European Journal of Epidemiology **11**: 569–573, 1995.

Trends in hepatitis A virus infection with reference to the process of urbanization in the greater Madrid area (Spain)

Carmen Amela[1], Isabel Pachón[1], Rafael Bueno[2], Carmen de Miguel[1] & Fernando Martinez-Navarro[1]

[1] *National Centre of Epidemiology, Instituto de Salud 'Carlos III', Madrid, Spain;* [2] *Epidemiology Department, Board of Public Health, Madrid Regional Authority, Spain*

Accepted in revised form 14 June 1995

Abstract. Hepatitis A is an infection transmitted by the fecal-oral route. Endemicity within a specific country is directly related to sanitation and hygienic standards, while being inversely related to socio-economic conditions. We studied how the process of urbanization witnessed in Madrid had influenced the transmission of hepatitis A infection. In the Madrid Autonomous Region, this process first began in the early sixties and was not brought to a close until the late seventies. Catalytic models were used to estimate the annual infection rate, λ, on the basis of seroprevalence data stratified by age. A cohort effect related to a fall-off in infancy-related hepatitis A virus (HAV) is to be observed in the results for the last few years. The model permits four birth cohort-based groups to be differentiated by λ: individuals born pre-1960, λ = 0.082 (95% CI 0.095–0.070); those born in the early sixties, λ = 0.052 (95% CI 0.060–0.042); whose members were born in the late sixties, λ = 0.033 (95% CI 0.041–0.025); and those born in the late seventies, λ = 0.017 (95% CI 0.020–0.013). The first group includes those born before the urbanization process had started. The second and third groups coincide with the development stage of that process, hence exhibiting transitional rates. The fourth group reflects the process in its consolidation stage. This reduction in the transmission of infection has changed the manner of presentation, so that while isolated cases or small outbreaks tend to be more common nowadays, occasionally epidemics may evolve explosively. The average age at presentation has risen and the likelihood of symptomatic infection is higher.

Key words: Epidemiological method, Hepatitus A virus, Seroprevalence, Transmission

Introduction

Hepatitis A is an infection transmitted by the fecal-oral route. Being an enterically transmitted organism, endemicity as well as risk groups within any country are directly related to sanitation and hygienic standards, and inversely related to socio-economic conditions [6]. Nowadays, these elements give rise to what are basically two patterns of presentation: the first, where most children become infected during the first 10 years of life and almost all adults are immune, a pattern characteristic of the less developed countries; and the second, where the population tends to come into contact with the virus at a later age, a pattern typical of developed countries. In the latter case, three different epidemiological situation are found simultaneously: the first corresponds to adults and is characterized by high prevalence of HAV infection related to the cohort effect, with high rates of infection being registered during infancy [11]; the second is marked by low prevalence during infancy, as improvement in sanitation is gradually consolidated in the developed countries, thereby considerably reducing the infection rate; lastly, there is the situation linked to the period of transition between the above two stages, giving rise to different slopes for each country, depending on the speed of improvement in hygiene and sanitation. A wide diversity is to be seen in the degree to and manner in which the three epidemiological situation combine in several European countries [7].

In 1988, an age-stratified seroprevalence study was carried out in the Madrid Region, the results of which were used to calculate the percentage of people infected with hepatitis A and to compile information on the transmission of the infection in this community. Age is a pointer to time and, as a consequence, changes in age-distribution of seropositivity in any given population can furnish information on that population's experience of the disease, and in particular, on the annual infection rate. In any community where an infection is endemic, prevalence will increase with age until it reaches a plateau of approximately 100% at a critical age, depending on the infection rate.

It is our view that the process of urbanization generated in modern societies is characterized by the tendency of the more dynamic urban areas to become part of a greater, outward-moving metropolitan sprawl. A feature of this process is for the quality of life enjoyed in the original urban centre to spread out towards the areas under the city's influence. In other words, we are faced here by a process – namely, that of the growth of the metropolis – which goes beyond mere demographic growth and the physical extension of any particular city. Indeed, it is a process whereby zones under the city's influence become urbanized in such a way that the creation of urban infrastructures, the introduction of city management techniques and the circulation of profits generated within the territory concerned give rise to a spacial construct far removed from the profile of the classic city [12].

The influence exerted by such a process upon the health of the population is, as regards communicable diseases, to be seen in the progressive change in traditional patterns of transmission associated with water and the like. The deçlining trend in typhoid fever, dysentery, hepatitis A and intestinal parasitoses would seem to reflect this process, a process whose manner of presentation will depend on the specific mode assumed in the different social environments.

We believe that the specific urbanization process experienced in the Madrid Region has influenced the strength of hepatitis A infection. The process was initially characterized by the development in the early sixties of a metropolitan area around a large-sized urban nucleus, accompanied by a parallel development in sanitation. Once development of this hub had attained an appreciable degree of progress, there followed a centrifugal dispersion of resources outwards, leading to the development of outlying areas, which in turn came to resemble the urbanized nucleus [12]. As a consequence of the consolidation of these urbanized areas, great strides were made in sanitation. 1975 marked an end to this chapter of change in the pattern of urbanization in Madrid [15].

Materials and methods

Between January and February 1988, sera and questionnaires were collected from 1632 patients who visited primary medical centres in the Madrid Autonomous Region for routine medical examinations; sera specimens were tested for antibodies against HAV. The following age groups were studied: 2–3 years old, 7–11 years old, 20–39 years old and over 50 years old. All persons examined were residents of the Madrid Region [5].

The technique used to determine the presence of anti-HAV antibodies was a commercial solid phase radioimmunoassay kit (HAVAB, Abbot Laboratories, Chicago, IL, USA). Cut-off point was calculated in accordance with the manufacturer's instructions.

The demographic data and the housing characteristics were obtained from the Spanish Population and Housing Census [3, 14]. Using seroprevalence data stratified by age, catalytic models allow for estimation of the parameter known as force of infection or annual infection rate [9, 10, 16]. The cumulative distribution function, $F(a)$, gives the probability of being infected by age a, and is represented by:

$$F(a) = 1 - \exp\left[-\int_0^a \lambda(\alpha)\, d\alpha\right]$$

where λ is the annual infection rate.

This model assumes that λ is independent of age and time, and that, after loss of maternally-derived antibodies, all individuals are susceptible. Furthermore, it is assumed that the random variable associated with the number of infections occurring in one year, has a Poisson distribution with mean μ; hence, the annual infection rate would be [4]:

$$\lambda = 1 - e^{-\mu}.$$

The probability of infection p_i in a person within the ith age group, for which the mean age is A_i, is:

$$p_i = 1 - e^{-\mu A_i}$$

where p_i is the expected proportion of seropositives in the population at ith age. Taking logarithms from the former equation, in GLIM terminology the natural logarithm is a function called %log, we get:

$$\log\,[-\log(1 - p_i)] = \log \mu + \log A_i = \beta_0 + x_i$$

where $\beta_0 = \log \mu$ and the explanatory variable $x_i = \log A_i$. Assuming that λ is constant and independent of age, the regression coefficient related to age x_i will be equal to one. When the model assuming a constant infection rate is rejected, a new model with a different infection rate for the individuals in each age group is fitted, using the levels of the factor age groups. The standard error (SE) in the estimated annual infection rate λ and the confidence intervals are given by:

$$\text{SE}\,(\hat{\lambda}) \approx e^{\hat{\beta}_i} \exp[-e^{\hat{\beta}_i}]\ \text{SE}\,(\hat{\beta}_i)$$

$$\text{CI} = \hat{\lambda} \pm 1.96\ \text{SE}\,(\hat{\lambda}).$$

Seropositive individuals y_i out of n_i, in the ith age group, have a binomial distribution. Estimation of parameters was effected by fitting maximum likelihood function [1]:

$$L = \prod_{i=1}^{n} F(a_i)^{y_i}[1 - F(a_i)]^{n_i - y_i}.$$

These models have been fitted using appropriate GLIM macros. For simple comparison of proportions the X^2 method was employed. The Mantel-Haenszel procedure was used to control for confounding. Use was made of multiple linear regression to investigate the relationship between the annual infection rate and, as indicators of the level of urbanization in the community, the following determinant factors: percentage of drinking water per home, percentage of hygienic services per home based on census data and the year in which the census was carried out. The Filliben correlation coefficient makes it possible to test whether the assumption of normal distribution has been correctly specified.

Results

The prevalence of anti-HAV among the 1632 persons tested (55.4% females and 44.6% males) was 51.6%. The prevalence of anti-HAV by age is shown in Table 1.

Table 1. Prevalence of Hepatitis A virus by age in Madrid (Spain), 1988

Age (years)	Numbers tested	Anti-HAV positive	
		N	%
2	89	2	2.25
3	190	14	7.37
7	48	4	8.33
8	126	13	10.32
9	100	16	16.00
10	120	16	13.33
11	81	15	18.52
22*	115	60	52.17
27*	194	147	75.77
32*	116	107	92.24
37*	95	91	95.79
57*	115	114	99.13
62*	129	129	100.00
67*	114	114	100.00
Total	1632	842	51.60

* Midpoints of age intervals.

Overall, 54.5% of females and 39.04% of males were positive, but sex-related differences were not statistically significant after controlling by age groups. On controlling by social class, no differences were observed.

Figure 1 shows age-specific prevalence of anti-HAV for: seven European countries, taken from surveys carried out between 1975–1977 [7]; Japan, based on a 1985 study [13]; and Madrid, representing the results obtained in this study. Anti-HAV prevalence in the Madrid area is similar to that described for Japan in 1985 and slightly lower than that of Greece, only in the younger ages. The rise by age in the population with anti-HAV is a common feature of all these studies, despite differences in distribution of antibodies according to age group and country.

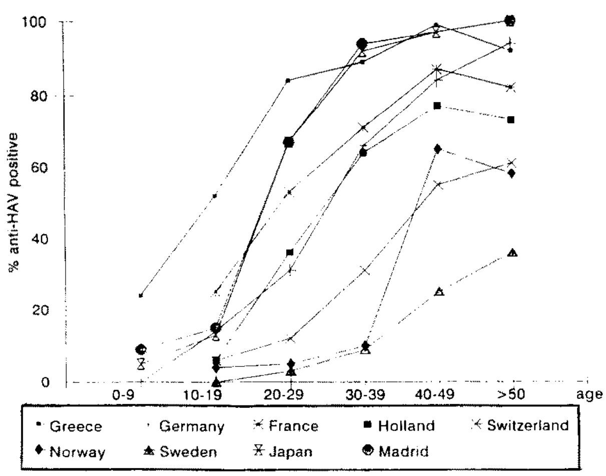

Figure 1. Age-specific prevalence of anti-HAV for seven European countries, 1975–1977, Japan, 1985, and Madrid, 1988.

Assuming a constant annual infection rate, the model applied to fit the observed infected fraction gives the results shown in Table 2. The deviance on fitting the complementary log-log model (deviance of 201.08 on 13 df; ($p < 0.001$) does not support constant infection as a feasible hypothesis for the explanation of our data. Based on the residuals obtained and using the age variable as a factor, we then fitted a model equipped with four levels corresponding to the following age groups: 2–11, 22, 27, and 32–67 years old. This new model has a deviance of 6.74 on 10 df, and supports the hypothesis that different annual infection rates are applicable to

Table 2. Maximum likelihood estimates for the λ parameters, assuming a constant annual HAV infection rate and the goodness-of-fit in Madrid (Spain), 1988

Age (years)	Age groups	Number tested	Number observed	Fitted	Standardized residuals
2	1	89	2	7.57	-2.12
3	1	190	14	23.73	-2.13
7	1	48	4	12.84	-2.88
8	1	126	13	37.72	-4.81
9	1	100	16	32.98	-3.61
10	1	120	16	43.07	-5.15
11	1	81	15	31.33	-3.73
22	2	115	60	71.77	-2.26
27	3	194	147	135.61	1.78
32	4	116	107	88.04	4.11
37	4	95	91	76.67	3.73
57	4	115	114	105.88	2.80
62	4	129	129	120.81	2.96
67	4	114	114	108.21	2.47

Estimate β_0: −3.113
Standard error: 0.038
Scaled deviance: 201.08
df: 13
Significance $p < 0.001$.

Table 3. Maximum likelihood estimates for the λ parameters, allowing for a different annual HAV infection rate and the goodness of fit of the model by age in Madrid (Spain), 1988

Age (years)	Age groups	Number observed	Estimate β_i	Standard error	λ	95% CI
2–11	1	7	-4.08	0.112	0.017	0.013–0.020
22	2	1	-3.39	0.132	0.033	0.025–0.041
27	3	1	-2.95	0.089	0.051	0.042–0.060
32–67	4	5	-2.45	0.081	0.082	0.070–0.095

Scaled deviance: 6.74
df: 10
Significance: ns.

individuals in line with their division into the four age groups. No change is seen in the results when adjusted by social class. These results are set out in Table 3.

In Figure 2a the observed age-specific prevalence is depicted, while in Figure 2b the annual infection rate by year of birth is shown.

The regression model for the annual infection rate using census data, exhibits the greatest $R^2 = 0.99$ for the model. The estimated parameters are:

Variable	*Estimate*	*Standard error*
intercep	21.13	0.56
'hyg'	–0.15	0.02
year	–0.06	0.02

where 'hyg' represents the percentage of hygienic services in housing in the Madrid Region and 'year' represents the census year (see Figure 3). The Filliben correlation coefficient = 0.99, signifying that the assumption of normal distribution is correctly specified.

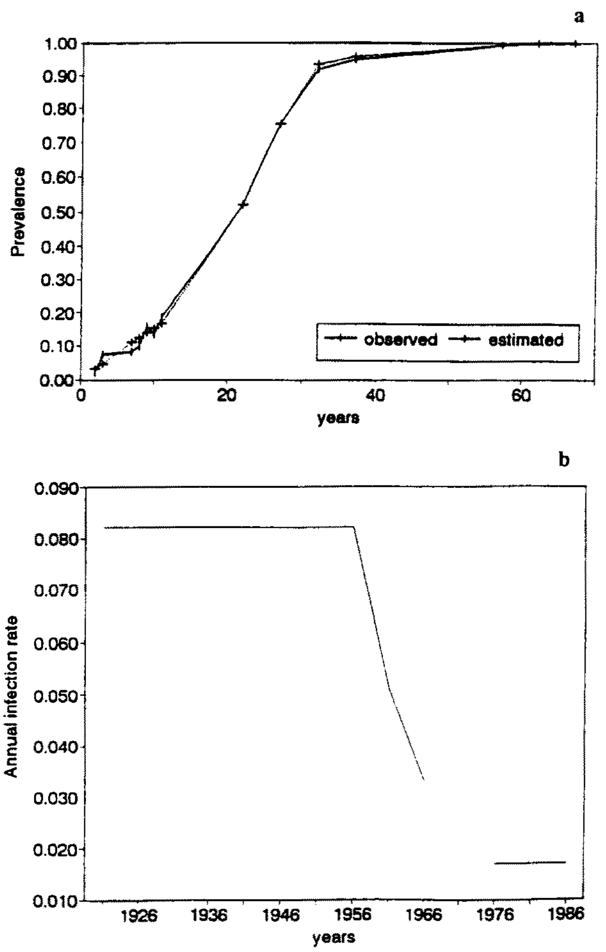

Figure 2. (a) Age-specific prevalence estimated and observated in Madrid in 1988; (b) The annual infection rate estimated by year of birth in Madrid in 1988.

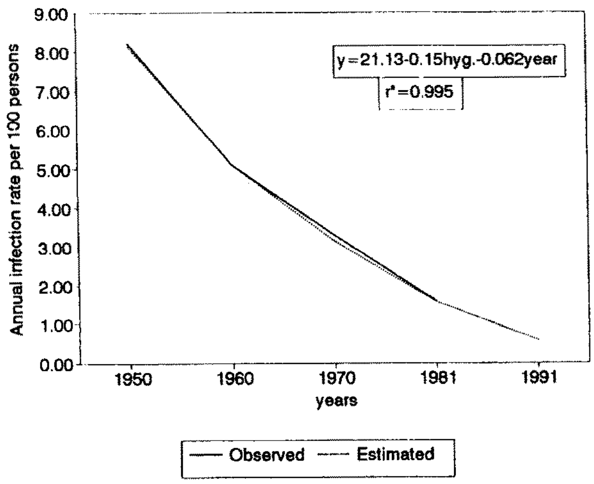

Figure 3. The regresion model for the annual infection rate using census based percentages of hygienic services.

Discussion

The results point to an important decline, over the last few decades, in the age-related increase in prevalence of anti-HAV. This might mirror the cohort effect observed in other countries [6, 8, 11, 13] and could be linked to the reduction in infancy-related HAV in the past few years, due to improved sanitation in the community.

If, despite the ten-year lag between studies, this situation is compared to that of other European countries [16], at that time, only Greece had a higher prevalence than those reported in this study, though account must be taken of possible selection bias in some countries where sera were collected from volunteer blood donors. Prevalences in Mediterranean countries are higher than those found in North European countries, most likely due to the later economic development of the more southern countries, as well as the better climatological conditions that prevail there and allow for an altogether different type of infant activity, through which virus transmission is made appreciable easier.

The annual infection rate estimated for Madrid makes it possible to differentiate four distinct groups, whose characteristics are as follows: firstly, there are those cohorts born pre-1960 and thus over 30 years old, with an annual infection rate of 0.082 (95% CI 0.095–0.070), namely 82 (95% CI 95–70) infections per 1000 persons per year. This group is characterized by the fact that its childhood coincided either with the Spanish Civil War, 1936–1939, or its aftermath when socio-economic and hygienic conditions were precarious, a period that continued until 1958. Secondly, there are the cohorts born in the early sixties, with an annual infection rate of 0.051 (95% CI 0.060–0.042). The third group comprises cohorts born in the late sixties, with an annual infection rate of 0.033 (95% CI 0.041–0.025). At the beginning of the sixties, there was a remarkable boom that led to the urban development of Madrid and a consequent improvement in the sanitary infrastructure. This trend continued without halt until 1975 and the relevant infection rates reflect this transitional period. Fourthly, there are those cohorts born in the late seventies, with an annual infection rate of 0.016 (95% CI 0.020–0.013). This last period is related to the consolidation of a heavily urbanized area, though marginal and underdeveloped areas are still to be seen within the overall process.

The above-described change in the hygienic-sanitary infrastructure, which took place as a result of urbanized development in the Madrid Region and upward socio-economic mobility, may be a determining factor behind the decline in HAV infections.

Until recently, person-to-person transmission by fecal-oral route and common-source outbreaks related to contaminated water were the main modes of transmission. In recent years the disease has been most common among school-aged children and young adults, the main transmission modes being: common-source outbreaks due to contaminated food or water, direct person-to-person transmission and travellers to countries where the disease is endemic [11]. Generally, presentation takes the form of isolated cases or small outbreaks, though occasionally epidemics may evolve explosively.

Any slowing in the speed of transmission of the infection within the Region under study is not expected to correspond directly to the number of clinical cases in existence, since the probability of the infection being asymptomatic is inversely related to age. As the average age of presentation of infection rises, the risk of suffering the disease and the degree of severity both become proportionately greater [6].

The reduction in exposure to HAV has led to an increase in the number of susceptibles, which already exceeds 50% in those under 30 and is set to gradually rise even further. This age group can be considered a risk group if travelling to endemic areas; accordingly, in cases of this nature, individual prophylaxis is called for.

References

1. Aitkin M, Anderson D, Francis B, Hinde J. Statistical modelling in GLIM. Oxford: Clarendon Press, 1990.
2. Benenson AS. Control of communicable diseases in man, 15th ed. Washington, DC: American Public Health Association, 1990.
3. Censos de Población y Vivienda en España, 1950, 1960, 1970, 1981. Instituto Nacional de Estadística.
4. Collet D. Modelling binary data. London: Chapman & Hall, 1991.
5. Encuesta seroepidemiologica en la Comunidad de Madrid. Madrid: Ed. Comunidad de Madrid, 1990.
6. Evans AS. Viral infections of humans: Epidemiology and control, 3rd ed. New York: Plenum, 1989.
7. Frösner GG, Papaevangelou G, Bütler R, et al. Antibody against hepatitis A in seven European countries, I: Comparison of prevalence data in different age groups. Am J Epidemiol 1979; 110: 63–69.
8. Green MS, Tsur S, Slepon R. Sociodemographic factors and the declining prevalence of anti-hepatitis A antibodies in young adults in Israel: Implications for the new Hepatitis A vaccines. Int J Epidemiol 1992; 21: 136–141.
9. Grenfell BT, Anderson RM. The estimation of age-related rates of infection from case notifications and serological data. J Hyg Camb 1985; 95: 410–436.
10. Griffiths DA. A catalytic model of infection for measles. Applied Statistics 1974; 23: 330–339.
11. Gust ID, Lehman NI, Lucas CR. Relation between prevalence of antibody to hepatitis antigen and age: a cohort effect (letter). J Infect Dis 1978; 138: 425–426.
12. Harvey D. Urbanismo y desigualdad social 2nd ed. Madrid: Ed Siglo XXI de España, 1979.
13. Ikematsu H, Kashiwagi S, Hayashi J, et al. A seroepidemiologic study of hepatitis A virus infections: Statistical analysis of two independent cross-sectional surveys in Okinawa, Japan. Am J Epidemiol 1987; 126: 50–54.
14. Informe sociológico sobre la situación social en Madrid. Madrid: Fundación FOESSA, 1967.
15. Precedo A. La red urbana. Madrid: Ed. Síntesis, 1988.
16. Schenzle D, Diezt K, Frösner GG. Antibody against hepatitis A in seven European countries, II: Statistical analysis of cross-sectional surveys. Am J Epidemiol 1979; 110:70–76.

Address for correspondence: Dr Carmen Amela, Centro Nacional de Epidemiología, Sinesio Delgado 6, 28029 Madrid, Spain
Phone: 34-1-3141654; Fax: 34-1-3147970