Epidemiol. Infect. (1996), **117**, 133–137

Hepatitis B virus infection in general population in Madagascar: evidence for different epidemiological patterns in urban and in rural areas

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(*Accepted 26 January 1996*)

SUMMARY

To describe the features of hepatitis B virus (HBV) infection in Madagascar, a randomized sero-epidemiological survey was undertaken in the general population ⩾ 1 year old of two provinces which represents 45% of the total population. In the 921 sera tested, the prevalence of HBV markers was 20·5% for HBsAg, 38·2% for anti-HBc and 6·9% for HBeAg. HBsAg and anti-HBc prevalence rates were significantly higher in males. A large difference in HBsAg prevalence was observed between urban (5·3%) and rural areas (26·0%). The same contrast in prevalence was noticed for the other HBV markers. In rural areas, HBV infection was more frequently acquired early in infancy, which suggests predominantly perinatal or postnatal transmission. The presence of HBV markers was not significantly associated with a history of blood transfusion, surgery or parenteral injection. High infectivity carriers represented 5·3% and the overall frequency of chronic carriers was 10·4%. These results place Madagascar among areas of high endemicity.

INTRODUCTION

Hepatitis B virus (HBV) infection is poorly documented in Madagascar. The few studies that have been carried out have been largely in the urban setting of the capital city Antananarivo. Hence, their conclusions cannot be considered as representative of the general population. According to these studies, the prevalence of hepatitis B surface antigen (HBsAg) in Antananarivo is 2·8–5·4%. On the other hand, the only study in a rural area [1] has shown high prevalences of HBsAg with rates of 18·9% and 30·5% in two villages of mid-western and western Madagascar. Detailed data about frequency of complications such as cirrhosis, and primary hepatocellular carcinoma resulting from chronic HBV infection do not exist in the country. At the time when introduction of hepatitis B immunization programmes have commenced in several nations, it seemed important to investigate further the epidemiology of HBV infection in Madagascar. Therefore, as a first stage, the present survey has been undertaken in the general population from two of the six provinces of Madagascar, in order to assess the prevalence of HBV infection.

PATIENTS AND METHODS

Sample population

The study was carried out in Antananarivo and Toamasina provinces, whose combined population of *c.* 5·7 million inhabitants represents 45% of the total population of the island (Fig. 1). The two regions have markedly different geographic and climatic profiles. Antananarivo, located in the central highlands (altitude 600–2600 m), has a tropical highland climate with a warm, rainy season from December–April and

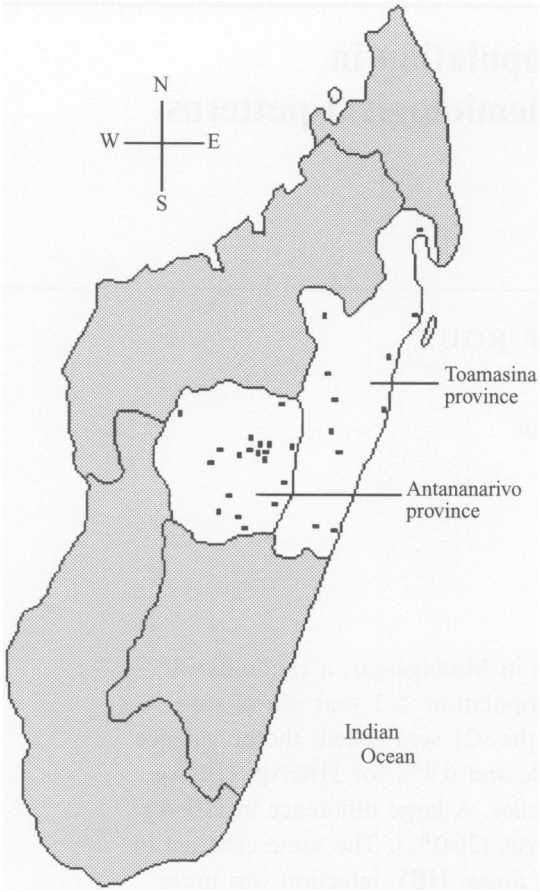

Fig. 1. Location of the 30 randomized sites in Antananarivo province and Toamasina province. Madagascar, 1994.

a cool, dry season especially marked from July–November. The coastal province of Toamasina (altitude 0–1500 m), with large areas of dense rain forest has a tropical humid climate.

According to a cluster sampling procedure [2], an initial sampling of 30 communities was performed, with a probability of inclusion proportional to the population size. The second stage consisted of randomized selection of households in each community. The sample size was computed for an expected prevalence of 20% HBsAg, a precision of the estimate of 5%, a type 1 error of 5% and a cluster design effect of 3·5. The total size of the sample was rounded to 900, to achieve 30 individuals per cluster, but it was decided that every member of a household would be included even if 30 was already reached with a preceding member of this household.

Serological methods

Serum samples were obtained from venous blood collected from all consenting individuals aged $\geqslant 1$ year old. The sample were stored at -20 °C until screened for HbsAg and IgG antibody to HBV core antigen (anti-HBc). HBsAg positive sera were tested for HBV e antigen (HBeAg) and HBsAg negative sera for HBs antibody (anti-HBs). All tests were performed using enzyme-linked immunosorbent assays (Monolisa® Ag HBs 2nd generation, Monolisa® anti HBs, Monolisa® HBe, Monolisa® anti HBc, Sanofi-Diagnostics Pasteur). The neutralization test for HBsAg was not used. The infection rate was defined by a positive result for at least one marker.

Analysis

Significance tests were done by Pearson's χ^2 or adjusted Mantel–Haenszel χ^2 tests wherever appropriate; $P < 0{\cdot}05$ was considered significant. In order to take into account the cluster design effect, the Fleiss quadratic approximation was used for calculation of the confidence intervals of proportions.

RESULTS

A total of 936 individuals 1–94 years old entered the study during the second half of 1994 (Fig. 1). Few refused to participate, except in one village where half of the randomized households refused to participate. Of the 936, 15 were excluded from the analysis because of inadequate blood samples. There was no significant difference between the age distribution of the study population and the general population in Madagascar. However, the distribution of gender was significantly different, with females representing 54·6% of the sample versus an expected percentage of 50·6% ($P < 0{\cdot}02$). The population was predominantly rural (73·6 *vs.* 76·0% expected). Of the 921 subjects, 12 had a history of blood transfusion and 24 had undergone surgery.

The overall HBsAg prevalence was 20·5% (95% CI 15·9–26·0), but significantly higher in males (24·6%) than females (17·1%), after adjusting for age ($P < 0{\cdot}02$). The HBsAg prevalence decreased steadily from age 1 year. HBsAg was detected in 35 of the 258 (13·6%) women of childbearing age (15–49 years). In 79 subjects (8·6%), HBsAg was the only marker. HBeAg was found in 6·9% (95% CI 4·3–10·9) of the total population and 33·0% (63 out of 189) of the HBsAg-positive individuals.

Anti-HBc was present in 352 individuals (38·2%, 95% CI 32·3–44·4). Prevalence of anti-HBc positivity was also significantly higher in males than in females

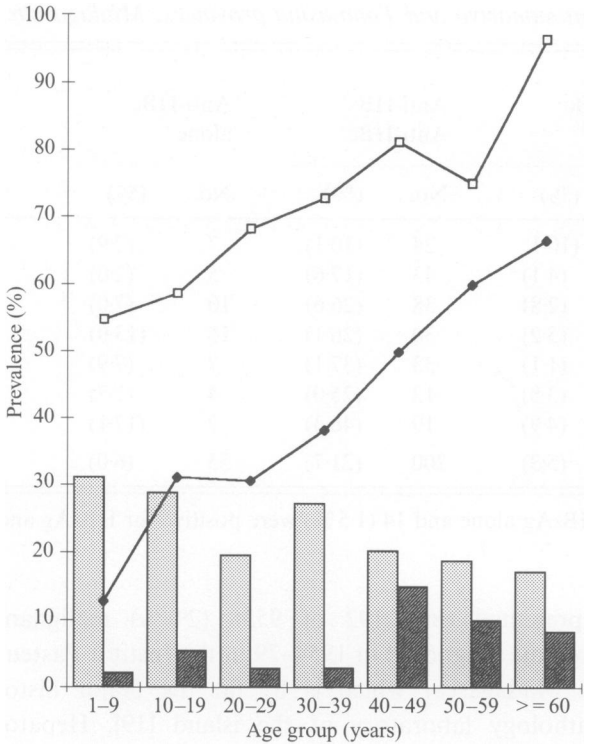

Fig. 2. Age-specific prevalence rate for HBsAg and infection rate for HBV in Madagascar (stippled bars: HBsAg Rural; hatched bars: HBsAg Urban; □, 1 marker positive rural; ◆, 1 marker positive Urban).

(42·6 *vs.* 34·6%), after adjusting for age ($P < 0{\cdot}01$). Anti-HBc was not associated with any other marker of HBV infection in 55 subjects (6% of the whole sample).

A positive titre for anti-HBs was observed in 282 individuals (30·6%), of whom 82 (8·9%) were positive for anti-HBs alone. The positivity for anti-HBs alone was not related to age or gender.

HBV infection was not related to climate, but the epidemiological pattern did appear to be radically different in urban and rural place of residence (Fig. 2). Among people living in urban areas, overall HBsAg and anti-HBc prevalence was respectively 5·3 and 23·0%, whereas, for the same markers in rural areas they were respectively 26·0 and 43·6%. These differences were highly significant ($P < 10^{-7}$). In rural areas, highest prevalence for HBsAg was observed in infancy and decreased steadily with age. Conversely, in urban areas HBsAg prevalence was 2·1–5·4% in individuals $\leqslant 39$ years old, and then suddenly increased to 15% after 40 years old. In all age groups, the overall infection rate was twofold higher in rural than in urban areas (65·4 *vs.* 34·2%). The positivity for anti-HBs alone was significantly higher in rural areas (11·1 *vs.* 1·1%).

Positive titre for HBsAg or anti-HBc were not related to a history of blood transfusion or surgery. Of the 892 individuals (97%) who reported a history of injection, 855 had a history of vaccination and 782 a history of parenteral therapy. The prevalence of HBV infection was not significantly associated to past history of parenteral injections.

We sorted the 921 subjects with regard to their immunological status according to the results for the different markers of HBV infection (Table 1). The total number of individuals without any marker was 394 (42·8%) and recovery from infection, defined on the basis of positivity for both anti-HBs and IgG anti-HBc, was observed in 200 individuals (21·7%). The overall frequency of chronic carriers, defined as individuals presenting positivity for HBsAg and IgG anti-HBc, was 10·4–13% in rural areas, 3·3% in urban areas ($P < 10^{-4}$). It was significantly higher in males than in females ($P < 0{\cdot}01$). Among chronic carriers, 49 also were positive for HBeAg (5·3% of the whole sample, 95% CI 3·1–8·9; 6·6% in rural areas and 1·6% in urban areas) and could be considered as high infectivity carriers. The 1–9 year age group represented 50% of the high infectivity carriers.

DISCUSSION

The overall prevalence for HBsAg of *c.* 20% is commonly reported in sub-Saharan Africa or in Asia (3–5). However such a marked difference as described here between rural and urban populations is uncommon. Usually, HBV infection occurs most often in underprivileged urban populations. Nevertheless, surveys in South Africa have shown a remarkably lower HBV carrier rate among urban black children compared with children in rural areas [6]. In Madagascar, similar differences were observed. This phenomenon cannot be attributed to ethnic factors because the same differences were observed in each of the two provinces where the main ethnic groups were represented in towns and countryside. Socio-economic conditions are not very different between urban and rural communities for a majority of individuals. The moderate prevalence of HBsAg-positivity in urban populations in the present survey is consistent with results of previous studies in Madagascar which were carried out for the most part in Antananarivo (7–12).

For rural areas, our results confirmed the very high HBV infection rate and are in agreement with a previous study [1] in which HBsAg was found in

Table 1. *Age-specific frequency of hepatitis B markers in Antananarivo and Toamasina provinces, Madagascar*

Age group (years)	No. tested	HBsAg$^+$ Anti-HBc$^+$ HBeAg$^-$		HBsAg$^+$ Anti-HBc$^+$ HBeAg$^+$		Anti-HBs$^+$ Anti-HBc$^+$		Anti-HBc$^+$ alone	
		No.	(%)	No.	(%)	No.	(%)	No.	(%)
1–9	237	4	(1·7)	24	(10·1	24	(10·1)	7	(2·9)
10–19	244	11	(4·5)	10	(4·1)	43	(17·6)	5	(2·0)
20–29	143	7	(4·9)	4	(2·8)	38	(26·6)	10	(7·0)
30–39	115	12	(10·4)	6	(5·2)	30	(26·1)	15	(13·0)
40–49	89	7	(7·9)	1	(1·1)	33	(37·1)	7	(7·9)
50–59	52	3	(5·8)	2	(3·8)	13	(25·0)	4	(7·7)
⩾ 60	41	3	(7·3)	2	(4·9)	19	(46·3)	7	(17·1)
Total	921	47	(5·1)	49	(5·3)	200	(21·7)	55	(6·0)

* Early acute infection: 79 individuals (8·6%) were positive for HBsAg alone and 14 (1·5%) were positive for HBsAg and HBeAg and negative for anti-HBc.

18·9% of individuals > 2 years old in a first village and in 30·5% of inhabitants > 1 year old in a second one. We cannot explain either the extent of the difference in prevalence of HBV infection between rural and urban communities, or the difference in the modalities of transmission. In rural areas, infection occurs mostly during infancy, suggesting predominant perinatal or postnatal transmission. The high frequency of HBsAg-positivity in infancy and in childhood cannot be explained solely by mother to child transmission because only 17·2% of rural women aged 15–45 years are positive. On the other hand, poor and crowded living conditions, which are the rule in rural areas, could permit horizontal transmission between siblings, facilitated by a high rate of HBeAg carriers, as described elsewhere [13, 14]. As for a potential participation of arthropod vectors such as ticks or bedbugs in mechanical transmission of hepatitis B virus [15–17], even if this appealing hypothesis has any basis, nothing allows the assessment of its epidemiological importance in Madagascar. Circumcision, systematically carried out in boys around 3 years old, does not seem to be a risk factor because there is no difference in the rates of HBV infection between males and females in childhood. The interpretation of frequency of subjects with anti-HBs alone set a problem insofar as hepatitis B vaccination is very seldom used in Madagascar.

The high prevalence of chronic carriage of HBsAg is a result of a contamination occurring mostly in infancy and early childhood [18]. With such conditions, a high incidence of cirrhosis and primary hepatocellular carcinoma (HCC) would be expected in Madagascar. However, identified cases are rare; HCC represented only 192 of 9538 (2·0%) malignant tumours diagnosed in 1954–79 in the Institut Pasteur de Madagascar which is by far the major histopathology laboratory of the island [19]. Hepatocellular carcinoma pathology could be underestimated because of the poor condition of health care delivery and the grossly inadequate means of diagnosis in most of the country. Post mortem examinations are rare in Madagascar, and the lack of this source of information is regrettable. The true rate of complications of HBV infection in Madagascar should be more thoroughly defined, in order to assess the need for hepatitis B immunization in early childhood on the island.

ACKNOWLEDGEMENTS

We gratefully acknowledge the Health Authorities of the provinces of Antananarivo and Toamasina for their support in the field. This study was supported by a grant from Pasteur-Mérieux Sérums & Vaccins. We thank Dr Suzanne Chanteau for critical reading, and Miss Alicia Jacobs for help in the translation.

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