0021-7557/11/87-03/213
Jornal de Pediatria

Shifting susceptibility to hepatitis A among children and adolescents over the past decade

Lenita S. Krebs,[1] Tani M. S. Ranieri,[2] Carlos O. Kieling,[3] Cristina T. Ferreira,[4] Themis R. da Silveira[5]

Abstract

Objectives: To estimate the prevalence of anti-hepatitis A virus (anti-HAV) antibodies in serum samples from children and adolescents obtained at two clinical pathology laboratories in the city of Porto Alegre, south of Brazil, and to compare findings to those of a study carried out in the 1990s.

Methods: In this cross-sectional study conducted between 2007 and 2008, 465 serum samples obtained from subjects aged 1-19 years were consecutively tested to determine the prevalence of total anti-HAV antibodies. Samples were provided by a public laboratory (group 1) that serves the Unified Health System exclusively, meant to represent the lowest socioeconomic strata, and by a private laboratory (group 2), meant to represent the higher socioeconomic classes. Tests were performed at a single laboratory using commercially available electrochemiluminescence kits. Antibody levels ≥ 20 UI/L were considered positive.

Results: The seroprevalence of anti-HAV in group 1 was 37.6%. The percentage of anti-HAV reactivity increased from 19.4% in the 1-to-4 group to 54.1% in the 15-to-19 group. In group 2, overall anti-HAV positivity was 46.1% and was inversely correlated with age, declining from roughly 50% in the youngest groups to 29.1% in the 15-to-19 group. Comparison of sample findings to those reported in a 1990s study showed a significant reduction in anti-HAV prevalence among 5-to-9-year-olds in group 1 ($p = 0.03$).

Conclusions: The results suggest that the endemicity of hepatitis A in Porto Alegre has been declining over the past decade, and that children and adolescents, particularly those in the lowest socioeconomic strata, are more susceptible to the disease.

J Pediatr (Rio J). 2011;87(3):213-218: Hepatitis A virus, hepatitis A prevalence, hepatitis A epidemiology.

Introduction

Hepatitis A remains a major public health issue worldwide. Although its course is generally self-limited, the disease can vary widely in intensity, with severe forms sometimes occurring, and is a cause of significant morbidity in developed and developing countries alike.[1] Transmission occurs mainly through contact with infected individuals, by the fecal-oral

1. Mestranda, Programa de Pós-Graduação em Saúde da Criança e do Adolescente, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil. Médica, Núcleo de Pesquisa em Vacinas (Nuclivac), Hospital de Clínicas de Porto Alegre (HCPA), UFRGS, Porto Alegre, RS, Brazil. Médica, Secretaria Estadual de Saúde do Rio Grande do Sul (SESRS), Porto Alegre, RS, Brazil.
2. Enfermeira sanitarista. Coordenadora, Núcleo de Doenças Transmissíveis, Divisão de Vigilância Epidemiológica, SESRS, Porto Alegre, RS, Brazil.
3. Mestre. Médico, Serviço de Pediatria, HCPA, UFRGS, Porto Alegre, RS, Brazil.
4. Doutora. Médica, Serviço de Pediatria, HCPA, UFRGS, Porto Alegre, RS, Brazil.
5. Doutora. Médica. Professora, Faculdade de Medicina, Universidade Luterana do Brasil, Canoas, RS, Brazil.

Financial support: Laboratório Sanofi-Pasteur and Fundo de Incentivo a Pesquisa e Eventos do Hospital de Clínicas de Porto Alegre.

Lenita Simões Krebs has participated as a sub-investigator in studies on vaccines manufactured by Wyeth and GlaxoSmithKline, and also in a conference sponsored by Sanofi-Pasteur. Currently, the author participates as a sub-investigator in a hepatitis A cost-effectiveness study sponsored by Sanofi-Aventis.
Tani Maria Schilling Ranieri has participated as a sub-investigator in studies on vaccines manufactured by Wyeth and GlaxoSmithKline. Currently, the author participates as a sub-investigator in a hepatitis A cost-effectiveness study sponsored by Sanofi-Aventis.
Carlos Oscar Kieling has participated as a sub-investigator in studies on vaccines manufactured by Wyeth, GlaxoSmithKline, and Roche.
Cristina Targa Ferreira has participated as a sub-investigator in studies on vaccines manufactured by GlaxoSmithKline, Merck, and Roche.
Themis Reverbel da Silveira has participated as an investigator in studies on vaccines manufactured by Wyeth, GlaxoSmithKline, and Roche.
The authors declare that the Sanofi-Pasteur laboratory did not participate in any of the study phases, e.g. research planning, data collection, analysis or interpretation, report writing, or in the decision to submit the paper for publication.

Suggested citation: Krebs LS, Ranieri TM, Kieling CO, Ferreira CT, da Silveira TR. Shifting susceptibility to hepatitis A among children and adolescents over the past decade. J Pediatr (Rio J). 2011;87(3):213-218.

Manuscript submitted Nov 08 2010, accepted for publication Mar 02 2011.

doi:10.2223/JPED.2088

route, or through ingestion of contaminated water or food, particularly produce (fruits and vegetables) and bivalves.[2-4] Several characteristics of the hepatitis A virus (HAV), such as environmental stability (particularly when in association with organic matter) and resistance to low pH conditions and heat, favor waterborne and foodborne transmission of the virus, and also account for detection of the virus in background water and sewage samples.[3] Even in countries where hepatitis A is considered non-endemic, evidence suggests circulating HAV, possibly introduced by travelers, in a significant number of sewage samples.[5] Transmission by other routes, such as percutaneous or parenteral, has been reported,[3,6] but occurs far less frequently due to the low viral load in the bloodstream.[7]

Such factors as changes in the worldwide epidemiology of hepatitis A, reflecting the growth of a susceptible population,[8,9] and the availability of effective vaccines[1,2] have renewed interest in the disease, highlighting the need for a more precise understanding of this new reality so that prevention strategies may be defined.[10,11] Serology studies conducted in Brazil have shown that the endemicity of hepatitis A is shifting in most of the country's regions, with significantly lower anti-HAV antibody seroprevalence rates among children and adolescents,[12-15] particularly those in higher socioeconomic strata.[12,14,15] In Northern Brazil[12] and in some isolated communities in other regions, however,[16-18] prevalence is still significantly above the 65% national average (as estimated by a study conducted in 1996-1997).[12]

In the mid-1990s, Ferreira et al.[14] reported the coexistence of several nearby regions with heterogeneous anti-VHA antibody seroprevalence patterns in the Brazilian city of Porto Alegre, state of Rio Grande do Sul. In this setting, susceptible adolescents and adults living of higher socioeconomic classes are at risk of exposure to circulating HAV, which predisposes to outbreaks in the community and their potentially serious consequences.[1] The present study sought to ascertain the seroprevalence of anti-HAV antibodies in a group of children and adolescents from two distinct socioeconomic strata in Porto Alegre and compare findings with those reported in the aforementioned 1990s study, outlining any shifts in the epidemiology of hepatitis A that may have occurred in the city over the past decade.

Methods

Patients

A cross-sectional study was conducted between April 2007 and January 2008 to ascertain the total anti-HAV prevalence in a group of children and adolescents (aged 1-19 years) from the city of Porto Alegre, Brazil. A convenience sampling strategy was chosen for the study, using serum samples obtained from patients of two clinical pathology laboratories in Porto Alegre serving very distinct populations: a public laboratory that only serves patients within the Unified Health System framework (group 1), chosen to represent the lower socioeconomic strata; and a private laboratory, in which patients were screened according to a strategy meant to ensure enrollment of individuals from higher socioeconomic strata (group 2): patients were selected when they had paid the full cost of all tests performed out-of-pocket, or when they were covered by high-cost family or individual health insurance plans, as suggested by the laboratory itself.

Both facilities provided residual aliquots of serum samples that would otherwise have been discarded. Subjects were enrolled consecutively.

A total of 501 subjects between the ages of 1 and 19 were included, from both facilities. Thirty-six subjects were excluded: two due to insufficient samples, nine due to duplicate enrollment, five due to insufficient age (< 1 year) and 20 who did not live in Porto Alegre. The final sample thus consisted of 222 subjects in group 1 and 243 in group 2.

Logistics

Each of the two laboratories assigned an employee to screen potential subjects and provide information required for the study. Samples taken from subjects who qualified after screening were frozen at -20 °C for later analysis of compliance with criteria for selection and inclusion. Control mechanisms for participant identification were established to prevent individuals from being included more than once in the sample. After compliance with the selection criteria was confirmed, subjects were included in the study sample according to the quota set for each age range.

All serum samples were tested for anti-HAV antibodies at a single laboratory, using commercially available electrochemiluminescence immunoassay kits (Elecsys Anti-HAV, Roche Diagnostics). Samples with an antibody concentration ≥ 20 UI/L were considered reactive (i.e. indicative of prior contact with viral antigens) and those with antibody levels < 20 UI/L were considered negative. Results were made available on the laboratory website and collected by the lead investigator (LSK) through a password-protected interface.

Ferreira et al. (1996)

One of the objectives of the present study is to compare the findings reported herein to those obtained by Ferreira et al.[14] in a cross-sectional study carried out in Porto Alegre in 1994. In this study, the authors assessed the seroprevalence of hepatitis A in children and adolescents (aged 1-19 years) of distinct socioeconomic strata and its association with socioeconomic level, age, and past history of hepatitis A infection. The laboratory from which samples were collected was used as an indicator of socioeconomic

status. The 199 subjects in the low socioeconomic status group were recruited from a public hospital that provided care exclusively within the Unified Health System, whereas the 188 subjects from the high socioeconomic status group were selected from a sample of patients who sought testing at a private laboratory and paid for all tests in full and out of pocket. As in the present study, anti-HAV antibody testing was performed at a single laboratory using commercially available enzyme immunoassay kits (Cobas Core anti-HAV®, Roche).[14]

Statistical analysis

Sample size was calculated by age range for a minimum statistical power of 80% and a significance level (α) of 0.05, using as a basis the differences in anti-HAV prevalence by socioeconomic group reported elsewhere in the literature.[12] Sample size was estimated as follows for each of the defined age strata: a) age 1-5, 39 subjects; b) age 6-10, 26 subjects; c) age 11-15, 102 subjects; d) age 16-20, 65 subjects, for a total of 232 patients per group (464 subjects overall).

Categorical data were expressed as absolute and relative frequencies (counts and percentages), with their respective 95% confidence intervals (95%CI), based on binomial distribution. Chi-square or Fisher's exact test were used as necessary for comparisons between strata. In order to estimate the size of differences, percent changes (%Δ) and their respective 95%CIs were calculated. Prevalence ratios were calculated to measure the differences between anti-HAV prevalence rates in the present study as compared to those found by Ferreira et al.[14] for each age range. The trend line shown in Figure 1 represents the linear relationship between the differences of both studies, stratified by age range. The direct standardization method was used to enable between-group comparison of overall anti-HAV positivity rates, taking into account the age distribution of the Rio Grande do Sul state population.[19] Data were analyzed in the SPSS 17.0 software package (SPSS Inc., Chicago, IL). The significance level was set at 0.05.

Ethical considerations

The study protocol was approved by the Research Ethics Committees of Hospital de Clínicas de Porto Alegre (judgment number 06/612) and Grupo Hospitalar Conceição (judgment number 028/07). The authors signed a commitment to maintain subject confidentiality and use any data obtained solely for the purposes of the present study.

Results

Table 1 shows the distribution of anti-HAV reactivity rates for the present study and those reported by Ferreira et al.,[14] stratified by age range and socioeconomic status.

Table 1 - Distribution of overall anti-HAV positivity by age range and socioeconomic status* in two studies performed 13 years apart, Porto Alegre, Brazil

Socioeconomic status*/ age range	Ferreira et al., 1996[14]		Krebs et al., 2007†		%Δ		
	n	Anti-HAV (%)	n	Anti-HAV (%)	%	95%CI	p
Group 1 (public laboratory)							
1-4	49	10 (20.4)	36	7 (19.4)	-1.0	-18.8 to 18.7	1.00
5-9	55	29 (52.7)	31	8 (25.8)	-26.9	-45.8 to -3.3	0.03
10-14	50	30 (60.0)	70	30 (42.9)	-17.1	-34.7 to 2.1	0.10
15-19	45	32 (71.1)	85	46 (54.1)	-17.0	-33.4 to 2.0	0.09
Total	199	101 (54.4‡)	222	91 (37.6‡)	-16.8	-26.7 to 6.9	0.001
Group 2 (private laboratory)							
1-4	35	1 (2.9)	32	16 (50.0)	47.1	24.7 to 65.1	< 0.001
5-9	44	3 (6.8)	34	19 (55.9)	49.1	27.1 to 66.3	< 0.001
10-14	46	5 (10.9)	91	47 (51.7)	40.8	23.6 to 53.3	< 0.001
15-19	63	11 (17.5)	86	25 (29.1)	11.6	-3.5 to 25.2	0.15
Total	188	20 (10.3‡)	243	107 (46.1‡)	35.8	27.7 to 43.9	< 0.001

%Δ = percent difference; 95%CI = 95% confidence interval; anti-HAV = anti-hepatitis A virus antibodies; n = frequency.
* Public laboratory and private laboratory, representing the lower and higher socioeconomic strata, respectively.
† Statistical analysis of the comparison between the lowest and highest socioeconomic strata in the sample of the present study. Data on %Δ, 95%CI, and p-value, respectively, stratified by age range. 1 to 4 years: 30.6; 5.9, 51.3; 0.02. 5 to 9 years: 30.1; 4.0, 51.2; 0.03. 10 to 14 years: 8.8; -7.5, 24.4; 0.34. 15 to 19 years: 25.0; -39.1, -9.5; 0.002. Overall: 8.5; -0.9, 17.9; 0.08.
‡ Standardized by age distribution according to 2007 data.[19]

In the present study, overall anti-HAV seroprevalence was 37.6% (95%CI 31.0-44.1) in group 1 and 46.1% (95%CI 39.7-52.6) in group 2; there were no significant between-group differences (p = 0.08). The percentage rate of anti-HAV seroprevalence in group 1 ranged from 19.4% (95%CI 8.9-34.7) in the 1-4 age range to 54.1% (95%CI 43.0-65.0) in the 15-19 age range. In group 2, the prevalence of anti-HAV antibodies was higher in the three youngest age strata, ranging from 50.0 to 55.9% and was markedly reduced in the 15-to-19-year age range (seroprevalence, 29.1%; 95%CI 19.8-39.9). Comparison of both groups showed that, in group 2, anti-HAV prevalence was significantly higher in the 1-to-4 and 5-to-9 age ranges (p = 0.02 and p = 0.03, respectively) and significantly lower (markedly so) in the 15-to-19-year age range (p = 0.002). The greatest susceptibility rates to the hepatitis A virus were found predominantly in the 1-to-4 and 5-to-9 age ranges of group 1, with susceptibility rates of 80.6 and 74.2% respectively, and in the 15-to-19-year subgroup of group 2, with a rate of 70.9% (Table 1).

Comparison of our results against those obtained by Ferreira et al.,[14] a study which used similar patient selection criteria, showed no statistically significant difference in anti-HAV prevalence rates among low socioeconomic status subjects in the 1-to-4, 10-to-14, and 15-to-19 age groups. Conversely, in the 5-to-9 age group, the anti-HAV positivity rate in the present sample was 25.8% – a significant decline from the 52.7% rate reported by Ferreira et al.[14] (p = 0.03) (Table 1).

Discussion

Hepatitis A is ubiquitous, but endemicity patterns vary widely between countries and even between different regions of a single country, due to the diversity of hygiene and sanitation conditions, which play a major role in determining the age of exposure to hepatitis A virus and, consequently, disease severity.[1,8] Although children generally develop a more benign form of the disease, severe clinical manifestations may occur.[20] In a recent study of 33 children and adolescents treated at the Hospital de Clínicas de Porto Alegre for acute liver failure, hepatitis A accounted for 39% of cases (13 of 33) and 69% of deaths (nine of 13).[21] A study conducted in the state of Minas Gerais, Brazil, by Mesquita et al.[22] found that, in a sample of 10 patients who received liver transplants due to fulminant hepatic failure, the etiology of liver failure was determined in only five, and was found to be related to hepatitis A in two.[22]

In Brazil, hepatitis A is part of the national list of notifiable diseases,[23] but the possibility of an asymptomatic disease course encourages undernotification. There are countless epidemiological studies of hepatitis A and reports of HAV outbreaks in the Brazilian medical literature, but data on hepatitis A in the city of Porto Alegre are scarce and have thus far been obtained from population subgroups. In the aforementioned study by Ferreira et al.,[14] the authors found a highly significant difference in prevalence rates between children of low socioeconomic status (51%) and those living in better socioeconomic conditions (11%), which shows the coexistence of viral circulation and infection-susceptible individuals in Porto Alegre.[14] Between 1996 and 1997, Clemens et al.[12] conducted a multicenter study meant to assess the prevalence of anti-HAV antibodies in individuals between the ages of 1 and 40 in four Brazilian regions. The overall seroprevalence rate was 65% (95%CI 63.2-66.3), with anti-HAV positivity rates reaching 35% in individuals between the ages of 1 and 5 and exceeding 90% only in older age groups (31-40 years), suggesting a shift toward an intermediate endemicity pattern. Endemicity rates were lower in Southern Brazil (represented in the study by 461 volunteers recruited from the community and from several schools in Porto Alegre), with a mean seroprevalence rate of 55.7%. After stratifying by age and socioeconomic status, the authors found a significantly higher prevalence of anti-HAV across all age ranges in the low socioeconomic status group, except among older subjects.[12]

In the present study, the overall seroprevalence of anti-HAV was statistically similar in groups 1 and 2 (37.6 and 46.1%, respectively, p = 0.08). In group 1, the percentage rate of anti-HAV positivity increased with advancing age, which is to be expected with infectious diseases that rely on environmental exposure for transmission.[13] The converse distribution of anti-HAV prevalence in group 2 – with higher rates in the youngest age groups – is not consistent with the findings of prior Brazilian studies[12,14,15] or international investigations[24] (Table 1).

On comparison with the results obtained by Ferreira et al.,[14] the significantly lower anti-HAV reactivity rate in the 5-to-9 age range in group 1 of the present study suggests that HAV transmission is currently in decline in Porto Alegre. We believe the similar anti-HAV prevalence rate found in the 1-to-4 age range is likely due to the sum of two factors: prior exposure to the hepatitis A virus and immunization of some individuals in the study sample. As for the similar frequency of anti-HAV reactivity found in the 10-to-14 and 15-to-19-year groups, our working hypothesis is that it is due to childhood infection (Table 1). Comparison of group 2 in both studies showed a significantly higher anti-HAV prevalence in the younger age groups of the present study – far in excess of those reported by Ferreira et al.[14] (p < 0.001). In the 15-to-19 age range, there was no statistically significant difference between studies (p = 0.15) (Table 1).

The prevalence ratios of anti-HAV reactivity in children of both studies show that anti-HAV antibodies occurred roughly 18 times more frequently in the 1-to-4-year age group in the present study, eight times more often in the 5-to-9 age range, five times more frequently in the 10-

to-14 age range, and approximately twice as frequently in the 15-to-19-year age group (Figure 1). Based on the size and trend of the aforementioned prevalence ratios, the authors believe the increased anti-HAV prevalence among children in the higher socioeconomic strata included in the present study was due to the cumulative effect of exposure to the hepatitis A vaccine in this socioeconomic class (cohort effect).

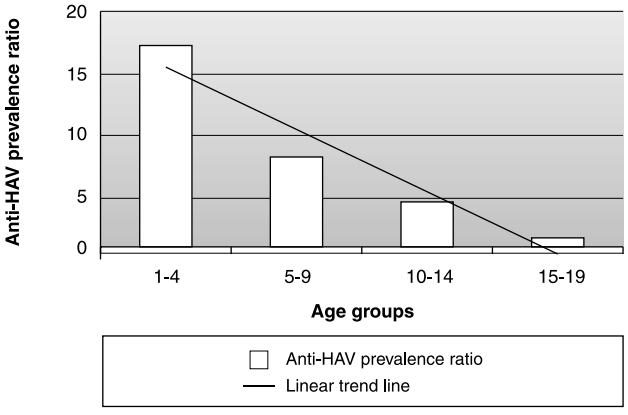

Figure 1 - Prevalence ratio of anti-HAV positivity among individuals in higher socioeconomic strata, present study vs. Ferreira et al.,[14] Porto Alegre, Brazil

In support of this hypothesis, it bears noting that the hepatitis A vaccine has yet to be added to the immunization schedule of the Brazilian National Immunization Program[25]; it is only available at Special Immunobiology Referral Centers (to specific population groups)[26] or at private immunization clinics. The Brazilian Society of Pediatrics has recommended that children be vaccinated against hepatitis A since 1998,[27] at first depending on "possibility and availability" and, since 2005, unconditionally, at age 12 months, followed by a booster dose 6 months later.[28] We believe that, due to its high cost, administration of the hepatitis A vaccine has been restricted to individuals with higher purchasing power and, therefore, indicated to children with a lower likelihood of past HAV infection. We have also analyzed data on use of the hepatitis A vaccine in Porto Alegre provided by a private immunization clinic in the city. In 1995, approximately 0.1% of patients seen at the clinic received the hepatitis A vaccine, 30% of whom were children between the ages of 1 and 4. In 1998, the vaccine was administered to roughly 4% of patients seen at the clinic, 46% of whom were in the 1-to-4 age group. By 2007, the year in which the study was performed, approximately 11% of patients in the clinic were receiving the hepatitis A vaccine – 52% in the 1-to-4 age range (Cunha J, unpublished data). These percentages are even more striking when one considers that children aged 1-4 are only expected to make up 17.4% of the population of the state of Rio Grande do Sul.[19] The fact that the vaccine was predominantly administered to children between the ages of 1 and 4 and the absence of an increased prevalence of hepatitis A among children in the more disadvantaged socioeconomic group corroborate the hypothesis that significantly greater anti-HAV antibody rates in the higher socioeconomic status group were due to vaccine exposure. Furthermore, the present study was conducted over a relatively long period of time (9 months), encompassing practically all seasons and thus preventing seasonal bias.

Some limitations of our study should be noted. Total anti-HAV antibody testing is used in epidemiological studies for measurement of disease prevalence and determination of immunity,[2] but it does not distinguish between exposure (past or current) to the actual disease-causing virus and exposure to vaccine antigens. The use of serum sample residuals made invasive blood collection unnecessary, but also hindered collection of information on subjects' past medical history and history of hepatitis A vaccination. A further limitation includes the socioeconomic status indicator chosen, that is, the laboratory where samples were collected. Despite its shortcomings, this strategy was chosen to allow comparison of our results with those of a past study in which this indicator was used.[14]

The high rate of susceptibility to the hepatitis A virus (> 70%) detected in younger children (in group 1) and adolescents (in group 2) in the present study shows that many children and adolescents in the Porto Alegre area are at risk of infection (Table 1). Gradual improvement in sanitation and health conditions reduces, but does not eliminate, transmission of hepatitis A, and promotes a shift in the occurrence of hepatitis A infection to individuals of higher socioeconomic status, producing a greater impact on public health[1] and fostering outbreaks that can be prolonged and refractory to control efforts.[8,9] In this context, the main concern lies in preventing symptomatic and, above all, severe cases of hepatitis A, such as those leading to acute liver failure. Routine immunization could quickly bring infection rates under control and decrease the burden of the disease on the health system, both through its individual efficacy and by inducing herd immunity.[29] Although the purpose of this study was not to justify inclusion of the hepatitis A vaccine in the Brazilian Ministry of Health immunization schedule, we believe the results obtained may constitute an argument in favor of this recommendation, or may prompt a future cost-effectiveness study that can provide inputs for planning of disease control strategies.

These results suggest that the endemicity of hepatitis A in Porto Alegre has declined over the past decade, and that susceptibility to the disease is higher in children and adolescents, particularly those of lower socioeconomic status.

Acknowledgements

The authors would like to thank the Fundo de Incentivo a Pesquisa e Eventos do Hospital de Clínicas de Porto Alegre and Sanofi-Pasteur.

References

1. World Health Organization. Hepatitis A vaccines: WHO position paper. Wkly Epidemiol Rec. 2000;75:38-44.
2. Advisory Committee on Immunization Practices (ACIP), Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006;55:1-23.
3. Nainan OV, Xia G, Vaughan G, Margolis HS. Diagnosis of hepatitis A virus infection: a molecular approach. Clin Microbiol Rev. 2006;19:63-79.
4. Pontrelli G, Boccia D, DI Renzi M, Massari M, Giugliano F, Celentano LP, et al. Epidemiological and virological characterization of a large community-wide outbreak of hepatitis A in southern Italy. Epidemiol Infect. 2008;136:1027-34.
5. Aw TG, Gin KY. Environmental surveillance and molecular characterization of human enteric viruses in tropical urban wastewaters. J Appl Microbiol. 2010;109:716-30.
6. Hutin YJ, Sabin KM, Hutwagner LC, Schaben L, Shipp GM, Lord DM, et al. Multiple modes of hepatitis A virus transmission among methamphetamine users. Am J Epidemiol. 2000;15:186-92.
7. Bower WA, Nainan OV, Han X, Margolis HS. Duration of viremia in hepatitis A virus infection. J Infect Dis. 2000;182:12-7.
8. Bell BP. Global epidemiology of hepatitis A: implications for control strategies. In: Margolis HS, Alter MJ, Liang TJ, Dienstag JL, editors. Viral hepatitis and liver disease. London: International Medical Press; 2002. p. 9-14.
9. FitzSimons D, Hendrickx G, Vorsters A, Van Damme P. Hepatitis A and E: update on prevention and epidemiology. Vaccine. 2010;28:583-8.
10. Hendrickx G, Van Herck K, Vorsters A, Wiersma S, Shapiro C, Andrus JK, et al. Has the time come to control hepatitis A globally? Matching prevention to the changing epidemiology. J Viral Hepat. 2008;15 Suppl 2:1-15.
11. Vitral CL, Souto FJ, Gaspar AM. Changing epidemiology of hepatitis A in Brazil: reassessing immunization policy. J Viral Hepat. 2008;15 Suppl 2:22-5.
12. Clemens SA, da Fonseca JC, Azevedo T, Cavalcanti A, Silveira TR, Castilho MC, et al. [Hepatitis A and hepatitis B seroprevalence in 4 centers in Brazil]. Rev Soc Bras Med Trop. 2000;33:1-10.
13. de Alencar Ximenes RA, Martelli CM, Merchán-Hamann E, Montarroyos UR, Braga MC, de Lima ML, et al. Multilevel analysis of hepatitis A infection in children and adolescents: a household survey in the Northeast and Central-west regions of Brazil. Int J Epidemiol. 2008;37:852-61.
14. Ferreira CT, Silva GL, Barros FC, Fereira-Lima J. Soroepidemiologia da hepatite A em dois grupos populacionais economicamente distintos de Porto Alegre. GED Gastroenterol Endosc Dig. 1996;15:85-90.
15. Zago-Gomes MP, Stantolin GC, Perazzio S, Aikawa KH, Gonçalves CS, Pereira FE. Prevalence of anti-hepatits A antibodies in children of different socioeconomic conditions in Vila Velha, ES. Rev Soc Bras Med Trop. 2005;38:285-9.
16. Almeida D, Tavares-Neto J, Vitvitski L, Almeida A, Mello C, Santana D, et al. Serological markers of hepatitis A, B and C viruses in rural communities of the semiarid Brazilian northeast. Braz J Infect Dis. 2006;10:317-21.
17. Lafer MM, de Moraes-Pinto MI, Weckx LY. Prevalence of antibodies against hepatitis A virus among the Kuikuro and Kaiabi Indians of Xingu National Park, Brazil. Rev Inst Med Trop Sao Paulo. 2007;49:155-7.
18. Matos MA, Reis NR, Kozlowski AG, Teles SA, Motta-Castro AR, Mello FC, et al. Epidemiological study of hepatitis A, B and C in the largest Afro-Brazilian isolated community. Trans R Soc Trop Med Hyg. 2009;103:899-905.
19. Instituto Brasileiro de Geografia e Estatística. População recenseada, por sexo, segundo a idade, Rio Grande do Sul, 2007. http://www.ibge.gov.br/home/estatistica/populacao/contagem2007/contagem_final/tabela1_2_23.pdf. Access: 10 Oct 2010.
20. Ciocca M. Clinical course and consequences of hepatitis A infection. Vaccine. 2000;18 Suppl 1:S71-4.
21. Ferreira CT, Vieira SM, Kieling CO, Silveira TR. Hepatitis A acute liver failure: follow-up of paediatric patients in southern Brazil. J Viral Hepat. 2008;15 Suppl 2:66-8.
22. Mesquita MC, Ferreira AR, Veloso LF, Roquete ML, Lima AS, Pimenta JR, et al. Pediatric liver transplantation: 10 years of experience at a single center in Brazil. J Pediatr (Rio J). 2008;84:395-402.
23. Brasil, Ministério da Saúde. Lista de notificação compulsória. Portaria N° 2.472, de 31 de agosto de 2010. Brasília: Ministério da Saúde; 2010. http://portal.saude.gov.br/portal/arquivos/pdf/port2472_31_08_10_doencas_not.pdf. Access: 16 Oct 2010.
24. Bell BP, Kruszon-Moran D, Shapiro CN, Lambert SB, McQuillan GM, Margolis HS. Hepatitis A virus infection in the United States: serologic results from the Third National Health and Nutrition Examination Survey. Vaccine. 2005;23:5798-806.
25. Brasil, Ministério da Saúde. Calendário básico de vacinação. Portaria N° 1.602 de 17 de julho de 2006. Brasília: Ministério da Saúde; 2006.
26. Brasil, Ministério da Saúde. Secretaria de Vigilância em Saúde. Manual dos Centros de Referência para Imunobiológicos Especiais. 3. ed. Brasília: Ministério da Saúde; 2006.
27. Weckx LY, Carvalho ES. Calendário vacinal: dinâmica e atualização. J Pediatr (Rio J). 1999;75 Suppl.1:S149-54.
28. Feijó RB, Cunha J, Krebs LS. Vaccination Schedule for childhood and adolescence: comparing recommendations. J Pediatr (Rio J). 2006;82:S4-14.
29. Armstrong GL, Billah K, Rein DB, Hicks KA, Wirth KE, Bell BP. The economics of routine childhood hepatitis A immunization in the United States: the impact of herd immunity. Pediatrics. 2007;119:e22-9.

Correspondence:
Lenita Simões Krebs
Rua Sacadura Cabral, 242/702 – Petrópolis
CEP 90690-420 – Porto Alegre, RS – Brazil
Tel.: +55 (51) 3338.5210
Fax: +55 (51) 3359.8748
E-mail: lskrebs@via-rs.net