding 66%, with an HBsAg prevalence of 33%,\(^12\) 33

Post-transfusion hepatitis B

There is a paucity of data on the risk of post-transfusion hepatitis in Latin America. However, a prospective longterm follow up study of 147 Venezuelan patients who received transfusions of either whole blood or blood components from volunteer donors that had been screened for HBsAg, anti-HBc, ALT, and anti-HCV, showed development of post-transfusion hepatitis in eight cases (6-1%).\(^37\) Five were associated with HBV infection and only three with HCV infection. It seems, therefore, that the risk of post-transfusion hepatitis B is comparable to or even greater than that for post-transfusion non-A, non-B-type C hepatitis in some South American countries with a moderate to high prevalence of HBsAg positivity.\(^37\)

Health care workers

As reported extensively worldwide, health care workers are at increased risk of acquiring HBV infection through percutaneous contact.\(^38\) In South America, anti-HBc positivity rates in health care workers seem to be even higher than those in health professionals at comparable risk in developed countries, but similar to those in local low risk populations (for example, 20% in Brazil, Peru, and Venezuela, and 15% in Argentina).\(^7\) 13 39-43 These indirect data provide confirmation of the intermediate level of HBV endemicity in many South

TABLE 2 Seroepidemiology of HBV infection in South America, including surveys in low risk populations\(^6\) 7 9 11 20 21 27 29

<table>
<thead>
<tr>
<th>Countries</th>
<th>HBsAg</th>
<th>Positive HBV serological markers (HBsAg, anti-HBc, or anti-HBs)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>1-1</td>
<td>18-6</td>
</tr>
<tr>
<td>Bolivia</td>
<td>1-6</td>
<td>31-5</td>
</tr>
<tr>
<td>Brazil</td>
<td>3-4</td>
<td>2-5</td>
</tr>
<tr>
<td>South</td>
<td>1-0</td>
<td>0-0</td>
</tr>
<tr>
<td>Middle West</td>
<td>1-0</td>
<td>0-0</td>
</tr>
<tr>
<td>South East</td>
<td>2-0</td>
<td>34-0</td>
</tr>
<tr>
<td>North East</td>
<td>2-5</td>
<td>0-0</td>
</tr>
<tr>
<td>North</td>
<td>8-0</td>
<td>0-0</td>
</tr>
<tr>
<td>Colombia</td>
<td>2-8</td>
<td>29-3</td>
</tr>
<tr>
<td>Chile</td>
<td>0-5</td>
<td>8-7</td>
</tr>
<tr>
<td>Ecuador</td>
<td>2-0</td>
<td>35-3</td>
</tr>
<tr>
<td>Paraguay</td>
<td>0-9</td>
<td>0-9</td>
</tr>
<tr>
<td>Peru</td>
<td>0-9</td>
<td>28-5</td>
</tr>
<tr>
<td>Suriname</td>
<td>1-4</td>
<td>41-0</td>
</tr>
<tr>
<td>Uruguay</td>
<td>0-9</td>
<td>0-9</td>
</tr>
<tr>
<td>Venezuela</td>
<td>2-0</td>
<td>16-5</td>
</tr>
</tbody>
</table>

*Methods: immunodiffusion, counterimmunoelectrophoresis, reverse passive haemagglutination, radioimmunoassay, enzyme linked immunoassay.
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American urban areas. They also support both the existence of special epidemiological conditions that maintain the prevalence of HBV infection in health care workers, and the potential benefit of mass HBV vaccination programmes. 41

High risk populations
Higher frequencies of HBV infection have been reported in high risk South American populations than in comparable populations from other parts of the world. 16 27 44 46 These include polytransfused patients, haemodialysis patients, homosexuals, and prostitutes. In haemodialysis patients, combined infection with both HBV and HCV seems to be prevalent in some regions. In one Venezuelan study, 50 of 123 (41%) anti-HCV positive haemodialysis patients were positive for at least one HBV serological marker, while only 27% of 191 anti-HCV negative patients were also HBV positive. 47 The occurrence of HBV/HCV coinfection was not only found to correlate directly with both the number of transfusions and the time on haemodialysis, but was also identified as a major cause of increased serum ALT values. 47 Other regional studies carried out in haemodialysis and renal transplant patients have shown anti-HBc/anti-HBs positivity rates of over 40%. 44 46 47 In a more recent survey of 227 patients from four metropolitan haemodialysis units in Caracas, 51% were found to be positive for anti-HBc, 22% for HBsAg, 0.4% for anti-HDV, and 67% for anti-HCV. 48 Importantly, HCV-RNA was shown not only in 90% of the 154 anti-HCV positive patients but also in up to 30% of anti-HCV negative patients, possibly indicating a high rate of recently acquired infections. Overall, no less than 62-5% of patients showed evidence of either chronic or acute HCV infection. 48 In addition, a sharp increase in the rate of HBV infection among intravenous drug abusers in Latin American urban communities has recently been identified, thus worsening an already precarious situation. 31 49 50

Schistosomiasis and HBV
Schistosomiasis and HBV infection coexist in large coastal areas of Brazil and Venezuela. Although there is no evidence to date that either disease represents a risk factor for the other, epidemiological and clinical data indicate that concomitant HBV infection does play a part in the acceleration of the chronic liver disease seen in uncomplicated hepatosplenic schistosomiasis (HSS). In fact, chronic HBV infection has been shown to be prevalent in patients with HSS, but not in those with the hepatointestinal form of the disease. 51 More recently, an appreciably increased rate of HBsAg positivity, with evidence of active viral replication (HBV-DNA positivity), has been seen in HSS patients with decompensated liver disease compared with that in patients with compensated disease or hepatointestinal schistosomiasis, suggesting that HBV is a major pathogenic factor in progression to more severe forms of HSS. 52

Summary
The results of many seroepidemiological surveys suggest that, in hyperendemic regions, the pool of chronic HBV carriers probably arises from perinatal or early childhood infection. On the other hand, studies performed in urban populations with lower HBV carrier rates suggest that sexual transmission is the predominant mode of HBV spread in those areas, and that HBV positive subjects are more common among adults than children. 2 13 20 Furthermore, some countries have reported a higher prevalence of HBV infection in the poorest urban areas or in lower socioeconomic population segments. 13 17 28 29 53 Generally, the results of the various retrospective and prospective investigations carried out to date suggest that horizontal transmission probably represents the major mode of HBV spread in the main Latin American cities. Undoubtedly, the reported prevalence of HBV in urban areas and in healthy populations is lower than that seen in aboriginal populations. 5 7 9 12 13 19 20 21 27 53

Hepatitis delta epidemiology
As HDV is dependent on HBV for its replication, it can only infect those people who are simultaneously infected with HBV (coinfection) or who are already carriers of HBV (superinfection). As a result, the distribution and prevalence of HDV in Latin America tend to parallel those of HBV, particularly in populations with overt factors predisposing to perinatal or sexual routes of transmission, such as some Amerindian communities. 4 6 9 12 13 15 54 However, as in other less developed tropical areas of the world, the epidemiology of HDV infection in South America is marked by great contrasts. Thus, HDV may cause widespread outbreaks of both fulminant and chronic hepatitis in the northern part of the continent, whereas it is virtually absent in other areas with a similar or even higher HBV endemicity. 5 12 13 26 54-56

Based on current worldwide estimates, at least 300 000 people in the region (5% of the estimated six million HBsAg carriers) are infected with HDV and most are suffering from significant liver disease. 13 16 In general, the occurrence of HDV infection is lowest in temperate zones of Latin America, with a prevalence gradient that increases in equatorial tropical and subtropical zones. In fact, certain populations in northern regions of South America have served as a high endemicity model of HDV transmission. 5 7 9 12-14 16 57 Moreover, HDV superinfection has been incriminated as the aetiological agent in a number of outbreaks of severe hepatitis, including Santa Marta hepatitis in western Colombia, large numbers of cases among Yucpa and Yanomamo Indians in Venezuela, and Labrea Fever and other related fulminant liver conditions occurring among the Upper Amazon Basin of Brazil and Peru, and the Upper Orinoco basin of Venezuela and Colombia. 5 5 9 12 13 55-58
GEOGRAPHICAL VARIATIONS

With regard to HDV infection, South America can be divided in two well defined areas. In the south, the problem appears negligible, particularly in Chile, Uruguay and, to a lesser degree, Argentina. In the north – particularly in the Amazon Basin, which is beset by poor sanitary conditions – the prevalence of HDV ranks among the highest in the world.12 13 15 31 55 56 Nevertheless, recent studies in countries with a low overall prevalence of HDV infection indicate that the penetration of HDV within high risk communities, such as intravenous drug abusers and homosexuals or bisexuals, is higher.6 26 Indeed, the rate of HDV infection among drug abusers from large South American cities such as Buenos Aires jumped fourfold to sixfold in a period of only three years, representing an increasingly important source of infection.6

An unexpectedly high rate of HBsAg (30-6%) and HDV infection (39-7%) has been found among isolated Yanomami in Venezuela.12 13 Most (75%) of the HBsAg positive cases were women of reproductive age and, remarkably, all HBV carriers had concomitant HDV infection.12 13 Perinatal transmission seemed to be the predominant route of HBV infection, while HDV infection occurred later in life. Interestingly, retrospective serological and epidemiological evidence suggests that the onset of a longstanding outbreak of severe acute and chronic liver disease affecting the same villages might have coincided with the introduction of HDV in a population with a high pre-existing level of HBV infection.12 13

Recent studies in central and western Brazilian populations highly endemic for HBV infection also showed a very high prevalence of HDV infection.26 Anti-HDV was found in 20–30% of HBsAg carriers and acute hepatitis cases, in 30–50% of fulminant hepatitis B cases, and in 85–90% of chronic active hepatitis and cirrhosis patients.4

In large urban areas in South America, few cases of HDV infection are currently reported other than among intravenous drug abusers. Indeed, serological surveys in asymptomatic HBV carriers in Chile have proved consistently negative for HDV, while in Rio de Janeiro (Brazil), HDV was found among only 0.5% of 200 HBV carriers.6 26 Furthermore, seroepidemiological studies in adult Venezuelans at high risk for HBV or HIV infection, or both, proved negative for HDV markers.5 45

The high rate of HBsAg positivity found in areas of the Amazon and Orinoco Basins resembles that seen among some Asian and African populations, where carrier rates of between 10 and 20% are not unusual.9 It is plausible that the Amazon and Orinoco Basins offer an ecological system especially favourable for the transmission of HDV. Possible influences include genetic differences, specific cultural habits, potential animal reservoirs, nutritional factors, a high prevalence of skin lesions, or even differences in virulence of the prevalent HDV strains.13 59 60

FULMINANT HEPATITIS

Investigations among Yucpa Indians of western Venezuela reported for the first time in an open community the importance of HDV superinfection as the cause of large outbreaks of fulminant hepatitis in populations with a high pre-existing HBV endemcity.55 58 A high percentage (70%) of HBV carriers with HDV superinfection showed persistently increased ALT values, reaching at least four times the upper limit of normal in 25% of cases. Significantly enlarged spleens were seen in about half of all simultaneously infected people. Necropsy specimens obtained during the same epidemic exhibited a histopathological picture consisting of microvascular fatty infiltration of hepatocytes ("morula cells") and various degrees of eosinophilic necrosis and inflammation. The clinical, epidemiological, and histopathological similarities between this outbreak and two other distinct entities recognised for over 40 years (Labrea Fever in northern Brazil, and Santa Marta Hepatitis in western Colombia) rapidly became evident. A retrospective review of a large number of seroconversions specimens collected in Colombia since 1936 showed the same typical histopathological pattern in at least four distinct areas of the country.1 Moreover, HDAG was eventually identified by immunoperoxidase staining in the nuclei of morula cells in up to 70% of the samples assayed.1 Similar findings have been noted in necropsy material collected from Yucpa Indians with severe or fulminant hepatitis and from patients with Labrea hepatitis.25 58

Labrea hepatitis presents clinically with intense vomiting, right upper quadrant pain, fever, jaundice, hepatic coma, and death within a few days of the onset of symptoms. Children, adolescents and young adults are mainly affected.22 Although Labrea hepatitis has generally been described as being the result of HDV superinfection in HBV carriers,5 it has also recently been reported as being related to HAV and HCV infections.22

CONCLUSIONS

Various aspects of the epidemiology of HDV infection in Latin America remain to be defined. However, while further epidemiological, clinical, and pathological studies are certainly needed, mass prevention programmes through hepatitis B immunisation of susceptible children are a clear priority for some hyperendemic areas.

Diagnosis and prevention of HBV infection in South America

Serological diagnosis of HBV is a complex process due to the multiple viral markers present during the different phases of the disease – that is, high and low viraemic phases, the acute period, the convalescence and resolution stages, and progression to chronic infection.35 61 62
DONOR SCREENING

The selection of a diagnostic and of an appropriate HBV screening system for blood banks in South America must depend largely upon the availability (or lack) of expensive imported reagents. As a result, the serological follow up of HBV infections and the incorporation of more reliable assays into blood bank procedures incur considerable expenses and are difficult to set up. Thus, first and second generation tests and pooling of blood for HBsAg screening are still the standard in some countries.7 20

In some regions, successful efforts have been made to develop and manufacture locally more reliable assays for the detection of HBsAg and anti-HBc. However, standard testing for anti-HBc as a surrogate marker for post-transfusion non-A, non-B, non-C hepatitis63 has been implemented in only a few local blood banks. As the prevalence of anti-HBc in South American blood donors and in low risk general populations is relatively high, and HBV-DNA may be documented in the serum of many such subjects,13 35 61 63 64 routine anti-HBc screening in urban as well as rural blood banks may prove highly beneficial. The technological transfer and further local development of non-ELISA or RIA based reagents are among the recommendations proposed by different national and international health organisations to improve the situation. Meanwhile, investigation of pre-S determinants and establishment of molecular techniques such as slot-blotting, dot-blotting, and PCR have already been incorporated into blood bank procedures in some countries, which are now able to provide complete HBV screening.13 61 64-66

DIAGNOSIS

According to various reports, the clinical features of acute and chronic HBV infection in South America are no different to those reported in other parts of the world.7 61 Thus, for example, there is a 4:1 preponderance of male over female patients in both acute and chronic cases, and a predominance of chronic disease during the third and fourth decades of life.7 61 It has been reported that anti-HBe positive patients — generally considered to be in a low or non-viraemic phase of the disease — represent the majority of chronic HBsAg carriers in Venezuela.51 However, around one third of these HBsAg positive/anti-HBe positive carriers test positive for HBV-DNA in serum, indicating ongoing viral replication and active hepatitis.51 64 In both types of carriers, infections appear to be due to the wild type virus. Most HBsAg carriers and anti-HBe positive subjects also have antibodies to pre-S2, thus confirming a true exposure to HBV. The possibility that some carriers might be infected with HBV mutants remains to be further investigated.61 67 In this respect, although preliminary studies in Brazilian anti-HBe positive patients with chronic hepatitis B did not reveal serum HBV-DNA positivity by dot-blot hybridisation, more recent assessments using PCR in 49 patients confirmed the occurrence of active viraemia in most cases.66 A plausible explanation for these findings is the occurrence of precore mutant infections.

IMMUNISATION

The high risk of morbidity and mortality associated with HBV infections has prompted the delineation and establishment of HBV control strategies in endemic areas.68-70 Approaches outlined by the World Health Organisation Programme for Control of Viral Hepatitis include HBsAg screening of pregnant women, vaccination of newborns of HBV carrier mothers, immunisation of health care personnel, and immunisation of other high risk groups.49 71 72

The introduction of standard HBsAg screening for pregnant women73 74 seems feasible only in those countries where HBsAg assay kits are currently manufactured or in favoured socioeconomic segments of the population. Routine universal HBsAg screening in pregnant women, therefore, has not yet been incorporated in South America. Moreover, as most mothers are anti-HBe positive, mass immunisation (whenever possible) of all children seems a more cost effective strategy.

The establishment of pilot HBV vaccination programmes is the most widely adopted strategy in South American countries.6 7 20 30 71 Priority has been given to the implementation of vaccination of newborns and children in hyperendemic areas, including the whole Amazonic territory.75 The largest of these immunisation programmes has been accomplished in Brazil.30 Since 1989, 11 rural and urban areas, with an estimated population of 95 011 children aged 0 to 10 years, have been targeted for protection. So far, more than 60 000 children (66.6%) have completed the course of all three doses of the HBV vaccine, as part of the Expanded Programme on Immunisation (EPI).30 75 In addition, a further 52 municipalities located in the Brazilian Amazon have been incorporated to the HBV vaccine programme.75 Other hyperendemic areas, such as Sierra de Perija and the Alto Orinoco Basin in Venezuela, or Sierra de Santa Marta in Colombia, where outbreaks of HBV and HDV infections with high death rates have been well documented, have initiated comprehensive vaccination programmes that include children and susceptible adult populations.

Little information exists on the serological response to vaccine among Amerindians from hyperendemic areas in South America. In one study, however, 226 HBsAg negative/anti-HBs negative volunteers from Jivar and Arawak communities in the Peruvian Amazon were vaccinated with a recombinant DNA vaccine.76 The overall seroconversion rate to anti-HBs was 84-9%, with 73-5% of people developing anti-HBs serum values higher than 10 mIU/ml. Importantly, it was observed that significantly better seroprotection rates and serum concentrations of anti-HBs were achieved in previously anti-HBe negative people.76 Therefore, when vaccinating in hyperendemic Amerindian communities, it...
might be beneficial to evaluate their serological response at the end of the vaccination.

There is no comprehensive national policy for vaccination of health care workers anywhere in the area but immunisation of personnel at risk is consistently performed in many health centres and in some medical and dental schools. Pilot vaccination projects for health care personnel are also being conducted in many countries, and cost-benefit studies evaluating the impact of either selective or mass vaccination for hospital and patient-care unit staff have clearly shown the economic advantages of both strategies. However, it has been estimated that the total financial burden derived from both the direct and indirect costs of HBV infection and the vaccination programmes is too high for most Latin American countries, partly because of the high price of commercially available HBV vaccines.

Low dose immunisation schedules, using either plasma derived or yeast derived vaccines given intradermally, have been tried successfully in Brazilian health care workers and in Venezuelan medical students. Seroconversion rates and levels of anti-HBs achieved after low intradermal doses were comparable to those obtained with standard intramuscular doses. Moreover, 91-4% of vaccinated health workers showed anti-HBs levels over 11 times the cut off level (that is, the level considered a good antibody response) 36 months later.

Local vaccine production or access to cheaper sources of HBV vaccines have been proposed as alternative solutions. In this respect, a genetically engineered Cuban HBV vaccine is currently being commercialised successfully in several South American countries. Ensuring that the market price of HBV vaccines is proportional to the particular economic capabilities of each country in the region is essential if mass control programmes are to be carried out effectively.

**SUMMARY**

In summary, strategies for global control of HBV in Latin America are similar to those recommended by the WHO worldwide. Universal HBsAg screening of blood and blood products, availability of suitable HBV marker reagents, and an extensive infant HBV immunisation programme integrated into the EPI are three desirable goals. Meanwhile, overall control of HBV infection and its sequelae in South America is urgently awaited.
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