

## RISK FACTORS AND PREVALENCE OF ANTIBODIES AGAINST HEPATITIS A VIRUS (HAV) IN CHILDREN FROM DAY-CARE CENTERS, IN GOIANIA, BRAZIL

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### SUMMARY

A seroepidemiologic survey about hepatitis A virus (HAV) infection was carried out in a group comprising 310 children, ranging in age from 3 months to 9 years, from day-care centers, in Goiania, a middle sized city in the central region of Brazil. The biomarkers employed in the investigation of previous infection include total IgG and IgM anti-HAV antibodies, and for the detection of more recent infection, IgM anti-HAV antibodies were analyzed. The study was performed in 1991 and 1992. According to the results, 69.7% of the children presented total IgG/IgM anti-HAV antibodies, with 60% of the group in the age range of 1 to 3 years.

Among 10 day-care centers analyzed, the prevalence of the biomarker IgM anti-HAV was 3.2%, with an uniform distribution of the cases in the group of children ranging in age from 1 to 4 years. Multivariate analysis was performed to investigate the sociodemographic factors that could influence the results. It was verified that the risk for the infection increased with the length of the attendance in the day-care centers, i.e., the risk for children with attendance of one year or more was 4.7 times higher, when compared with children with one month attendance (CI 95% 2.3-9.9).

According to the results, hepatitis A is an endemic infection in day-care centers in the study area. The length of attendance in the day-care settings was demonstrated to be a risk factor for the HAV infection. Such findings suggest that if hepatitis A vaccination becomes available as a routine policy in our region, the target group should be children under one year. Moreover, those children should receive the vaccine before they start to attend the day-care centers.

**KEYWORDS:** Hepatitis A survey; Seroepidemiology; Day-care children.

### INTRODUCTION

Hepatitis A virus (HAV) infection is a public health problem in several regions of the world. High prevalence for the infection has been associated with low socioeconomic conditions of the population<sup>7,11,16</sup>. In developed countries, the improvement of sanitary and hygienic programs has been considered as the main cause for the decrease in the prevalence of HAV infection<sup>7,32,35</sup>. However,

such procedure has been considered as a paradox, because it delays the exposure of the population to the virus, and the infection seems to be more severe in older individuals<sup>7,11,22,35</sup>.

Seroepidemiologic surveys have been accomplished in several different countries. It has been demonstrated

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that the prevalence of antibodies anti-HAV in human population ranges from 1.6% (as it has been found in people from Iceland with ages under 20 years)<sup>5</sup> to 90%, as demonstrated in children from India with ages between 5 and 10 years<sup>20</sup>.

In Brazil, epidemiologic investigations have shown high levels for the prevalence of anti-HAV antibodies in children belonging to less favored socioeconomic classes. Such studies have demonstrated that in São Paulo<sup>20</sup>, the prevalence of anti-HAV antibodies in the study groups was 75%, while levels ranging from 59.4% to 83.6%, have been found in groups from the Amazon region<sup>3</sup>. In Rio de Janeiro, the prevalence of 71.4% has been found in a study group<sup>1</sup>.

In the several groups of children analyzed, it has been also observed that the attendance to day-care centers is associated to the transmission of the hepatitis A infection<sup>2,13,34</sup>. The life style and the poor hygienic habits developed in such environments, seem to facilitate the dissemination of the virus, propagating the infection to other children in the facilities, and also to relatives and neighbors<sup>12,16,21,24</sup>.

This study comprises the first seroepidemiologic investigation about the HAV infection biomarker (anti-HAV) in the central-west region of Brazil. The objectives of this research are: to determine the prevalence of anti-hepatitis A virus antibodies (total anti-HAV and IgM anti-HAV) in day-care children (since they are considered the risk group for the infection), and to assess the sociodemographic risk factors that are associated to the seropositivity of HAV infection.

## MATERIAL AND METHODS

### Population Study Group

The study group includes children ranging in age from three months to 9 years (mean 3.6 years; SD=2.0). During the period between May 1991 and April 1992, such group was attending public day-care centers, in Goiania, Goias, Brazil. Using simple probabilistic sampling, 310 children attending ten different day-care centers were chosen and analyzed. All the ten centers were giving assistance to similar number of children. All the children were in the same age-range and belonged to families with low socioeconomic standards. The size of the sample was calculated according to the prevalence of anti HAV antibodies previously estimated in 60% (error=10%).

A standard questionnaire was applied to the parents or relatives of the children. The data obtained included

identification, parents educational level, family income, number of people in the same home, type of home, availability of treated water filter and sewage, previous hepatitis/jaundice history, and the length of attendance in the day-care centers.

### Serological tests

Five (5) ml blood samples were collected from each children by venocubital puncture. Serum samples were analyzed for total anti-HAV antibodies, using a competitive enzyme-immunoassay (ELISA) test<sup>31</sup>. When positive results were obtained for this test, the samples were also analyzed for IgM anti-HAV antibodies, using a direct ELISA test. The HAV antigen used in the tests was prepared in our laboratory by culturing the sample HM175 in FRhK-4 cells<sup>30</sup>. Immunobiological reagents were gently provided by the Centro de Referencia Nacional para Hepatites Virais - Fundação Oswaldo Cruz, Rio de Janeiro.

### Statistical Analysis

Univariate and multivariate analysis were used to evaluate the association between the presence of anti-HAV antibodies and sociodemographic variables. Differences between proportions were compared using Chi-Square test ( $X^2$ ), and Mantel-Haenzel test was used to calculate the tendencies ( $X^2$ )<sup>17</sup>. The relative risks were estimated with a confidence interval of 95% (prevalence ratio CI 95%). Using multivariate analysis, the relative risk was calculated for the HAV biomarker and the risk factors, correcting for all the potential variables<sup>8</sup>. Sensitivity and specificity of the test were evaluated by comparing information about previous hepatitis/jaundice history and the presence of the HAV biomarker<sup>9</sup>.

## RESULTS

In the group of children analyzed in this study, the prevalence for total anti-HAV biomarkers was 69.7% (216/310). Table 1 shows the distribution of the anti-HAV biomarkers and their relationship with demographic variables and risk factors. Similar results were obtained for the prevalence of the biomarkers in boys and girls, with no significant difference between genders. A crescent (positive) tendency was observed when the prevalence of the biomarker was analyzed according to the age. The prevalence ranged from 9.1%, in the group of children with ages under one year, to 86.7%, in the group of children with ages equal or above 7 years. A significant statistical difference was demonstrated for the distinct groups ( $x^2=34.8$ ;  $p<0.001$ ).

A slight decrease in the tendency of prevalence for total anti-HAV biomarkers was observed for the study

group according to the family income. However, such decrease was not statistically significant. Since a very small fraction of the sample was in the range above five minimum salaries, the statistical power for this fraction was hampered. No significant statistical difference (correlation) was observed when variables, such as parents educational level, number of people in the same home, availability of treated water and sewage were analyzed according to the prevalence of anti-HAV biomarkers (data not shown).

The availability of filters at home, and the length of attendance in the day-care centers were demonstrated to be associated with an increased prevalence for the total anti-HAV biomarkers (Table 1). However, after correcting the data for confounding variables, such as age and

gender, only the time attendance in the day-care nurseries showed to be statistically associated with the presence of the biomarker. It was demonstrated that children attending the nurseries during periods above one year, presented a risk, for previous exposure, 4.7 (CI 95%, 2.3-9.9) times higher, when compared to children attending the nurseries during periods under one month (Table 2). Such findings were demonstrated to be independent of age and gender.

Figure 1 shows that more than 60% of the three years old children were immune to the HAV. Figure 1 also shows the presence of the IgM biomarker in 3.2% of the children, indicating, therefore, the existence of recent infection. It is important to emphasize that the group comprising ten children bearing the IgM biomarker were

**TABLE 1**  
Prevalence of total anti-HAV biomarker according to socioeconomic characteristics of the study group, Goiania, Brazil, 1991-1992.

CHARACTERISTICS	No.	POSITIVE (%)	
Gender			
Male	171	119 (69.6)	$X^2 = 0.01$ $p=0.9$
Female	139	97 (69.8)	
Age Range (Years)			
< 1	11	1 (9.1)	$X^2_1 = 34.8$ $p < 0.001$
1-3	155	93 (60.0)	
4 - 6	129	109 (84.5)	
7 - 9	15	13 (86.7)	
Family Income*			
< 1 Minimum Salary	36	26 (72.2)	$X^2_1 = 0.38$ $p = 0.5$
1 - 5 Minimum Salaries	263	183 (69.6)	
> 5 Minimum Salaries	4	2 (50.0)	
Availability of Water Filter at Home			
Yes	254	184 (72.4)	$X^2_1 = 5.1$ $p = 0.02$
No	56	32 (57.1)	
Attendance in the Day-Care Center **			
≤ 1 month	60	28 (46.7)	$X^2_1 = 32.0$ $p < 0.005$
> 1 month - 11 months	85	51 (60.0)	
≥ 1 year	157	131 (83.4)	

\* 7 children without information about family income

\*\* 8 children without information about length of attendance on the day-care centers

**TABLE 2**

Risk factors associated to seropositivity of total anti-HAV in children from day-care centers, in Goiania, Brazil, 1991-1992.

RISK FACTORS	TOTAL	PR(CI 95%)	PR*(CI 95%)
Availability of Water Filter at Home			
No	56	1	1
Yes	254	2.0(1.0-3.7)	0.5(0.2-1.0)
Attendance in the Day-Care Center **			
≤ 1 month	60	1	1
> 1 - 11 months	85	1.7(0.8-3.5)	1.9(0.9-4.1)
≥ 1 year	157	5.8(2.8-11.8)	4.7(2.3-9.9)

\* Prevalence Ratio (PR) corrected for age and gender

\*\* 8 cases without information were excluded

assymptomatic for the infection and were distributed in different day-care centers. Information about the seropositivity for the HAV were supplied to the administration of the day-care centers.

A comparison between the hepatitis/jaundice history, supplied by the group, and the presence of anti-HAV antibodies, used in this case as "golden-standard", is presented in Table 3. The sensitivity of the hepatitis/jaundice history was sufficient to identify only 18.0% of the positive cases. Nevertheless, 86.7% of the individuals with negative hepatitis/jaundice history showed negative results for the HAV biomarker (specificity).

It was demonstrated that 75.5%(37/49) of the individuals with positive hepatitis/jaundice history exhibited positive results for the HAV biomarker, indicating a high positive predictive value (PPV) for the test. It means that among such group, 12 positive answers were indeed false-positive. However, the negative predictive value for the test was 31.7% (78/246), indicating that a negative answer for the questionnaire, or the absence of symptoms, does not really indicate the absence of the biomarker. 68.3% (168/246) of the negative answers to the hepatitis/jaundice questionnaire were considered as false-negatives, when compared to the results obtained with the serology. The prevalence of previous hepatitis/jaundice history was 16.6%, while the prevalence of the total anti-HAV biomarker was 69.7%.

## DISCUSSION

According to the results, a high prevalence (69.7%) of anti-HAV antibodies was demonstrated in a group of

children attending day-care centers, in Goiania, Brazil. The length of attendance in the facilities showed to be an important risk factor for the seropositivity of the infection. Since the anti-HAV vaccine is not available in the public health programs of the country, the presence of the biomarker stands for acquired immunity induced by viral exposure.

From the group of eleven children with ages under 01 (one) year, only 01 (one) child, aged 03 (three) months, demonstrated total anti-HAV antibodies. This result suggests a passive antibody transference from the mother to the child<sup>4</sup>. The rest of the group comprised 10 (ten) children with ages above 06 (six) months. The presence of such biomarker in children under 06 (six) months

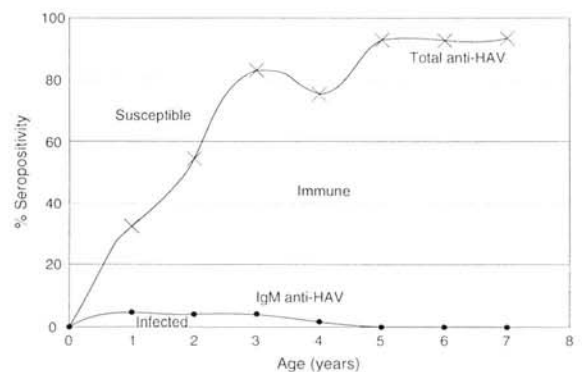


Fig. 1 - Prevalence of total anti-HAV antibodies and IgM anti-HAV antibodies according to age in children from day-care centers, in Goiania, Brazil.

TABLE 3

Prevalence of total anti-HAV antibodies and previous hepatitis/jaundice history in children from day-care centers, in Goiania, Brazil, 1991-1992.

HEPAT/JAUNDICE HISTORY*	SEROLOGY			VALIDITY INDICATORS
	POSITIVE	NEGATIVE	TOTAL	
Yes	37	12	49	S = 18% E = 86.7% PPV = 75.5% NPV = 31.7%
No	168	78	246	
Total	205	90	295	

S = Sensitivity; E = Specificity; PPV = Positive Predictive Value; NPV = Negative Predictive Value; Prevalence of seropositivity = 69.7%; prevalence of previous hepatitis/jaundice history = 16.6%.

\* 15 cases without information about hepatitis/jaundice history.

associated with negative results for IgM anti-HAV, was proposed to be due to passive transference of antibodies from the mother to the child<sup>18</sup>.

Almost 70% of the children aged less than 3 years showed positive results for the HAV biomarker. Furthermore, children who attended the day-care centers during periods equal or above one year showed a risk 4.7 times higher for the infection, comparing to those who were attending such places for one month. Several studies have suggested that in endemic zones, the HAV might be transmitted specially by children with the sub-clinical infection to their relatives and friends in the day-care centers<sup>10,24,26</sup>.

It was clearly demonstrated in our study that the prevalence of HAV infection increases according to age. Such finding has been verified by several epidemiological studies<sup>3,15,28,32,33</sup>, indicating, therefore, higher chances for virus exposure in older children. Similar results were found in a group of children, with low socioeconomic standards, in São Paulo<sup>20</sup>, Boca de Acre (Amazon)<sup>3</sup>, and also in children under 5 years old in Nova Iguaçu (Rio de Janeiro)<sup>1</sup>. An interesting difference can be noticed, when our results are compared to those obtained in children from Mexico<sup>25</sup>. Differences are observed specially in the prevalence of the infection in the group ranging in age from 1 to 3 years. While Mexican children showed a seropositivity of 38.3%, our children showed a seropositivity of 60%. However, similar results were obtained for children ranging from 4 to 6 years in both studies.

A negative association between the prevalence of the HAV infection and the educational level of the parents, was demonstrated in studies carry out in Taiwan<sup>6</sup> and Italy<sup>28</sup>. However, a statistically significant difference related to those variables could not be substantiated in our study. (Such difference was probably observed because the families in our study presented similar socio-economical levels, and did not differ substantially in their lifestyle).

The prevalence of the previous hepatitis/jaundice history was 16.6%, while the prevalence for the HAV infection biomarker was 69.7%. This observation could suggest that in the majority of the cases, the HAV infection is not characterized by jaundice. According to several authors, the virus is endemically transmitted from one individual to another, specially during the childhood, when the infection is generally unnoticed<sup>27</sup>. We observed that 75.5% of the children with previous hepatitis/jaundice history demonstrated the serological biomarker for the HAV infection. We consider that the previous history of the infection seemed to predict the HAV infection. A seroepidemiologic study carried out in a group of students from the public university of Rio de Janeiro, Brazil, showed a high PPV (87.5%) in the group of individuals with previous hepatitis history<sup>19</sup>.

Although this study was not designed to investigate the incidence of recent infection, the IgM biomarker was demonstrated in 3.2% of the population. All the positive cases (10 cases) were asymptomatic, and were equally distributed among the nurseries. Since the etiology and the mode of transmission of the disease are well recog-



nized, hepatitis A is an example of infection in which control measures can be empirically adopted during outbreaks. In developed countries, a single case of hepatitis A detected in a day-care setting is enough to lead the administration to immune globulin prophylaxis in the exposed children and in the staff<sup>23</sup>. The guidelines for hepatitis A vaccination are straightforward and such issue has been controversial during the last years. Vaccination at early ages may not yield long term protection. It may delay natural viral infection which seems to cause more severe clinical hepatitis<sup>22,35</sup>. If hepatitis A vaccination becomes available as a routine policy in our region, children under one year should be considered the target group, particularly before they start to attend day-care settings. However, we understand that this study is not sufficient to draw vaccine recommendations for the entire population in the region.

Our investigation shows the prevalence for the HAV immunity biomarker in a low income populational group. Since the vaccine containing the inactivated virus (HAVRIX<sup>tm</sup>)<sup>14</sup> is nowadays commercially available, further epidemiological studies become necessary to evaluate the level of HAV infection in children from different socioeconomic groups, and also to define the risk groups that will, in the future, undergo the vaccination in our country.

## RESUMO

### Fatores de risco e prevalência de anticorpos contra o vírus da hepatite A (VHA) em crianças de creche em Goiânia, Brasil.

Um estudo soropidemiológico para o vírus da hepatite A (VHA), investigando os marcadores de infecção passada (anti-VHA total - IgG e IgM) e infecção recente (anti-VHA IgM), foi realizado entre 1991 e 1992, em crianças de creche de Goiânia-Brasil central. Das 310 crianças com idade entre 03 meses e 09 anos, 69,7% mostraram soropositividade ao anti-VHA total, sendo 60%, na faixa etária entre 1 e 3 anos.

A prevalência do marcador anti-VHA IgM foi de 3,2%, visto em idade de 1-4 anos e com distribuição uniforme nas 10 creches estudadas. Entre as variáveis sócio-demográficas estudadas, apenas o tempo de frequência das crianças nas creches, igual ou superior a um ano, mostrou, em análise multivariada ajustada para idade, um risco 4,7 vezes maior quando comparado com o período de um mês (LC 95% 2,3-9,9).

De acordo com os resultados, a hepatite A é uma infecção endêmica no tipo populacional estudado e o tempo de frequência prolongado das crianças, nas creches

públicas, constitui um fator de risco para infecção ao VHA. Tais resultados sugerem que, uma vez que a vacina seja instituída na região, as crianças de creche devem recebê-la antes de um ano de idade, ou no mais tardar antes de ingressarem nas creches públicas.

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