HEPATITIS A IN LATIN AMERICA: A CHANGING EPIDEMIOLOGIC PATTERN

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Abstract. In a multicenter study, hepatitis A virus (HAV) seroprevalence was surveyed in six countries in Latin America in which in 12,000 subjects were stratified for age. The highest rates of seroprevalence were recorded in the Dominican Republic (89.0%) and Mexico (81.0%), with lower rates in Brazil (64.7%), Chile (58.1%), Venezuela (55.7%), and Argentina (55.0%). The seroprevalence of HAV in children between 1 and 5 years of age was less than 50%, except in the Dominican Republic. In the 5–10-year-old age group, seroprevalence rates have also decreased compared with previous reports. This suggests that the epidemiology is shifting from high to intermediate endemicity, with the population susceptible to HAV infection shifting from children to adolescents and adults. Furthermore, data from Brazil, Argentina, and Mexico show that HAV seroprevalence is significantly lower in people living in medium and high socioeconomic conditions. This study suggests the need for appropriate vaccination programs to be implemented targeting children, adolescents, and adults, particularly in higher socioeconomic groups.

Hepatitis A virus (HAV) has a worldwide distribution and is the most frequent etiologic agent in cases of viral hepatitis in Latin America.1-5 The major route of transmission is the fecal-oral route, with hygiene levels and living conditions being major influences on the incidence of the disease. Different patterns of the prevalence of antibody to HAV have been described, with variations reflecting the level of economic development.6 In areas of high endemicity, 90% of the children are infected by the age of 10. Infection is largely asymptomatic and hepatitis A is not a clinical problem.7 In areas of intermediate endemicity, a seroprevalence of 90% is not reached until early adulthood.8 In developed countries, the endemicity is low. A high prevalence of antibodies is found only in older cohorts possibly reflecting historical exposure. These patterns may vary within countries, and in countries or regions with lower endemicity hepatitis A outbreaks can be frequent.6

Improvements in public health programs and sanitary conditions have had an impact on the epidemiologic pattern of HAV infection6,9 in developing economies. Thus, previous studies showing a virtual universal infection to HAV before the age of 10 in developing areas2,4,10-12 may no longer be valid for Latin America. Furthermore, information on seroprevalence patterns of HAV infection stratified by age, socioeconomic conditions, and social patterns in different Latin American countries is scattered. We have therefore carried out a regional seroprevalence study in six Latin American countries. The data will help to identify susceptible populations and allow recommendations for prevention of hepatitis A in this region.

METHODS

Study population. This was a multicenter, cross-sectional study including subjects from six different Latin American countries: Mexico (where the study was conducted in cities in the northern, central, and southern), Chile (North Santiago de Chile), Brazil (Rio de Janeiro, Manaus, Porto Alegre and Fortaleza), the Dominican Republic (three centers in Santo Domingo), Venezuela (Caracas), and Argentina (Buenos Aires and Cordoba). The study was conducted between June 1996 and November 1997. Subjects were of both genders, age stratified between 1 and 40 years. Written informed consent was given by the subjects, or the subject’s parents/guardians. The study received local ethical approval in each country and was conducted according to Good Clinical Practice and the Declaration of Helsinki.

For all study sites there was a limit of 1 subject per household or family to prevent clusters. The study populations were recruited as follows.

Mexico. The sampling was a two-stage cluster sampling with primary sample units made up of Federal Entities randomly selected in each region and the secondary sample units selected in urban areas belonging to each state. The sample size was distributed proportionately throughout the entire population of each region and sub-age group. Selection of the Federal Entities was carried out with a random sample without replacement and with proportionate probability to the total population in the 1–40-year-old age groups of each region.

Chile. Subjects were recruited among randomly selected households from northern Santiago de Chile. The characteristics of the household sampled corresponded very well with those of the last census of the metropolitan population of Santiago de Chile (an average of 4–5 subjects per household, more than 92% of the households had access to potable water, > 95% of all households were equipped with a sewage system, and 4 of 5 women had a basic education but only 1 of 5 had more than 12 years of education).

Venezuela. The study population was recruited from 8 different places in Caracas: preschool nurseries, colleges, public schools, and companies randomly selected and willing to participate.

Brazil. The study population was recruited in various outpatient clinics attached to public and private hospitals located mainly in poor and middle class areas. The higher socioeconomic group (3%) was recruited in first-class economic schools.

Argentina. Study subjects were recruited among people
attending ambulatory primary health care centers attached to three public hospitals.

**Dominican Republic.** The study population was recruited from three health care centers where a mixed population from a low socioeconomic background attended health clinics for regular checkups.

Demography, social class, type of community, current health status, and relevant medical background were recorded on a questionnaire. Socioeconomic groups were defined according to local scales (based on income, tap water provision, sewage system, refrigerator, electric power, number of people per room). In Argentina and Mexico the Bronfman scale was used, while in Brazil a local scale was used. In Venezuela and Chile all subjects were from the low or low-medium socioeconomic groups, while in the Dominican Republic people were recruited only from the low socioeconomic group.

**Serology.** Five to ten milliliters of blood were drawn from all subjects and sera were stored at −20°C. Antibodies against hepatitis A were detected using a commercially available enzyme immunoassay kit (HAVAB EIA; Abbott Laboratories, Abbott Park, IL). Antibodies to HAV were detected at the Instituto Nacional de Diagnóstico y Referencia Epidemiológicos (Mexico City, Mexico) for samples from Mexico and Venezuela, at the Laboratorio de Gastroenterología, Hospital Clínico Universidad de Chile (Santiago de Chile, Chile) for samples from Chile, at the Centro de Tecnología en Salud Pública, Universidad Nacional de Rosario (Rosario, Argentina) for samples from Argentina and Dominican Republic, and at the Laboratório de Análises Clínicas Carlos Lieberenz (Rio de Janeiro, Brazil) for samples from Brazil. All laboratories were validated and subjected to quality control.

**Statistical analysis.** The study populations were stratified according to country, gender, age, and socioeconomic group. Data was recorded on individual case report forms, entered into Dbase IV (Borland International, Inc., Scotts Valley, CA), and descriptive statistical analysis was performed using SPSS (SPSS, Inc., Chicago, IL) and Epi-Info version 6.04 (Centers for Disease Control and Prevention, Atlanta, GA). Comparative statistical analyses were performed using Fisher’s exact test.

**RESULTS**

**Demographics.** A total of 12,085 subjects were enrolled from Mexico (5,262), Chile (496), the Dominican Republic (478), Brazil (3,879), Venezuela (495), and Argentina (1,475). A total of 328 subjects were subsequently excluded because of hemolysis of their blood sample or missing information on the subject sheets. This resulted in the following study populations: 5,212 in Mexico, 496 in Chile, 473 in the Dominican Republic, 3,653 in Brazil, 469 in Venezuela, and 1,454 in Argentina. The gender composition of each age group is given in Table 1.

**Gender and age distribution in the different countries.** Table 2 shows the overall age specific anti-HAV seroprevalence by country. The anti-HAV seroprevalence rates were highest in the Dominican Republic and Mexico and lowest in Brazil, Chile, Venezuela, and Argentina. The age-stratified prevalence per country shows that with the exception of the Dominican Republic, all children in the 1–5-year-old age range had seroprevalence rates around or below 40%, being as low as 11% in Chile (Table 2). In the Dominican Republic, 63.4% of the children in this age range already had serum markers against HAV. The overall pattern is that of intermediate endemicity in all countries except the Dominican Republic, where the pattern is of high endemicity and Mexico, where the pattern is between high and intermediate endemicity. In Chile, we observed a more than two-fold increase in anti-HAV seroprevalence between the 6–10- and 11–15-year-old age groups. In the other countries, the increase over the age groups is more linear. Table 3 shows the gender-specific anti-HAV seroprevalence rates stratified per age group for each of the 6 countries.

**Socioeconomic influences.** Data from the countries with the largest study populations were stratified into high, medium, and low socioeconomic levels (Figure 1). We pooled the data from the high and medium socioeconomic groups in Brazil due to low recruitment in the highest group. In all three countries differences were found between low and higher socioeconomic groups, with significantly higher anti-HAV seroprevalence rates in the lower socioeconomic groups (Table 4).

**DISCUSSION**

Because hepatitis A infection is often asymptomatic in children and there is substantial under-reporting of cases, seroprevalence studies allow a more exact determination of existing immunity, and thus susceptibility, of parts of the population to hepatitis A. The six countries surveyed have very young populations with ±30% of their populations less...
than 15 years old and population growth rates between ± 1.3% for Argentina, Brazil, and Chile and ± 1.7% for the Dominican Republic, Mexico, and Venezuela.

Although the study populations surveyed were heterogeneous, the shift in HAV seroprevalence towards intermediate endemicity was seen in all countries except the Dominican Republic, which is still an area of high endemicity. Nearly 90% of the children in this country are infected by the age of 10. This is likely to be a reflection of the recruitment exclusively from low income groups, but since the gross domestic product (GDP) per capita of the Dominican Republic is the lowest of the 6 countries surveyed ($4,700), the high endemicity rates may be valid for large parts of the population. Economic improvements over the last 10 years will be reflected in the seroprevalence rates in younger age groups. The lowest rates are seen among 1–5- and 6–10-year-old individuals in Chile, which has the highest GDP per capita, $11,600. Data from Brazil, Venezuela, Argentina, and Mexico show seroprevalence rates (30–60%) in those age groups, typical for intermediate endemicity. Their respective GDPs per capita are $6,300, $8,300, $9,700, and $7,700. The steep increase in anti-HAV seroprevalence between the 6–10- and 11–15-year-old age groups observed in Chile could be explained by a rapid and more sudden improvement in sanitation infrastructure. A detailed stratification per gender did not reveal gender-related differences in seroprevalence.

Historical data indicate that this shift to an intermediate seroprevalence pattern in Latin America coincides with economic development. In 1982, seroprevalence studies in Mexico showed antibodies in 75% of the children less than 5 years old, and almost 90% by the age of 10. By 1987, seroprevalence rates had decreased to 50% in the 1–5-year-old age group, and there is currently a level of 40% in this age group. Similarly, studies conducted in 1989 in Venezuela and Chile illustrate a similar evolution.

Our data show lower seroprevalence rates in the younger age groups compared with older children and adolescents and higher seroprevalence rates in people living in less favorable socioeconomic conditions. This is consistent with the rapid economic development of many Latin American countries with fast growing populations. One consequence is that the asymptomatic children remain a common source of spreading the disease, mainly to older susceptible subjects, in whom disease is more serious. In addition, infection in children appears to have more serious consequences than previously thought. A recent study showed that 64% of fulminant hepatic failure cases requiring liver transplantation in Argentinean children was linked to HAV infection. Similar data were obtained shown in Brazil and Chile.

Regions of intermediate endemicity are also often characterized by a coexistence of low seroprevalence in urban areas and high endemicity in rural zones. Typical for large cities is that low and high socioeconomic populations reside in close geographic proximity to each other. This creates favorable conditions for outbreaks of hepatitis A. Their risk

<table>
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<tr>
<th>Table 2</th>
<th>Age distribution of hepatitis A (HAV) seroprevalence in Latin America</th>
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<tbody>
<tr>
<td>Age groups (years)</td>
<td>Mexico % (n)</td>
</tr>
<tr>
<td>1–5</td>
<td>40.5 (850)</td>
</tr>
<tr>
<td>6–10</td>
<td>37.3–43.7</td>
</tr>
<tr>
<td>11–15</td>
<td>68.6 (866)</td>
</tr>
<tr>
<td>16–20</td>
<td>65.9–71.9</td>
</tr>
<tr>
<td>21–30</td>
<td>88.0 (847)</td>
</tr>
<tr>
<td>31–40</td>
<td>85.9–90.1</td>
</tr>
<tr>
<td>All ages</td>
<td>97.8 (767)</td>
</tr>
</tbody>
</table>

* Values in parentheses are sample sizes. 95% confidence intervals are given below each percentage.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Gender distribution of hepatitis A (HAV) seroprevalence in Latin America</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age groups (years)</td>
<td>Mexico % (n)</td>
</tr>
<tr>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>1–5</td>
<td>39.8</td>
</tr>
<tr>
<td>6–10</td>
<td>67.2</td>
</tr>
<tr>
<td>11–15</td>
<td>84.5</td>
</tr>
<tr>
<td>16–20</td>
<td>92.6</td>
</tr>
<tr>
<td>21–30</td>
<td>96.5</td>
</tr>
<tr>
<td>31–40</td>
<td>98.2</td>
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</tbody>
</table>
could be compared with that of travelers from a low endemic country to intermediate and high endemic countries with a difference in continuous exposure. Previous experience has shown that strategies based on hygiene management are insufficient to prevent the spread of infection during outbreaks. Rapid vaccination of the community in these cases is the most effective means of protecting the population and controlling outbreaks.\textsuperscript{21,22} Recently, the economic burden of a community-wide hepatitis A outbreak was calculated in Puglia, Italy.\textsuperscript{23} Costs were calculated to be 662 US $ for the individual patient, whereas total societal costs amounted to 24.45 million US $ for the 5,889 cases of hepatitis A monitored during this outbreak in Italy. Currently, a study surveying mortality and morbidity caused by hepatitis A virus infections is ongoing and a health economics study is planned in several Latin American countries.

In conclusion, our data illustrate a change in several Latin American countries from a high towards an intermediate endemicity pattern of HAV seroprevalence in specific groups such as high/medium income urban groups. This shift leaves large groups of the population at risk of infection and can result in a paradoxical increase in clinical cases of hepatitis A and outbreaks of disease.

Vaccination strategies should therefore be reviewed. Vaccination against hepatitis A offers a reliable tool both for individual protection and control of outbreaks. Vaccination campaigns could target children as early as the first or second year of life since they are an important primary source of infection for parents and caretakers, and since the disease in children seems to undergo a severity shift, indicated by the fact that there are recent reports of fulminant hepatic failure following HAV infection requiring liver transplantation.\textsuperscript{17} A second vaccination target could be adolescents, possibly in combination with the hepatitis B vaccine, which would improve the cost-effectiveness for both HAV and HBV vaccination. A third target for vaccination should be adults from the medium and higher socioeconomic groups of society since they are continuously exposed to infection. Finally, hepatitis A vaccination is the most important public health tool to stop community-wide or common source HAV outbreaks since immunoglobulins offer incomplete protection for a limited time.

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\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Seroprevalence (%) of antibody to hepatitis A virus according to socioeconomic groups, stratified per age group, in Mexico, Argentina, and Brazil. Vertical bars indicate the 95\% confidence intervals.}
\end{figure}
Hepatitis A in Latin America

| Table 4 |
|------------------------|-----------------|-----------------|
|                        | **Mexico**      | **Argentina**   | **Brazil**    |
|                        | **OR** | **95% CI** | **P** | **OR** | **95% CI** | **P** | **OR** | **95% CI** | **P** |
| Low vs medium           | 1.49   | 1.23–1.81  | <0.001 | 1.26   | 0.98–1.63  | 0.06  | 2.19   | 1.90–2.53  | <0.001 |
| Medium vs high          | 1.35   | 1.15–1.59  | <0.001 | 2.24   | 1.68–2.97  | <0.001 | NA     | NA         | NA     |

*OR* = odds ratio; *CI* = confidence interval; *NA* = not applicable. The sample size in the high socioeconomic group in Brazil was too low for this analysis.

### References


