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Prevalence of antibodies against hepatitis A and E viruses among rural populations of the Chaco region, south-eastern Bolivia

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Summary We conducted a cross-sectional study to determine the seroprevalence of antibodies against hepatitis A and hepatitis E viruses (HAV and HEV) in the population of two rural areas, Camiri and Villa Montes, of the Chaco region, south-eastern Bolivia. HAV antibodies were detected in 461 (94.1%) of 490 serum samples tested, not differing significantly between sexes and study areas. The HAV seropositivity rate (64.7%) was high even in the youngest age group (1–5 years). The prevalence of HEV was 7.3%, with no significant differences between sexes. The prevalence of HEV antibodies in the population of the Camiri area (10.4%) was significantly higher than in the Villa Montes area (4.4.%), possibly due to the better quality of drinking water in the Villa Montes area. In the population ≤ 30 years of age, the HEV seropositivity rate (4.4%) was significantly lower than in the ≥ 31 year-old group. This is consistent with findings in other countries. This is the first report of the prevalence of HEV infection in Bolivia.

keywords hepatitis E virus, hepatitis A virus, epidemiology, Bolivia

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Introduction

Hepatitis A virus (HAV) and hepatitis E virus (HEV) are nonenveloped RNA viruses that share the faecal-oral route of transmission. However, their epidemiological patterns differ (Arankalle *et al*. 1995). Hepatitis A infection has a worldwide distribution with the highest prevalence of HAV antibodies in developing countries, where environmental and socio-economic conditions favour nearly universal exposure to HAV in early childhood (Hollinger & Ticehurst 1990). Improvements in public health and sanitation led to a decline in the incidence of HAV infections and to a shift of the time of first exposure to older age groups (Hadler 1991). Since the expression of clinical infections is highly age-related, older age of first exposure increases the number of symptomatic HAV infections and the probability of epidemics.

HEV has recently been recognized as the responsible agent for outbreaks of enterically transmitted hepatitis in Asia, Africa, Central and South America, the Middle East, and the republics of the former USSR. There is evidence that HEV infection is endemic in most tropical as well as subtropical countries (Balayan 1991; Krawczynski 1993). Transmission of HEV from person to person is rare and faecally contaminated drinking water is the primary vehicle of infectious spread. In contrast to HAV, HEV infection predominantly affects young adults aged 15–40. HEV hepatitis is usually a self-limiting disease and, like HAV hepatitis, does not progress to an apparent chronic hepatitis or a chronic carrier state. A very high mortality rate (up to 24%) has been reported in pregnant women infected during the last trimester of pregnancy (Bradley 1992). To date, only one study reported HAV prevalence in Bolivia (Bartoloni *et al*. 1989): this sero-epidemiological survey conducted in 1987 in the Cordillera province, south-eastern Bolivia, found HAV antibodies in 97% of the studied population, with an 87% prevalence in 1–5 year-old children. To our knowledge, no information about the epidemiology of hepatitis E in Bolivia is available.

The aims of this study were to reassess the epidemiological pattern of HAV infection and to examine, for the first time, evidence for HEV infection in the population of south-

eastern Bolivia. A cross-sectional survey was therefore carried out in November 1997 with the agreement of the Bolivian National Department of Epidemiology of the Ministry of Social Welfare and Public Health and with the support of the Guaraní political organization (Asamblea del Pueblo Guaraní, APG).

Methods

The Chaco region is situated in south-eastern Bolivia between longitude 64°30′ and 58°50′ east of the Greenwich meridian and at latitude 17°58′ and 22°20′ south, and includes five provinces: Cordillera, Luis Calvo, Hernando Siles, Gran Chaco, and O'Connor. The areas selected were located in Cordillera and Gran Chaco. Cordillera, with a population of 88628 (INE 1992), occupies the broad northern area (86245 km^2), whereas Gran Chaco is in the south with an area of 17428 km^2, and a population of 17612. The survey was conducted in 8 rural communities, 4 near Camiri (Cordillera province), and 4 near Villa Montes (Gran Chaco province). The communities near Camiri are 5–10 km from the town on the rivers Parapeti and Yuti, at altitudes of about 800 m. The rural communities near Villa Montes are located about 6 km from the town at an altitude of about 380 m. The study populations consist of Guaraní indians and mestizos living in poor dwellings with walls of sticks, straw and clay and thatched roofs. The local economy is based on agriculture (mainly maize) and animal farming (cattle, pigs, goats, chicken, etc.).

The rural areas near Camiri and Villa Montes each have approximately 3300 inhabitants. The sample size was determined based on expected prevalences of HAV and HEV antibodies of 90% and 8%, respectively, with a worst acceptable error of 5% and a confidence interval of 95%. A random cluster survey method was used, with each community constituting one cluster and 4 communities in each area selected at random. The study populations consisted of 295 individuals (162 females and 133 males) from Camiri and 292 individuals (147 females and 145 males) from Villa Montes. Their ages varied between 1 and 85 years.

A meeting with the inhabitants of the communities was organized to explain the purpose of the study and its procedures. Samples of 5 ml venous blood were taken from all available subjects of the selected communities. The sera were stored at −20 °C in Bolivia, transported to Italy in dry ice and stored at −70 °C until tested. Serum samples were screened by commercial anti-HEV IgG ELISA (HEV EIA, Abbott GmbH Diagnostika, Wiesbaden, Germany) and anti-HAV IgG ELISA (Enzygnost®, Behring, Marburg, Germany) according to manufacturer's instructions. Reactive samples in the hepatitis E assay were repeatedly tested and considered positive only if reactive in duplicate. Data analysis, with adjustment for clustering, was done using the Epi-Info6 package.

Results

Of 587 subjects selected, 97 (16.5%) were excluded from analysis: 88 subjects (48 in the Camiri area and 40 in the Villa Montes area) who declined to provide a blood sample, and 9 (7 in the Camiri area, 2 in the Villa Montes area) whose age was not recorded. The results on seroprevalence of antibodies to HAV are shown in Table 1. Of 490 serum samples tested, 461 (94.1%) were positive for HAV antibodies. Females had a higher prevalence of HAV (94.7%) antibodies than males (93.3%) although this did not reach statistical significance ($P = 0.5$). There were no statistically significant differences

Table 1 Prevalence of anti-HAV antibodies by age, sex and area in the rural population of the Chaco region, south-eastern Bolivia

Age group	Female			Male			Total		
	Tested	Positive	%	Tested	Positive	%	Tested	Positive	%
1–5	26	16	61.5	25	17	68	51	33	64.7
6–10	56	53	94.6	49	44	89.8	105	97	92.4
11–20	46	46	100	44	44	100	90	90	100
21–30	33	32	97	25	25	100	58	57	98.3
31–40	36	36	100	25	24	96	61	60	98.4
41–50	19	19	100	20	19	95	39	38	97.4
51–60	22	22	100	16	16	100	38	38	100
> 60	28	28	100	20	20	100	48	48	100
Area									
Camiri	134	128	95.5	106	96	90.6	240	224	93.3
Villa Montes	132	124	93.9	118	113	95.8	250	237	94.8
Total	266	252	94.7	224	209	93.3	490	461	94.1

Table 2 Prevalence of anti-HEV antibodies by age, sex and area in the rural population of the Chaco region, south-eastern Bolivia

Age group	Female			Male			Total		
	Tested	Positive	%	Tested	Positive	%	Tested	Positive	%
1–5	26	2	7.7	25	0	0	51	2	3.9
6–10	56	2	3.6	49	2	4.1	105	4	3.8
11–20	46	1	2.2	44	4	9.1	90	5	5.5
21–30	33	2	6.1	25	0	0	58	2	3.4
31–40	36	7	19.4	25	2	8	61	9	14.7
41–50	19	4	21	20	2	10	39	6	15.4
51–60	22	1	4.5	16	3	18.7	38	4	10.5
> 60	28	0	0	20	4	20	48	4	8.3
Area									
Camiri	134	14	10.4	106	11	10.4	240	25	10.4
Villa Montes	132	5	3.8	118	6	5.1	250	11	4.4
Total	266	19	7.1	224	17	7.6	490	36	7.3

between prevalences in the two areas ($P = 0.5$). Universal exposure to HAV at an early age is evident from the high percentage (64.7%) of seropositive children in the ≤ 5 age group. The prevalence increased gradually with age, reaching almost 100% in over 10-year-old subjects. The median age of the 29 individuals without HAV antibodies was 5 years (range 1–50).

Thirty-six (7.3%) of the 490 tested sera had HEV antibodies (Table 2). There were no significant gender-related differences with seropositivity rates of 7.6% in males and 7.1% in females ($P = 0.8$). The median age of the 36 individuals with HEV antibodies was 37 years (range 4–78). All but two HEV-seropositive subjects had HAV antibodies. The two HEV-seropositive and HAV-seronegative subjects were girls of 4 and 5 years, respectively, living in different communities of the Camiri area. Neither child had a history of jaundice.

The prevalence of HEV antibodies in the population of the Camiri area (10.4%) was significantly higher than in the Villa Montes area (4.4%) ($P = 0.007$). The absence of significant differences in seroprevalence between sexes was confirmed when the population of the two areas was considered separately. Both areas shared a pattern of seropositivity in relation to age (Figure 1). The prevalence rate of HEV antibodies in

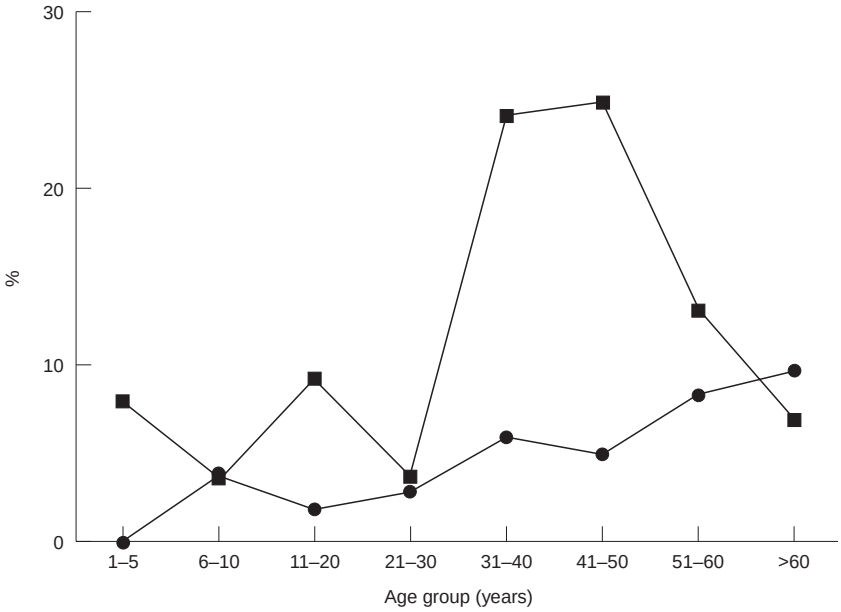

Figure 1 Distribution of HEV antibodies by age and area in the rural population of the Chaco region, south-eastern Bolivia. ● HEV Villa Montes; ■ HEV Camiri

the population ≤ 30 years was significantly lower than that in the ≥ 31 year-old group (4.4% *vs*. 14.1%, $P = 0.001$). In the Camiri area anti-HEV seroprevalence increased sharply in the 31–40 age group (21.1%) and peaked at 25% in the 41–50 age group. The seroprevalence declined in the older age groups, reaching 7.1% in over 60-year-olds. In Villa Montes the seropositivity rates did not differ significantly across adult age groups, with the highest prevalence (10%) in the over 60 age class. No jaundice outbreaks have been reported in the surveyed areas, and there are no data on jaundice in pregnant women.

Discussion

This survey documents an unchanged pattern of hepatitis A infection and exposure to infection with hepatitis E virus in the population of south-eastern Bolivia. In a serosurvey carried out in 1987 in south-eastern Bolivia, we found a very high prevalence (97%) of HAV antibodies together with nearly universal exposure to HAV of the population in early childhood, as evidenced by a seroprevalence rate of 87% in children ≤ 5 (Bartoloni *et al*. 1989). The results of this survey, conducted 10 years later in the same area, indicate that the global prevalence is still very high (94%). However, there is a suggestion of declining prevalence in the 1–5 year-old age group (65%) although it was not significant ($P = 0.9$) (Figure 2). Similar downward trends have been observed in other developing countries and are due to improved socioeconomic and hygienic conditions leading to a decrease in the circulation of HAV (Innis *et al*. 1991; Vranckx *et al*. 1997). When the cholera epidemic reached the study area in January 1992 (Guglielmetti *et al*. 1992), the efforts of local health authorities to educate people about the importance of hygiene may have contributed to the decline of HAV transmission. The change in the epidemiological pattern of HAV infection has an impact on its clinical expression and economic consequences. Almost universal exposure to HAV in early childhood leads to only mildly symptomatic or asymptomatic infection and the development of solid immunity to HAV before adolescence, when hepatitis A is more likely to be symptomatic (Villarejos *et al*. 1982; Lednar *et al*. 1985). If our findings reflect a real change in HAV transmission, we can predict an increase in the number of clinical infections and the occurrence of epidemics of hepatitis A in future years.

HEV infection is widely spread in tropical and subtropical countries and outbreaks of hepatitis E have occurred in South-East Asia, the Middle East, Mexico, and Africa (Lok *et al*. 1992; Krawczynski 1993; Arankalle *et al*. 1995). However, few studies have examined the prevalence of HEV infection in South American populations and, until now, there was no evidence of HEV infection in Bolivia. The global prevalence rate (7%) of HEV antibodies indicates that HEV circulates in these rural communities and is higher than in Brazilian blood donors (2%), rural populations (3.9%) and rural Amerindians (5.4%) of Venezuela, but lower than in Araucanian Indians (17%) of Southern Chile (Pujol *et al*.

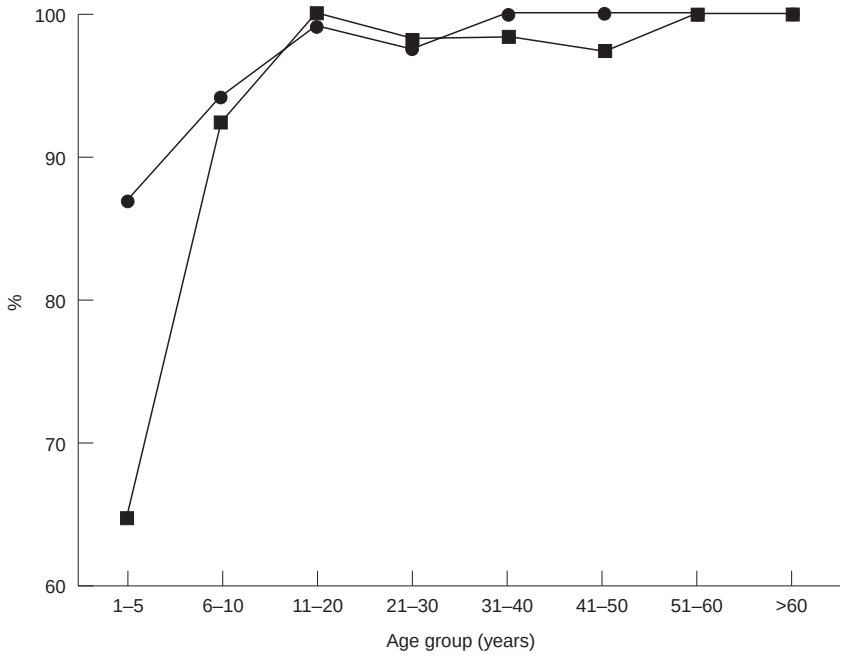

Figure 2 Distribution of HAV antibodies by age, in the 1987 and 1997 sero-survey, in the population of the Chaco region, south-eastern Bolivia. ● 1987; ■ 1997

1994; Ibarra *et al*. 1997; Parana *et al*. 1997). The age distribution of anti-HEV is similar to that of other countries with a relatively high prevalence in young adults and low prevalence in children (Favorov *et al*. 1992; Thomas *et al*. 1993; Karetnyi *et al*. 1995). It is unclear whether this represents a low level of exposure in childhood, some form of protection, or rapid decay of antibody titres (Balayan 1993). One possible reason for the difference between Camiri and Villa Montes is that there was an epidemic in Camiri some 20–30 years ago, i.e. this could be a birth cohort effect. However, we have no evidence for or against this hypothesis. The difference in anti-HEV seroprevalence in the over 50-year-old group in the two studied areas is difficult to interpret due to the small number of positive subjects. The statistically significant difference between prevalences in two rural areas with similar living conditions and socioeconomic status may be explained by the different water supply systems. The communities of the Camiri area source their water from superficial open wells on the river bank, whereas the population of the communities near Villa Montes use water from a small stream about 4 km away which is distributed by a pipeline equipped with two filtering stations. The better-quality drinking water in the Villa Montes area probably limits the circulation of HEV while not affecting person-to-person transmission of HAV. Recent evidence of HEV antibodies in domestic animals in areas with a high endemicity of human infection suggests the zoonotic nature of HEV disease (Favorov *et al*. 1998). If this hypothesis were to be confirmed, interpretation of the sero-epidemiological studies in humans should be probably reconsidered.

Our findings demonstrate that HEV transmission occurs in the surveyed rural areas of south-eastern Bolivia. Considering the uncertainty about the long-term antibody status after HEV infection, with some studies (Goldsmith *et al*. 1992; Coursaget *et al*. 1994) suggesting a short duration, our data may underestimate the previous population exposure to HEV (Miller *et al*. 1998). On the basis of these data, travellers coming to this area from countries with little HAV and HEV exposure should be considered at risk of enterically transmitted hepatitis (Piper Jenks 1998).

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References

Arankalle VA, Tsarev SA, Chadha MS *et al*. (1995) Age-specific prevalence of antibodies to hepatitis A and E viruses in Pune, India, 1982 and 1992. *Journal of Infectious Diseases* **171**, 447–450.

Balayan MS (1991) HEV infection: historical perspectives, global epidemiology, and clinical features. In *Viral Hepatitis and Liver Disease* (eds. FB Hollinger *et al*.) Williams and Wilking, Baltimore, pp. 498–501.

Balayan MS (1993) Hepatitis E virus infection in Europe: regional situation regarding laboratory diagnosis and epidemiology. *Clinical and Diagnostic Virology* **1**, 1–9.

Bartoloni A, Aquilini D, Roselli M *et al*. (1989) Prevalence of antibody to hepatitis a virus in the Santa Cruz region of Bolivia. *Journal of Tropical Medicine and Hygiene* **92**, 279–281.

Bradley DW (1992) Hepatitis E: epidemiology, aetiology and molecular biology. *Review of Medical Virology* **2**, 19–28.

Coursaget P, Depril N, Buisson Y, Molinié C & Roué R (1994) Hepatitis type E in a French population: detection of anti-HEV by a synthetic peptide-based enzyme-linked immunosorbent assay. *Research in Virology* **145**, 51–57.

Favorov MO, Fields HA, Purdy MA *et al*. (1992) Serological identification of hepatitis E virus infections in epidemic and endemic setting. *Journal of Medical Virology* **36,** 246–250.

Favorov M, Nazarova O & Margolis H (1998) *Is hepatitis E an emerging zoonotic disease?* Abstract submitted to the 2nd International Conference on Emerging Zoonoses, Strasbourg, France, 5–9 November 1998.

Goldsmith R, Yarbough PO, Reyes GR *et al*. (1992) Enzyme-linked immunosorbent assay for diagnosis of acute sporadic hepatitis E in Egyptian children. *Lancet* **339**, 328–331.

Guglielmetti P, Bartoloni A, Roselli M *et al*. (1992) Population movements and cholera spread in Cordillera Province, Santa Cruz Department, Bolivia. *Lancet* **340**, 113.

Hadler SC (1991) Global impact of hepatitis A virus infection: changing patterns. In *Viral Hepatitis and Liver Disease* (eds. FB Hollinger *et al*.) Williams and Wilking, Baltimore, pp. 14–20.

Hollinger FB, Ticehurst J (1990) Hepatitis A virus. In *Virology*, 2nd edn (eds. BN Fields *et al*.) Raven Press, New York, pp. 631–667.

Ibarra H, Riedemann S, Reinhardt G *et al*. (1997) Prevalence of hepatitis E virus antibodies in blood donors and other population groups in southern Chile. *Revista Medica de Chile* **125**, 275–278.

Innis BL, Snitbhan R, Hoke CH, Munindhorn W & Laorakpongse T (1991) The declining transmission of hepatitis A in Thailand. *Journal of Infectious Diseases* **163**, 989–995.

Instituto Nacional de Estadística (INE) (1992) *Indicadores Sociodemográficos por Provincias, Censo 1992.* INE, La Paz.

Karetnyi YV, Favorov MO, Khudyakova NS *et al*. (1995) Serological evidence for hepatitis E virus infection in Israel. *Journal of Medical Virology* **45**, 316–320.

Krawczynski K (1993) Hepatitis E. *Hepatology* **17**, 932–941.

Lednar WE, Lemon SM, Kirkpatrick JW, Redfield RR, Fields ML & Kelley PW (1985) Frequency of illness associated with epidemic hepatitis A virus infections in adults. *American Journal of Epidemiology* **122**, 226–233.

Lok AS, Kwan WK, Moeckli R *et al*. (1992) Seroepidemiological survey of hepatitis E in Hong Kong by recombinant-based enzyme

immunoassays. *Lancet* **340**, 1205–1208.

Miller WC, Shao JF, Weaver DJ, Shimokura GH, Paul DA & Lallinger GJ (1998) Seroprevalence of viral hepatitis in Tanzanian adults. *Tropical Medicine and International Health* **3**, 757–763.

Parana R, Cotrim HP, Cortey-Boennec ML, Trepo C & Lyra L (1997) Prevalence of hepatitis E virus IgG antibodies in patients from a Referral Unit of Liver Diseases in Salvador, Bahia, Brazil. *American Journal of Tropical Medicine and Hygiene* **57**, 60–61.

Piper Jenks N (1998) Hepatitis E virus: is it a risk to travelers? *Shoreland's Travel Medicine Monthly* **2**, 1–5.

Pujol FH, Favorov MO, Marcano T *et al*. (1994) Prevalence of antibodies against hepatitis E virus among urban and rural populations in Venezuela. *Journal of Medical Virology* **42**, 234–236.

Thomas DL, Mahley RW, Badur S, Palaoglu KE & Quinn TC (1993) Epidemiology of hepatitis E virus infection in Turkey. *Lancet* **341**, 1561–1562.

Villarejos VM, Serra CJ, Anderson-Visona K & Mosley JW (1982) Hepatitis A virus infection in households. *American Journal of Epidemiology* **115**, 577–586.

Vranckx R, Alisjahbana A, Devillé W & Meheus A (1997) Hepatitis A antibodies in Indonesian neonates and children. *International Journal of Infectious Diseases* **2**, 31–33.