

Hepatitis B seroprevalence in Latin America

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ABSTRACT

The seroprevalence of hepatitis B was investigated in over 12 000 subjects in six countries of Latin America: Argentina, Brazil, Chile, the Dominican Republic, Mexico, and Venezuela. Each study population was stratified according to age, gender, and socioeconomic status. Antibodies against hepatitis B core antigen (anti-HBc) were measured in order to determine hepatitis B infection. The highest overall seroprevalence was found in the Dominican Republic (21.4%), followed by Brazil (7.9%), Venezuela (3.2%), Argentina (2.1%), Mexico (1.4%), and Chile (0.6%). In all the countries an increase in seroprevalence was found among persons 16 years old and older, suggesting sexual transmission as the major route of infection. In addition, comparatively high seroprevalence levels were seen at an early age in the Dominican Republic and Brazil, implicating a vertical route of transmission.

Parts of Latin America have previously been described as high-endemicity areas for hepatitis B. However, there is a wide variation in seroprevalence within Latin America, with the highest rates around the Amazon basin and the lowest in the temperate southern portion of South America (1, 2). Furthermore, Latin American coun-

tries share many traits with other developing countries, such as the migration from rural communities to cities that creates urban areas with low incomes and social deprivation. Under such conditions, health problems, especially communicable diseases, are a major concern and impose a large economic burden. However, in urban environments, health care programs have the potential to quickly reach large numbers of people.

All major authorities agree that vaccination is the most effective means to reduce the health care burden of hepatitis B. In 1992 the Expanded Programme on Immunization (EPI) of the World Health Organization (WHO) set targets for the incorporation of hepatitis B virus (HBV) vaccination into national programs by 1995 for high-endemic countries, and for all countries by 1997 (3). Having an understanding of the epidemiology of the virus is essential in order to opti-

mize the use of vaccination as a means of controlling the infection and disease. In Latin America, analysis of blood banks has previously been the main source of epidemiological data (2). However, the data were not stratified by age or social class. In addition, blood donors are almost exclusively healthy adults in urban areas where there are sufficient facilities to perform routine serological screening. In order to determine the seroprevalence of hepatitis B infection in six countries of Latin America and the carrier rate in three of them, we carried out a cross-sectional multicenter study.

METHODOLOGY

Study design

This was a multicenter cross-sectional study with subjects in six countries: Argentina (cities of Buenos Aires

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and Córdoba), Brazil (Rio de Janeiro and Porto Alegre, in the southeast; Manaus, in the Amazon basin; and Fortaleza, in the northeast), Chile (north Santiago de Chile), the Dominican Republic (three centers in Santo Domingo), Mexico (in cities in the north, center, and south regions of the country), and Venezuela (Caracas). The study was conducted between June 1996 and November 1997. Subjects included both men and women between the ages of 1 and 40 years old. The same study population was used for the gender, age, and socioeconomic analyses that were done. Written informed consent was given by the subjects or the subjects' parents or guardians.

Study populations and selection

To prevent clusters, in all the study sites there was a limit of one subject per household or family. The recruitment procedures for the study populations varied from country to country. The following paragraphs describe the procedures in each of the study sites.

In Mexico the study used two-stage cluster sampling, with primary sample units made up of states, plus the Federal District, randomly selected in each of the three regions. The secondary sample units were urban areas belonging to each of the selected states, plus Mexico City. The sample size was distributed proportionately throughout the entire population of each region and also the total population between 1 and 40 years old in each of the regions.

In Chile subjects were recruited among randomly selected households from the north of Santiago de Chile. The characteristics of the sampled households corresponded very well with those of the last census of the metropolitan population of that city.

The Venezuelan study population was recruited from eight different places in Caracas, including pre-school nurseries, colleges, public schools, and companies randomly selected and willing to participate.

In Brazil, one part of the study population was recruited in various out-

patient clinics attached to public and private hospitals mainly located in poor and middle-class areas. Another proportion, mainly the higher socioeconomic group, was recruited at schools in wealthy neighborhoods.

The Argentine study subjects were recruited among people attending ambulatory primary health care centers attached to three public hospitals.

In the Dominican Republic the study population was recruited from three health care centers, where the attendees were from a low socioeconomic background. (The higher proportion of females in this study population as compared with the other countries was due to the fact that one of the recruitment centers was a maternity hospital.)

Assessment of criterion

Subjects completed a questionnaire and provided such demographic data as social class, type of community, present health status, and relevant medical background. A history of prior HBV vaccination was an exclusion criteria. Socioeconomic groups were defined according to local scales, which were based on income, tap water service, sewage service, refrigerator ownership, electric power access, and the number of people per room in the home. In Argentina and Mexico a modified Bronfman scale (4) was used, and in Brazil a government scale (5) was applied. In Venezuela and Chile all subjects were from the middle socioeconomic group while in the Dominican Republic people were only recruited from the lower socioeconomic group. All data requested in the study protocol were documented on individual case report forms.

Assessment of serology

A minimum of 5 mL of blood was taken from each of the subjects, and the sera were stored at -20°C . Immunoglobulin G (IgG) antibodies against hepatitis B core antigen (anti-HBc) were assessed with the Corzyme enzyme-

linked immunosorbent assay (ELISA) test (Abbott Laboratories, Abbott Park, Illinois, United States of America) to determine seroprevalence. The qualitative determination of hepatitis B surface antigen (HBsAg) was carried out using the Auszyme commercial enzyme immunoassay (Abbott Laboratories, Abbott Park, Illinois, United States) and was used to determine the carrier population. For both assays, values greater than 1.0 mIU/mL were considered to be seropositive. Serology was conducted at the National Institute of Epidemiological Diagnosis and Reference, Mexico City, Mexico, for samples from Mexico and Venezuela; at the J. J. Aguirre Hospital, University of Chile, Santiago, for samples from Chile; at the Public Health Technology Center, National University of Rosario, Rosario, Santa Fe, Argentina, for samples from Argentina and the Dominican Republic; and at the Carlos Lieberenz Laboratory of Clinical Analyses, Rio de Janeiro, for samples from Brazil.

Statistical analysis

The study population was stratified according to country, gender, age, and socioeconomic status. Data were entered into the Dbase IV computer program (Boland International Inc., Scotts Valley, California, United States), and the descriptive statistical analysis was performed using two other computer programs, SPSS (SPSS Inc., Chicago Illinois, United States) and Epi Info 6.04 (U.S. Centers for Disease Control and Prevention, Atlanta, Georgia, United States). Odds ratios and 95% confidence intervals (95% CIs) were also calculated.

RESULTS

Of the 12 085 subjects who were enrolled in the study, 328 of them were eliminated due to an inability to analyze their blood sample and/or missing data on their case report form. The study attrition by country is shown in Table 1.

TABLE 1. Study population attrition, hepatitis B seroprevalence in Latin America, 1996–1997

	Argentina	Brazil	Chile	Dominican Republic	Mexico	Venezuela	Total
Enrolled	1 475	3 879	496	478	5 262	495	12 085
Less: hemolysis, insufficient volume, or loss of sample	1	49	0	5	43	22	120
Available for serology	1 474	3 830	496	473	5 219	473	11 965
Less: missing data	20	177	0	0	7	4	208
CRF ^a study population	1 454	3 653	496	473	5 212	469	11 757

^a CRF = case report form.

Gender and country distribution

Table 2 shows the seroprevalence of anti-HBc in the study population by country and gender. The highest overall seroprevalence was observed in the Dominican Republic (21.4%), followed by Brazil (7.9%), Venezuela (3.2%), and Argentina (2.1%). The lowest levels were found in Mexico (1.4%) and Chile (0.6%). In the different regions of Brazil a wide range of seroprevalences was found, with a high rate in Manaus (21%), followed by Porto Alegre (7.5%), Rio de Janeiro (5.5%), and Fortaleza (1.2%). The only significant difference in seroprevalence between males and females was in Brazil, with a higher seroprevalence for males (odds ratio =

1.32, 95% CI: 1.01–1.65, $P = 0.02$), and in the Dominican Republic, with a higher rate for females (OR = 2.19, 95% CI: 1.05–3.07, $P = 0.01$).

The hepatitis B carrier population was assessed by the detection of HBsAg in sera in Argentina, the Dominican Republic, and Mexico. As with the seroprevalence data, the highest carrier rate was found in the Dominican Republic (1.9%). Comparatively low rates were found in Argentina (0.2%) and Mexico (0.1%).

Age distribution

The seroprevalence of hepatitis B among different age groups in the var-

ious countries is detailed in Table 3 and shown graphically in Figure 1. The countries exhibited noticeable increases in seroprevalence among persons aged 16 and older.

At one year of age, children found anti-HBc-positive were 0/10 in Chile, 0/7 in the Dominican Republic, 0/41 in Mexico, and 0/30 in Venezuela, but 4/129 (3.1%) in Brazil and 5/71 (7.0%) in Argentina.

Socioeconomic factors

Table 4 shows the seroprevalence data analyzed by socioeconomic level, which was available for Argentina, Brazil, and Mexico. In Argentina and Mexico there was an even distribution over the socioeconomic groups. However, there was a clear association of increasing seropositivity with decreasing socioeconomic status in Brazil, where there was a significant difference between the low socioeconomic group (10.7% seropositive for anti-HBc antibodies, 95% CI: 9.2–12.2) and the high/medium one (5.4% seropositive, 95% CI: 4.3–6.3) ($P < 0.001$).

DISCUSSION

The present study was performed to assess the current status of hepatitis B seroprevalence in Latin America, with respect to age, gender, and socioeconomic status. This study showed a variation in seroprevalence rates from one country to another within Latin America. Possibly influencing the epidemiology of hepatitis B infection from

TABLE 2. Seroprevalence of anti-HBc antibodies in the study populations, by gender, Latin America, 1996–1997

Country	Gender	Total study population	Seropositive			
			Number	%	95% CI	<i>P</i> value
Argentina	Male	631	14	2.2	1.1–3.3	0.817
	Female	823	17	2.1	1.1–3.0	
	Total	1 454	31	2.1	1.4–2.8	
Brazil	Male	1 773	158	8.9	7.6–10.2	0.025
	Female	1 880	130	6.9	5.8–8.0	
	Total	3 653	288	7.9	7.0–8.7	
Chile	Male	229	2	0.9	0.0–2.1	0.475
	Female	267	1	0.4	0.0–1.1	
	Total	496	3	0.6	0.0–1.3	
Dominican Republic	Male	111	14	12.6	6.6–18.6	0.010
	Female	362	81	24.0	19.7–28.3	
	Total	473	101	21.4	17.8–25.0	
Mexico	Male	2 007	27	1.3	0.8–1.8	0.064
	Female	3 205	48	1.5	1.0–1.9	
	Total	5 212	75	1.4	1.1–1.7	
Venezuela	Male	205	5	2.4	0.4–4.4	0.409
	Female	264	10	3.8	1.6–6.0	
	Total	469	15	3.2	1.7–4.7	

TABLE 3. Age distribution of anti-HBc antibodies (seropositivity) in Latin America, 1996–1997

Age group (years)	Argentina			Brazil			Chile			Dominican Republic			Mexico			Venezuela		
	No./TP ^a	%	95% CI	No./TP	%	95% CI	No./TP	%	95% CI	No./TP	%	95% CI	No./TP	%	95% CI	No./TP	%	95% CI
1–5	12/306	3.9	1.7–6.0	25/655	3.8	2.3–5.2	0/100	0.0	0.0–0.0	7/71	9.9	2.9–16.7	7/850	0.8	0.2–1.4	2/121	1.7	0.0–3.9
6–10	8/293	2.7	0.8–4.5	58/726	8.0	6.0–9.9	0/100	0.0	0.0–0.0	5/76	6.6	1.2–12.1	7/866	0.8	0.2–1.4	3/74	4.1	0.0–8.5
11–15	3/289	1.0	0.0–2.2	30/621	4.8	3.1–6.5	0/97	0.0	0.0–0.0	6/55	10.9	2.6–19.1	7/847	0.8	0.2–1.4	0/120	0.0	0.0–0.0
16–20	2/295	0.7	0.0–1.6	37/665	5.6	3.8–7.3	1/97	1.0	0.0–3.0	17/65	26.2	15.4–36.8	9/763	1.2	0.4–1.9	3/65	4.6	0.0–9.7
21–30	1/183	0.5	0.0–1.6	77/625	12.3	9.7–14.8	0/52	0.0	0.0–0.0	33/119	27.7	19.6–35.7	20/1119	1.8	1.0–2.5	3/53	5.7	0.0–11.8
31–40	5/88	5.7	0.8–10.5	60/361	16.6	12.7–20.4	2/50	4.0	0.0–9.4	33/87	37.9	27.7–48.1	25/767	3.3	2.0–4.5	4/36	11.1	0.8–21.3

^a No./TP = number of seropositive persons/total population in that age group in that country.

country to country are differences in geography, climate, wealth, degree of urbanization, and ethnic origin.

We found the highest overall seroprevalence rates in the Dominican Republic (21.4%) and Brazil (7.9%), which both also showed high seroprevalence levels in children. Furthermore, in Brazil and Argentina more than 3% of children were anti-HBc-seropositive by the age of 1 year, indicating a vertical route of transmission. This study showed a dramatic and highly significant increase in hepatitis B seroprevalence among those 16 and older in all the countries studied, which is compatible with the fact that sexual activity and other adult life behaviors are a major route of trans-

mission (6). An association of higher seroprevalence with lower socioeconomic status was only found in Brazil. The similar seroprevalence levels we found among different socioeconomic groups in Mexico and Argentina might mean that such differences may only become visible when dealing with larger numbers of seropositive individuals. Even if there had been differences in the seroprevalences among the socioeconomic groups in Mexico and Argentina, the overall levels would still be considered low and therefore such socioeconomic differences would be of limited significance.

The levels of anti-HBc antibodies found in this study were consistently lower than those that have been re-

ported in other studies (1, 2, 7, 8). However, the levels we found are comparable when just the adult population is considered, and the *pattern* of seroprevalence throughout Latin America is similar between this and other studies. Earlier studies were conducted mainly on adult populations using samples from blood banks. In contrast, the current study investigated a diverse cross-section of the population, including infants and children, and is more likely to be a realistic representation of the population.

In the Dominican Republic we found a high seroprevalence of hepatitis B, which was in agreement with a previous study (2). However, the Dominican Republic is atypical of the Caribbean, which is generally a low-endemic region (2). Typical of high-endemic countries, in the Dominican Republic a high seroprevalence was observed in early life, suggesting a vertical or horizontal mode of transmission. In addition, there was an increase for the adolescent and older age groups, emphasizing the impact of sexual transmission.

Brazil also showed a higher overall seroprevalence than the other countries in the study, except for the Dominican Republic. Brazil is a large country with a previously reported spectrum of HBV prevalence and carrier rates, with the highest values in the western Amazon region and the lowest in the south of the country (9, 10). As with other studies (1), we observed a high seroprevalence in Manaus, in the western Amazon basin.

FIGURE 1. Seroprevalence of hepatitis B in different age groups in countries of Latin America, 1996–1997

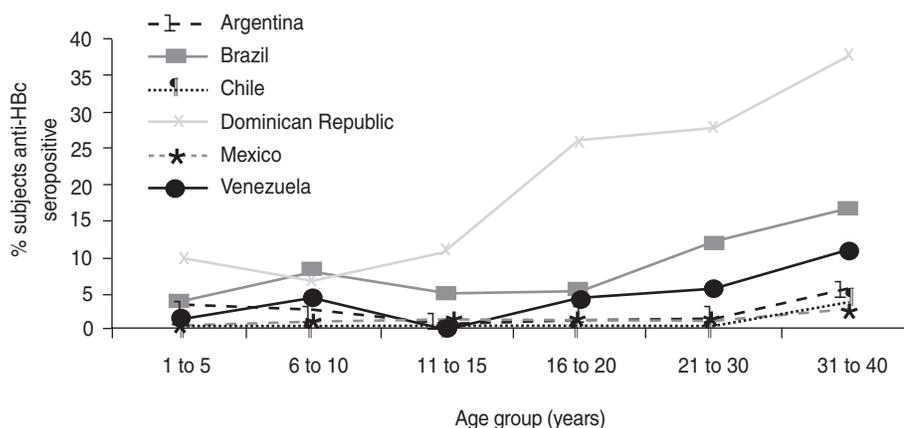


TABLE 4. Seroprevalence of anti-HBc antibodies analyzed for different socioeconomic groups in Latin America, 1996–1997

Socioeconomic level	Argentina			Mexico		
	No./TP ^a	%	95% CI	No./TP	%	95% CI
High	11/382	2.9	1.3–4.5	29/1 962	1.5	1.0–2.0
Medium	10/484	2.1	0.9–3.3	18/1 661	1.1	0.8–1.6
Low	10/588	1.7	0.7–2.7	27/1 589	1.7	1.1–2.3

Socioeconomic level	Brazil ^b		
	No./TP	%	95% CI
High/Medium	106/1 955	5.4	4.3–6.3
Low	182/1 698	10.7	9.2–12.2

^a No./TP = number of seropositive persons/total population in that socioeconomic group in that country.

^b Comparison of high/medium group with low group in Brazil, $P < 0.001$.

Hepatitis delta virus (HDV) is dependent on HBV for its replication, therefore HDV can only infect people who are simultaneously infected with HBV (coinfection) or who are already carriers of HBV (superinfection) (11). As a result, HDV seroprevalence tends to parallel that of HBV. Although HBV infection is largely perinatal, HDV is sexually transmitted in later life (12–16). HDV superinfection has been implicated as the etiological agent in a number of outbreaks of severe hepatitis, including in the upper Amazon basin in Brazil and Peru, the upper Orinoco basin in Venezuela and Colombia, and in western Colombia. Given the severity of hepatitis resulting from HDV infection, priority has been given to the immunization of all infants and newborns in hyperendemic regions, including the Amazon region (17). The largest such program was introduced in Brazil in 1989, and since then two-thirds of all children have completed a three-dose course of HBV vaccination as part of the WHO Expanded Programme on Immunization (1).

HDV has generally not been found in other regions of South America with

HBV prevalence rates similar to those in the Amazon region of Brazil. Recently, however, HDV infection appears to be increasing among high-risk groups in Buenos Aires and other large South American cities (2). If this trend continues, protection of adolescents against hepatitis B will be increasingly important in order to prevent HDV transmission.

HBV vaccination has been part of the WHO EPI since 1992 (3). Reports from countries outside Latin America clearly demonstrate that neonatal vaccination programs can produce a dramatic reduction in HBV seroprevalence in the infant population within just a few years (18–20). In Latin America, neonatal vaccination programs have been successfully implemented in areas of high endemicity in Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, Honduras, Mexico, Peru, Uruguay, and Venezuela (1, 21). The extensive awareness that persons in those areas have of the disease has contributed to the high levels of coverage. However, in the rest of Latin America, it appears there is a broad deficiency in knowledge about HBV, with the exception of such high-risk

groups as intravenous drug users (1). Given this lack of awareness of HBV, along with the impact that sexual transmission has on seroprevalence rates, as shown in this study, the persons most at risk in many areas of Latin America are those ranging in age from infancy to young adulthood. Studies in Italy have demonstrated the benefits of vaccinating both neonates and 12-year-olds (22). This dual-target vaccination strategy will lead to the coverage of the population between the ages of 0 and 24 years within 12 years, after which time only neonates will need to be vaccinated.

This strategy has cost benefits, as well as a rapid impact on the disease burden. Furthermore, the WHO has recommended combining HBV vaccines with mandatory childhood vaccines, such as the diphtheria, tetanus, and pertussis (DTP) vaccine (23). DTP vaccination has reached greater than 80% coverage globally, so combining HBV with it could rapidly expand HBV coverage. The availability of DTPw-HBV and DTPw-HBV-Hib combination vaccines will facilitate the implementation of hepatitis B vaccination programs and also significantly reduce the delivery and storage costs associated with childhood vaccination programs (24). Furthermore, having to give fewer injections will reduce the discomfort to infants, increase acceptance among parents and health care workers, and lead to improved compliance (23, 24).

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RESUMEN

La seroprevalencia de hepatitis B en América Latina

Se investigó la seroprevalencia de hepatitis B en más de 12 000 sujetos en seis países de América Latina: Argentina, Brasil, Chile, México, República Dominicana y Venezuela. Cada una de las poblaciones estudiadas fue estratificada por edad, sexo y nivel socioeconómico. Se hicieron determinaciones de anticuerpos contra el antígeno nuclear del virus de la hepatitis B (anti-HBc) con el fin de detectar la infección. La seroprevalencia general más alta se encontró en la República Dominicana (21,4%), seguida del Brasil (7,9%), Venezuela (3,2%), Argentina (2,1%), México (1,4%) y Chile (0,6%). En todos los países se encontró un aumento de la seroprevalencia en personas de 16 años de edad o mayores, lo cual indica que la transmisión sexual es la principal fuente de infección. También se hallaron tasas de seroprevalencia elevadas en personas jóvenes en la República Dominicana y el Brasil, fenómeno que apunta hacia la vía de transmisión vertical.