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The effects of socioeconomic development on worldwide hepatitis A virus seroprevalence patterns

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The effects of socioeconomic development on worldwide hepatitis A virus seroprevalence patterns

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Background Hepatitis A virus (HAV) infection confers long-term immunity, so mathematical analysis of age-specific seroprevalence in populations can reveal changes in the infection rate over time. HAV transmission is related to access to clean drinking water, personal hygiene and public sanitation.

Methods We used an SIR (susceptible-infectious-recovered) compartmental model with age structure to fit a time-dependent logistic function for HAV force of infection for 157 published age-seroprevalence data sets. We then fit linear regression models for socioeconomic variables and infection rate.

Results The proportion of the population with access to clean drinking water, the value of the human development index (HDI), and per capita gross domestic product (GDP) are all inverse predictors of HAV infection rates. Declining infection rates were observed in 65.6% of the surveys.

Discussion This work demonstrates the utility of HAV seroprevalence studies to reveal patterns of change in force of infection and to assess the association between socioeconomic risk factors and transmission rates.

Keywords Hepatitis A virus, seroprevalence studies, socioeconomic development, water

Hepatitis A virus (HAV) infection is a common infection, responsible for about 1.4 million new infections worldwide each year.[1] Infection is generally acquired by the faecal–oral route either through person-to-person contact or ingestion of contaminated food or water.[2] Low income, low educational level, crowding and lack of access to safe drinking water and sanitation facilities are associated with increased HAV infection.[3] As socioeconomic status (SES) and access to safe drinking water are increasing, the HAV infection rate is declining in most parts of the world.[3] However, because HAV infection in children is often asymptomatic but most infected adults present with jaundice and other potentially severe symptoms, this decrease in the infection rate has a paradoxical effect. As socioeconomic conditions improve, individuals become infected at a later age when disease is more severe. Thus, hepatitis A morbidity may increase as the incidence rate of infection decreases.

Population age-immunity structure is important in predicting HAV transmission patterns. In areas with very high endemicity, $\geqslant$30–40% of children acquire infection before 5 years of age and almost all persons have been infected by early adulthood.[1] In these regions there is very little hepatitis A disease. In areas with low endemicity, few children have anti-HAV antibodies, and many adults remain susceptible. Epidemics are uncommon in highly endemic areas because most adults have acquired immunity but in regions with lower levels of adult immunity HAV infections may occur primarily as outbreaks.[4]

Because infection with HAV generally confers lifelong immunity to all strains of HAV, age-specific seroprevalence rates are indicators of the level of susceptibility to severe disease in a population. Furthermore, the shapes of population age-seroprevalence curves reflect the changes in force of infection that have occurred over the lifetimes of the people in the populations (Figure 1). For example, in a population that had a high infection rate until 40 years ago and then experienced a rapid increase in SES and access to improved water sources, the population seroprevalence curve would show that nearly all adults >40 years have antibodies while few persons <40 years of age have immunity. A population with a more gradual decline in the infection rate over time would have a rounder age-seroprevalence curve. A population with a consistently high force of infection would have a steep rise in seroprevalence

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in young children. Thus, it is possible to use data about age-seroprevalence distributions in real populations to determine both when changes in the infection rate occurred and the rate of change over time.

In this paper we use a deterministic model to calculate time-dependent infection rates for 157 sets of age-seroprevalence data from surveys conducted across the globe. We assess regional differences in infection rates and the trend of declining infection rates seen in most regions of the world. We also use linear regression to examine measures of socioeconomic development which might be related to changes in the infection rate over time.

Methods

Mathematical model

We formulated a mathematical model that represents the transmission dynamics for populations with various age and immunity structures. An SIR (susceptible-infectious-recovered) compartmental model with 80 age groups (one-year age compartments for ages 1–80) was used. We assumed that infants entered the population at 1 year of age, when maternal immunity had waned, and all adults were removed from the population before age 81. The distribution of the population by age was estimated using international data from the US Census Bureau,[5] and age-specific death rates were calculated to maintain population size and age-structure.

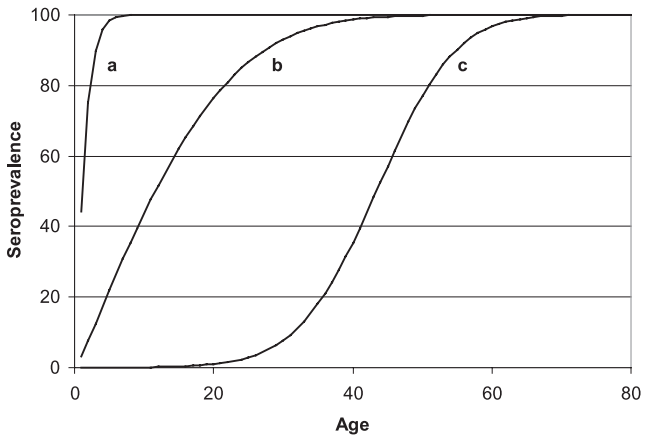

Figure 1 Sample age-seroprevalence curves: (a) high rate of transmission, (b) gradual decrease in force of infection and (c) rapid decrease in force of infection

A flow diagram of the model, which consists of ordinary differential equations, and definitions of model parameters are shown in Figure 2. The equations used are as follows:

$$dS_i/dt = aS_{i-1} - \lambda S_i - (\mu_i + a)S_i$$

$$dI_i/dt = aI_{i-1} + \lambda S_i - \rho I_i - (\mu_i + a)I_i$$

$$dR_i/dt = aR_{i-1} + \rho I_i - (\mu_i + a)R_i$$

where S is the proportion of susceptible persons, I is the proportion of infectious persons, and R is the proportion of immune (recovered) persons in the total population. The subscript i indicates age-specific values, a represents aging, μ_i is the age-specific death rate, ρ is the recovery rate, and λ is the infection rate. For the first age group a birth function, rather than an aging function, was used to add susceptible one-year-olds to the population.

This model structure requires a number of key assumptions. (i) All persons in the population are susceptible to infection until they become infected. (ii) Infection produces lifelong immunity, which can be detected by serological examination. (iii) Mortality due to infection is negligible. (iv) Populations are homogeneous with respect to susceptibility and exposure. (v) The samples consist of individuals who have spent their entire lives in the same population. This assumes, for instance, that members of low-endemicity populations have not travelled to endemic areas. (vi) The immunization rate is very low such that we can assume that immunity is the result of infection and not immunization.

We used a three-parameter symmetric logistic function to describe the infection rate λ over time:

$$\lambda(t) = \frac{\lambda_\infty}{1 + \theta\alpha^{-t}}$$

where λ_∞ is the constant representing the asymptote of the past force of infection, θ and α are constants, $0 < \theta \leq 1$, and $0 < \alpha < \infty$. We set $t = 0$ as the time 100 years before the collection of data. We assumed that the initial population had very high seroprevalence, with all children acquiring immunity in early childhood. The conclusions of the model were not sensitive to the assumption of very high endemicity at the start of the run because the model was run long enough to replace the entire population.

The value of the infection rate, λ, in a given time period (set as one month) determined the proportion of susceptible persons

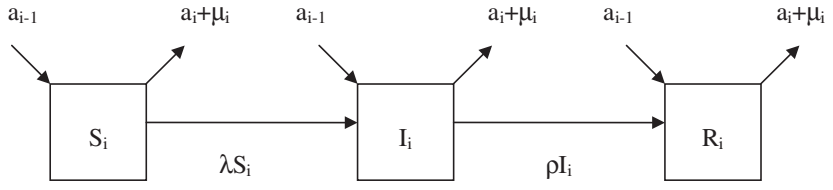

Figure 2 Model of population transmission dynamics. *S*, the proportion of susceptible persons in the total population; *I*, the proportion of infectious persons in the total population; *R*, the proportion of immune (recovered) persons in the total population; N_i, the proportion of the total population of age *i*, where $1 \leq i \leq 80$; *a*, rate of aging from age *i* to age $i + 1$; μ_i, death rate for age *i*; λ, infection rate; ρ, recovery rate (end of infectious stage). In this model we assumed that recovery from the infectious stage occurred after an average of 3 months

in the model population who acquired new infections during that time period. The rate and magnitude of change in λ during the 100 years the model was run defined the shape of the age-seroprevalence curves. The infection rate over time, $\lambda(t)$, was described by λ_∞, θ and α.

For each of the 157 data sets we analysed, we used Berkeley Madonna software to fit the values of λ_∞, θ and α that generated age-seroprevalence curves that most closely matched the actual data. These values were fit by writing a least squares function for each dataset. The equation of the optimizing function was:

$$\frac{\sum_{j=1}^{k} m_j(\hat{p}_j - p_j)^2}{\sum_{j=1}^{k} m_j}$$

where $\hat{p}$ was the reported fraction of a particular age group with anti-HAV antibodies from the literature, p was the seroprevalence for that age group generated by the computer, and m was the age range in each of the k number of age groups j. The optimizing function minimized the average difference between observed seroprevalence rates and the corresponding seroprevalence rates generated by the computer for each age or age group.

Each model was run for 100 years, ending at the time of data collection, and the calculated infection rate at the time of data collection was recorded. Age-group seroprevalence rates for model populations, such as the proportion of adults aged ⩾30 with immunity, were calculated from the one-year age compartments. We also calculated the derivative of the equation for the infection rate so that we could find both the slope of the change in λ over time and the time when the decrease in λ was most rapid:

$$\lambda(t)' = \frac{\lambda_\infty \theta \alpha^t (\ln \alpha)}{(\alpha^t + \theta)^2}$$

Data collection

Seroprevalence data

An extensive search of the hepatitis literature identified 172 reports of anti-HAV seroprevalence by age group. From the analysis, 15 small datasets, defined as averaging <5 persons per age within the age range covered by the study, were removed. The remaining 157 datasets (Table 1) included 7 studies from sub-Saharan Africa,[6–12] 31 from the Americas,[13–36] 40 from Asia and the Pacific,[37–62] 62 from Europe[63–108] and 17 from the Middle East and North Africa.[109–124]

For our sample data we assumed that reported seroprevalence rates provide a correct measure of population immunity and that the sample population was representative of the source population. In particular, we assumed that the distribution of study participants by age within reported age groups reflected the actual distribution by age of the source population and that the sample population was not skewed towards the young or old within each age group.

Water data

The United Nations' estimates of the percentage of each nation's population with access to improved water in 1980, 1990 and 2000, or as many years as were reported, were collected.[125] A line was fit through these points and used to estimate the level of water coverage for each study at the time of data collection.

Table 1 Location of included studies, by region

Region	Countries
Africa (*n* = 7)	Cameroon
	Dem. Rep. Congo
	Ethiopia
	Senegal
	Sierra Leone
	South Africa (2)
Americas (*n* = 31)	Argentina (2)
	Belize
	Bolivia (3)
	Brazil (10)
	Canada (3)
	Chile (2)
	Costa Rica
	Dominican Republic
	Jamaica
	Mexico
	Peru
	Uruguay (2)
	USA
	Venezuela (2)
Asia (*n* = 40)	Australia (2)
	China (9)
	Hong Kong (2)
	India (6)
	Indonesia (2)
	Japan (8)
	Korea
	Malaysia
	Nepal
	Singapore
	Sri Lanka
	Thailand (5)
	Vietnam
Europe (*n* = 62)	Austria (2)
	Belgium (2)
	Czech Republic
	Denmark
	France
	Germany (4)
	Greece (5)
	Greenland
	Iceland (2)
	Italy (13)
	Netherlands (2)
	Poland (4)
	Portugal (2)
	San Marino

Table 1 continued

Region	Countries
	Spain (14)
	Sweden (3)
	Switzerland
	United Kingdom (3)
Middle East (n = 17)	Algeria
	Iran
	Lebanon
	Morocco
	Pakistan
	Saudi Arabia (6)
	Syria
	Turkey (5)

When study populations were clearly identified as urban or rural, an urban- and rural-specific water coverage estimate was also recorded. When data on water coverage for high-income nations (Europe, United States, Canada, Australia and Japan) were missing, we assumed that those nations had 100% water coverage. Data for six of the surveys conducted in low-income areas were not available.

Socioeconomic data

The Human Development Index (HDI) calculated by the United Nations Development Programme (UNDP) incorporates data on life expectancy, education and standard of living [gross domestic product (GDP)] into an index number. The HDI for each nation in 1975, 1980, 1985, 1990, 1995 and 2001, or as many years as were reported, were collected and a linear fit used to estimate HDI for each study year.[126] Data for four surveys were unavailable. We also collected the United Nations estimates of the per capita GDP in current international dollar purchasing power parity (PPP) for 1986, 1990 and 2000, or as many years as were reported.[127] A line was fit through these points and used to estimate GDP per capita for each study at the time of data collection. Data for 17 surveys were unavailable.

Linear regression was used to fit models for predicting the infection rate at the time of data collection. Predictor variables included the proportion of the population with access to clean water, HDI, per capita GDP and survey year. Simple and multiple regressions, with and without interaction terms, were fit.

Results

Force of infection plots (Figure 3) and their corresponding age-seroprevalence curves (Figure 4) were obtained for 157 datasets using the techniques described in the Methods section.

A crude value for the average annual infection rate in each region was calculated by taking the mean infection rate of all the studies from that region (Table 2). Average annual infection rates were highest in Africa (0.60, or 600 infections per 1000 susceptible persons per year), followed by the Americas (0.34), the Middle East (0.22), and Asia (0.21). Rates in Europe (0.01, or 10 infections per 1000 susceptible persons per year) were the lowest of any region.

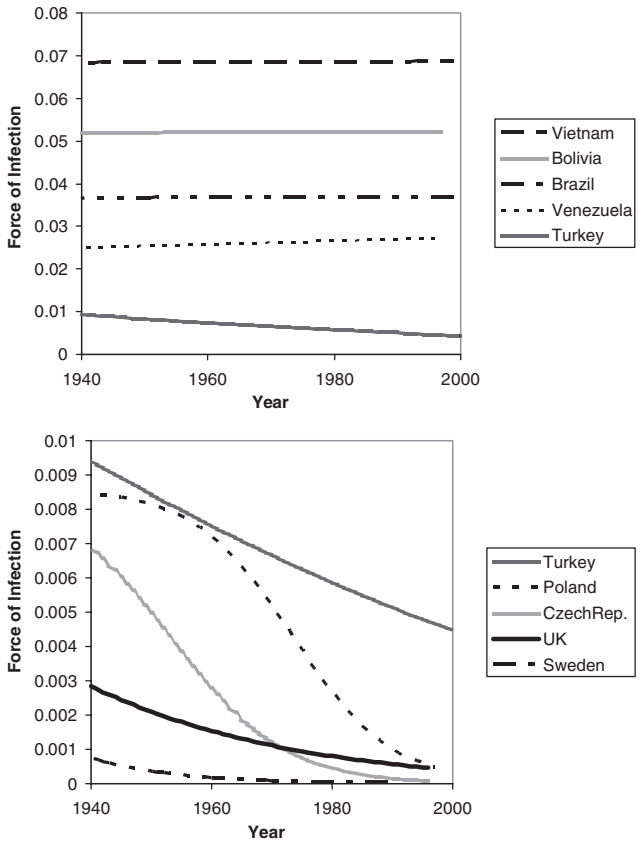

Figure 3 Sample force of infection plots at the time of data collection for selected countries.[24,27,30,72,75,96,113,118,133]

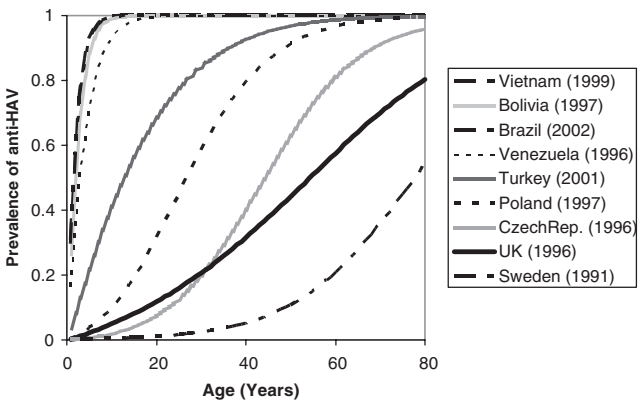

Figure 4 Corresponding age-seroprevalence curves at the time of data collection for selected countries.[24,27,30,72,75,96,113,118,133]

The ability of water and two measures of socioeconomic development to predict infection rates was assessed using simple linear regression (Table 3). The estimated percentage of the population with access to an improved water source, as defined by the United Nations, is a significant predictor of the force of infection (r^2 = 0.37) (Figure 5). A correlation for region-specific mean water coverage rates and mean forces of infection showed a very strong correlation (r^2 = 0.98) (Figure 6).

Table 2 Regional statistics for force of infection

	Total	Africa	Americas	Asia	Europe	Middle East
Number of surveys	157	7	31	40	62	17
Average infection rate (at time of data collection) (mean ± SD)	0.18 ± 0.41	0.60 ± 0.24	0.34 ± 0.74	0.21 ± 0.37	0.01 ± 0.02	0.22 ± 0.24
Surveys from 1990 and later ($n = 83$)	0.19 ± 0.36	0.49 ± 0.25	0.25 ± 0.44	0.31 ± 0.45	0.01 ± 0.01	0.21 ± 0.30
Surveys from before 1990 ($n = 74$)	0.16 ± 0.47	0.62 ± 0.22	0.68 ± 1.35	0.11 ± 0.22	0.02 ± 0.03	0.23 ± 0.19
Studies with decreasing force of infection (%)	66	0	42	57	97	41
Mean % of susceptible adults (ages 30–80)	13	0	7	8	24	3

Table 3 Linear correlation for force of infection

	Total	Africa/ Middle East	Americas	Asia	Europe
Water	$r^2 = 0.37$	$r^2 = 0.24$	$r^2 = 0.60$	$r^2 = 0.08$	$r^2 =$ NA
	$P < 0.0001$	$P = 0.032$	$P < 0.0001$	$P = 0.075$	$P =$ NA
	$n = 151$	$n = 19$	$n = 30$	$n = 40$	$n = 62$
HDI	$r^2 = 0.26$	$r^2 = 0.48$	$r^2 = 0.30$	$r^2 = 0.33$	$r^2 = 0.21$
	$P < 0.0001$	$P = 0.0003$	$P = 0.001$	$P = 0.0001$	$P = 0.0002$
	$n = 153$	$n = 23$	$n = 31$	$n = 39$	$n = 60$
GDP	$r^2 = 0.13$	$r^2 = 0.52$	$r^2 = 0.08$	$r^2 = 0.12$	$r^2 = 0.08$
	$P < 0.0001$	$P = 0.0003$	$P = 0.133$	$P = 0.052$	$P = 0.038$
	$n = 140$	$n = 21$	$n = 31$	$n = 33$	$n = 55$
Year	$r^2 = 0.01$	$r^2 = 0.08$	$r^2 = 0.01$	$r^2 = 0.11$	$r^2 = 0.12$
	$P = 0.137$	$P = 0.192$	$P = 0.656$	$P = 0.035$	$P = 0.005$
	$n = 157$	$n = 24$	$n = 31$	$n = 40$	$n = 62$

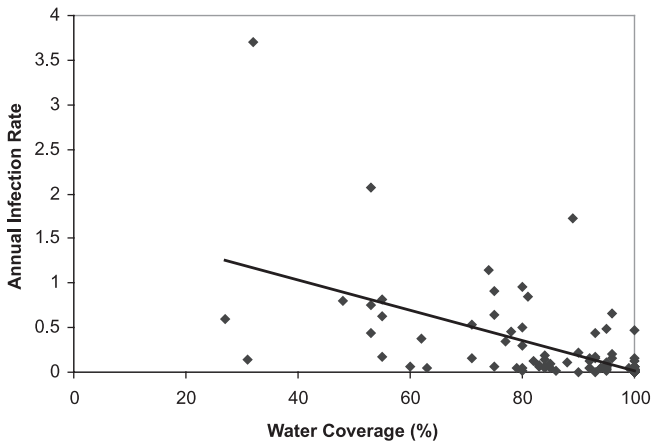

Figure 5 Water Coverage vs Force of Infection ($r^2 = 0.37$). Each point represents one of the 157 studies included in this analysis. Infection rates were calculated from age-seroprevalence data using our mathematical model. Water coverage data is from the UN [124]

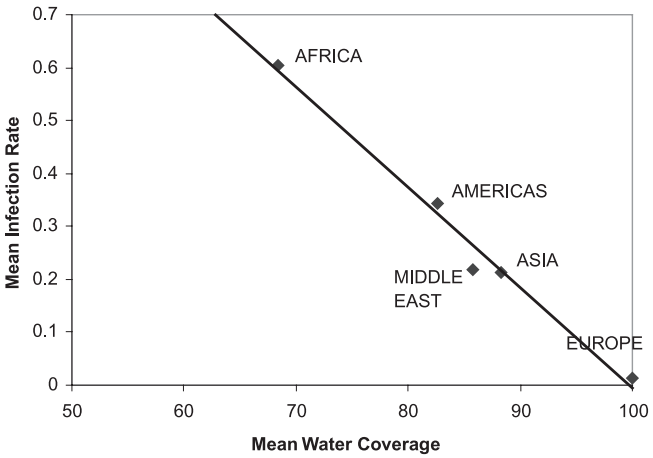

Figure 6 Correlation for Regional Means ($r^2 = 0.985$). Mean water coverage is the estimated proportion of each region's population with access to safe drinking water. The estimates for regional infection rates were calculated by taking the mean of the infection rates calculated for studies in each region

The HDI and per capita GDP are also significant independent predictors of infection rate (Table 3). When variables for both water coverage and HDI are included in the model, both water ($P < 0.0001$) and HDI ($P = 0.038$) are significant predictors ($r^2 = 0.39$). When variables for both water coverage and GDP are included in the total model, water remains a significant variable ($P < 0.0001$) and the correlation increases to $r^2 = 0.42$, although GDP is not significant ($P = 0.354$).

Study year is an independent predictor of infection rate for both Europe ($r^2 = 0.12$, $P = 0.005$) and Asia ($r^2 = 0.11$, $P = 0.035$), where water coverage rates in high-income nations have not changed significantly over the survey years. In most

nations with complete water coverage and relatively low forces of infection, the infection rate has continued to decrease over time. To assess possible co-effects of SES, water coverage and study year, interaction terms were added to the model. None of the interaction terms are significant predictors of the infection rate.

Declining infection rates were observed in 65.6% of the surveys (Table 2). None of the studies from Africa showed a decrease in infection rate whereas nearly all of the studies from Europe (97%) did. About half the studies from the Middle East (41%), the Americas (42%) and Asia (57%) indicated decreases in force of infection. An analysis of the factors that predict a decreasing infection rate, regardless of the value of the infection rate at the time of data collection, showed that higher values for HDI, per capita GDP and water coverage are strongly associated with a declining infection rate. Of the surveys >80% showing decreasing infection rates were from nations reporting complete water coverage. The mean water coverage rate was 80% for surveys indicating no decline compared with 97% for surveys showing a decline. Mean HDI values were 0.65 and 0.83, respectively. Although surveys that showed no decrease in the infection rate were found for the entire range of values for water coverage and HDI, a decline in infection rate was seen only in surveys from areas with an HDI value >0.58 or a water coverage rate >55%.

The proportion of adults aged ⩾30 without immunity to HAV, an indication of the risk of severe hepatitis A disease, ranged from 0% in Africa to nearly 24% in Europe. The proportion of susceptible adults in surveys showing a decreasing infection rate was 18% compared with only 4% in surveys showing no decrease.

Discussion

We used a symmetric logistic function to fit a time-dependent infection rate for 157 age-seroprevalence datasets. We found evidence that HAV infection rates are decreasing in most regions of the world and that water development is crucial in reducing transmission rates. This work demonstrates the utility of HAV seroprevalence studies in revealing patterns of change in force of infection and in assessing the association between socioeconomic risk factors and transmission rates.

A number of previous studies have calculated HAV infection rates using seroprevalence data and symmetric logistic functions,[49,91,128,129] a least squares parametric survival model,[130] a stochastic Markov chain model[39] and a binomial likelihood function.[131] Others have assessed the effect of decreases in the basic reproduction number, R_0, on the shape of age-seroprevalence plots.[132,133] No previously published works have evaluated more than eight forces of infection or compared data from across the globe.

Caution must be used when interpreting the results of our correlations because studies were selected for inclusion based on availability and sample size, rather than on demographic or geographic representativeness. Within each region, certain countries were overrepresented while data from the majority of countries were not included (Table 1). Within each nation, the populations included in our sample may not have been representative of the total national population with regard to SES, urban or rural residence, water coverage or age structure. Missing data on sample size may have led to the inclusion of some surveys that did not meet the selection criteria and limited reporting of urban/rural status may have caused errors in the water coverage estimates. The estimate of regional infection rates did not account for variations in sample size or quality among included studies.

Studies at the local level have found evidence of an association between type of water source and water storage, the quantity and quality of water available, the reliability of water treatment and sanitation facilities and the number of taps in the home in addition to income, crowding, family size and education.[3] Water improvements are closely related to other aspects of socioeconomic development, including decreased crowding, increased education and increased income, so it is difficult to separate out the effects of water access from economic growth. Regardless, the higher correlation between water and infection rate indicates that access to clean water may be very important in reducing HAV transmission. We believe that more accurate information on water coverage levels for the surveys included in our sample, such as data for the state or provincial level rather than the national level, would probably yield a higher correlation between higher water coverage and lower infection rates. For example, several of the studies included in our analysis indicated that their study site was rural or urban. Using the United Nations' urban- or rural-specific estimates of water coverage rather than the total estimate of water coverage improved the fit of the models, although we did not include this information in our Results section because few studies could be classified by population density.

Determining the mechanism by which water improvements cause a decrease in transmission is challenging. Declining transmission could result from improved hygiene practices (which reduce direct transmission), better sanitation (which reduces waterborne transmission) or a combination of hygiene and sanitation. The separate effects of increased water quantity and improved water quality are also difficult to distinguish. Increased quantity allows more water for washing and cleaning and a decreased need for water storage, which is associated with increased HAV infection risk.[3] Increased quality directly decreases risk of disease transmission because of a reduction in the ingestion of the virus in water. Further studies of the mechanisms for water-related transmission of HAV would improve both our understanding of the factors that lead to decreasing transmission and our ability to model the various modes of transmission of HAV. Serological data will be tremendously useful in developing more detailed studies of transmission.

More detailed information on the changes in SES over time would also improve our model. We focused on the relationship of water, SES, average GDP and force of infection at the time of data collection so as to minimize the error that could be introduced by using water and socioeconomic data collected at different times using different methods and standards. We, therefore, did not fully explore the information on past infection rates provided by the model. In particular, our analysis of the experience of older persons in the population in this paper was limited since the immunity of older adults is probably more reflective of their exposure experience in the distant past than in the recent past.

Given that HAV has multiple modes of transmission, safe drinking water does not eliminate risk of infection. We observed that even in areas with 100% water coverage, the infection rate is decreasing over time. One limitation of the force of infection model we used is that it is unable to fit infection rates for

epidemics. Adding a sine function to our force of infection equation would allow for these epidemic fluctuations in the infection rate to be modelled. However, because epidemics are seen only in low infection rate areas and because our correlations looked only at the infection rate at the time of data collection (which is the same for either force of infection model), this limitation should not change the conclusions of this study. Also, the lack of realistic age structuring of contacts in the model is a limitation that we do not feel invalidates any of our conclusions.

We also chose to treat all samples as independent rather than as part of a longitudinal study. Although we found many examples of data collected over time from the same location (as was the case for some studies from Japan, Italy and other areas), the infection rates for some of the data could not be fit because the seroprevalence rate of the presumed age cohort decreased over time, violating our assumption of lifelong immunity. For example, a series of studies in secondary schools in Bangkok, Thailand, showed decreasing seroprevalence in age cohorts over time.[134] In this case, the decreasing seroprevalence was probably due to a replacement population—higher SES students replacing lower SES students—rather than a true decrease in seroprevalence in the initial population. Although we were unable to use longitudinal data to assess if the initial populations experienced a change in the force of transmission over time, a force of infection curve was fit to each individual dataset. The information provided by each is valid if independence is assumed.

This analysis of HAV seroprevalence has revealed important patterns about regional risk factors for transmission. Water and socioeconomic development are associated with decreasing infection rates and increasing adult susceptibility levels. In Africa, where transmission is highly endemic, the provision of clean water for both drinking and hygiene is a priority for disease control. Developed countries in Europe, North America and other parts of the world may be rapidly increasing their potential for epidemics as the proportion of individuals susceptible to HAV infection increases. Targeted vaccination for high-risk groups should be considered in these populations.[2] In the transition economies of Asia, Latin America and the Middle East, infection rates are beginning to decrease. The gradient of the decline, whether rapid or gradual, may determine if HAV transmission remains endemic or shifts to epidemic patterns. In this paper we have demonstrated that HAV serology provides an excellent tool for assessing infection rates in populations. Studies that sample different risk groups by water quality, economic status and/or sanitary conditions and gather lifetime histories of exposure should be able to further elucidate risk factors for transmission.

KEY MESSAGES

- Seroprevalence by age data can be used to calculate the hepatitis A virus (HAV) infection rate over time.
- Mathematical models indicate that HAV infection rates are declining in most regions of the world.
- Hepatitis A virus infection rate is correlated with access to clean drinking water and socioeconomic indicators.

References

[1] World Health Organization. Hepatitis A vaccines. *Wkly Epidemiol Rec* 2000;**75:**38–44.

[2] Centers for Disease Control and Prevention. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 1999;**48:**1–37.

[3] Jacobsen KH, Koopman JS. Changing hepatitis A seroprevalence: a global review and analysis. *Epidemiol Infect* 2004;**133:**1005–22.

[4] Bell BP, Shapiro CN, Alter MJ *et al*. The diverse patterns of hepatitis A epidemiology in the United States—implications for vaccination strategies. *J Infect Dis* 1998;**178:**1579–84.

[5] U.S. Bureau of the Census. International Data Base. Table 094: Midyear population by age and sex (2003).

[6] Stroffolini T, Chiaramonte M, Ngatchu T *et al*. A high degree of exposure to hepatitis A virus infection in urban children in Cameroon. *Microbiológica* 1991;**14:**199–203.

[7] Tsega E, Nordenfelt E, Mengesha B, Hansson BG, Tsega M, Lindberg J. Age-specific prevalence of hepatitis A virus antibody in Ethiopian children. *Scand J Infect Dis* 1990;**22:**145–48.

[8] Barin F, Denis F, Chotard J *et al*. Early asymptomatic hepatitis A in Senegalese children. *Lancet* 1980;**1:**212–13.

[9] Hodges M, Sanders E, Aitken C. Seroprevalence of hepatitis markers: HAV, HBV, HCV, and HEV amongst primary school children in Freetown, Sierra Leone. *West Afr J Med* 1998;**17:**36–37.

[10] Abdool Karim SS, Coutsoudis A. Sero-epidemiology of hepatitis A in black South African children. *S Afr Med J* 1993;**83:**748–49.

[11] Sathar MA, Soni PN, Fernandes-Costa FJTD, Wittenberg DF, Simjee AE. Racial differences in the seroprevalence of hepatitis A virus infection in Natal/Kwazulu, South Africa. *J Med Virol* 1994;**44:**9–12.

[12] Werner GT, Frösner GG, Fresenius K. Prevalence of serological hepatitis A and B markers in a rural area of Northern Zaire. *Am J Trop Med Hyg* 1985;**34:**620–24.

[13] López H, Zitto T, Baré P, Vidal G, Vukasovic J, Gómez R. Prevalence of anti-hepatitis A antibodies in an urban middle class area of Argentina: some associated factors. *Int J Infect Dis* 2000;**4:**34–37.

[14] Tapia-Conyer R, Santos JI, Cavalcanti AM *et al*. Hepatitis A in Latin America: a changing epidemiologic pattern. *Am J Trop Med Hyg* 1999;**61:**825–29.

[15] Craig PG, Bryan JP, Miller RE *et al*. The prevalence of hepatitis A, B and C infection among different ethnic groups in Belize. *Am J Trop Med Hyg* 1993;**49:**430–34.

[16] Bartoloni A, Aqauilini D, Roselli M *et al*. Prevalence of antibody to hepatitis A virus in the Santa Cruz region of Bolivia. *J Trop Med Hyg* 1989;**92:**279–81.

[17] Bartoloni A, Bartalesi F, Roselli M *et al*. Prevalence of antibodies against hepatitis A and E viruses among rural populations of the Chaco region, south-eastern Bolivia. *Trop Med Int Health* 1999;**4:**596–601.

[18] Gandolfo GM, Ferri GM, Conti L *et al*. Prevalence of infections by hepatitis A, B, C and E viruses in two different socioeconomic groups from Santa Cruz, Bolivia. *Med Clin* (*Barc*) 2003;**120:**725–27.

[19] Alameida LM, Werneck GL, Cairncross S, Coeli CM, Costa MCE, Coletty PE. The epidemiology of hepatitis A in Rio de Janeiro: environmental and domestic risk factors. *Epidemiol Infect* 2001;**107:**327–33.

[20] Assis SB, Souto FJD, Fontes CJF, Gaspar AMC. Prevalence of hepatitis A and E virus infection in school children of an Amazonian municipality in Mato Grosso State. *Rev Soc Bras Med Trop* 2002;**35:**155–58.

[21] Clemens SA, Fonseca JC, Azevedo T *et al*. Hepatitis A and hepatitis B seroprevalence in four centers in Brazil. *Rev Soc Bras Med Trop* 2000;**33:**1–10.

[22] Gaze R, Carvalho DM, Werneck GL. Hepatitis A and B seroprevalence in Macae, Rio de Janeiro State, Brazil. *Cad Saude Publica* 2002;**18:**1251–59.

[23] de Paula VS, Arruda ME, Vitral CL, Gaspar AMC. Seroprevalence of viral hepatitis in riverine communities from the western region of the Brazilian Amazon Basin. *Mem Inst Oswaldo Cruz* 2001;**96:**1123–28.

[24] Quieroz DA, Cardoso DD, Martelli CM *et al*. Risk factors and prevalence of antibodies against hepatitis A virus (HAV) in children from day-care centers in Goiania, Brazil. *Rev Inst Med Trop Sao Paulo* 1995;**37:**427–33.

[25] Santos DCM, Souto FJD, Santos DRL, Vitral CL, Gaspar AMC. Seroepidemiological markers of enterically transmitted viral hepatitis A and E in individuals living in a community located in the North Area of Rio de Janeiro, RJ, Brazil. *Mem Inst Oswaldo Cruz* 2002;**97:**637–40.

[26] Vitral CL, Yoshida CFT, Lemos ERS, Teixeira CS, Gaspar AMC. Age-specific prevalence of antibodies to hepatitis A in children and adolescents from Rio de Janeiro, Brazil, 1978 and 1995: relationship of prevalence to environmental factors. *Mem Inst Oswaldo Cruz* 1997;**93:**1–5.

[27] Crewe MD, Embil JA, Garner JB. Prevalence of antibodies to hepatitis A in Nova Scotia children. *CMAJ* 1983;**128:**1195–97.

[28] Harb J, Lem M, Fyfe M *et al*. Hepatitis A in the Northern interior of British Columbia: an outbreak among members of a first nation community. *Can Commun Dis Rep* 1995; **26:**157–61.

[29] Payment P. Antibody levels to selected enteric viruses in a French-Canadian population in the province of Quebec (Canada). *Immunol Infect Dis* 1991;**1:**317–22.

[30] Fix AD, San Martin O, Gallicchio L, Vial PA, Lagos R. Age-specific prevalence of antibodies to hepatitis A in Santiago, Chile: risk factors and shift in age of infection among children and young adults. *Am J Trop Med Hyg* 2002;**66:**628–32.

[31] Villarejos VM, Serra CJ, Anderson-Visona K, Mosley JW. Hepatitis A virus infection in households. *Am J Epidemiol* 1982;**115:**577–86.

[32] Brown MG, Lindo JF, King SD. Investigations of the epidemiology of infections with hepatitis A virus in Jamaica. *Ann Trop Med Parasitol* 2000;**94:**497–502.

[33] Kilpatrick ME, Escamilla J. Hepatitis A in Peru: the role of children. *Am J Epidemiol* 1986;**124:**111–13.

[34] Montano DA, Baranano R, Legeard B *et al*. Prevalencia de hepatitis A en niños de 2 a 14 años y en poblacion laboral de 18 a 49 años en Montevideo, Uruguay. *Rev Med Uruguay* 2001;**17:**84–98.

[35] Maynard JE, Bradley DW, Hornbeck CL, Fields RM, Doto IL, Hollinger FB. Preliminary serologic studies of antibody to hepatitis A virus in populations in the United States. *J Infect Dis* 1976;**134:**528–30.

[36] Amesty-Valbuena A, Gonzalea-Pirela Y, Rivero M. Estudio seroepidemiologico para virus de hepatitis A en niños de Maracaibo, Venezuela. *Invest Clin* 1989;**30:**215–28.

[37] Boughton CR, Hawkes RA, Ferguson V. Viral hepatitis A and B: a sero-epidemiologic study of a non-hepatitic Sydney population. *Med J Aust* 1980;**1:**177–80.

[38] Lehmann NI, Gust ID. Prevalence of antibody to hepatitis A virus in two populations in Victoria, Australia. *Med J Aust* 1977;**2:**731–32.

[39] Geng J, Xu D, Gong J, Li W. Assessing hepatitis A virus epidemic stochastic process in eight cities in China in 1990. *Int J Epidemiol* 1998;**27:**320–22.

[40] Chin KP, Lok ASF, Wong LSK, Lai CL, Wu PC. Current seroepidemiology of hepatitis A in Hong Kong. *J Med Virol* 1991;**34:**191–93.

[41] Acharya SK, Batra Y, Bhatkal B *et al*. Seroepidemiology of hepatitis A virus infection among school children in Delhi and north Indian patients with chronic liver disease: implications for HAV vaccination. *J Gastroenterol Hepatol* 2003;**18:**822–27.

[42] Arankalle VA, Tsarev SA, Chadha MS *et al*. Age-specific prevalence of antibodies to hepatitis A and E viruses in Pune, India, 1982 and 1992. *J Infect Dis* 1995;**171:**447–50.

[43] Arankalle VA, Chadha MS, Chitambar SD, Walimbe AM, Chobe LP, Gandhe SS. Changing epidemiology of hepatitis A and hepatitis E in urban and rural India (1982–1998). *J Viral Hepat* 2001;**8:**293–303.

[44] Batra Y, Bhatkal B, Ojha B *et al*. Vaccination against hepatitis A virus may not be required for schoolchildren in northern India: results of a seroepidemiological survey. *Bull World Health Organ* 2002;**80:**728–31.

[45] Corwin AL, Putri MP, Winarno J *et al*. Epidemic and sporadic hepatitis E virus transmission: West Kalimantan (Borneo), Indonesia. *Am J Trop Med Hyg* 1997;**57:**62–65.

[46] Juffrie M, Graham RR, Tan RI *et al*. Seroprevalence of hepatitis A virus and varicella zoster antibodies in Javanese community (Yogyakarta, Indonesia). *Southeast Asian J Trop Med Public Health* 2000;**31:**21–24.

[47] Furusyo N, Hayashi J, Sawayama Y, Kawakami Y, Kishihara Y, Kashiwagi S. The elimination of hepatitis B virus infection: changing seroepidemiology of hepatitis A and B virus infection in Okinawa, Japan, over a 26-year period. *Am J Trop Med Hyg* 1998;**59:**693–98.

[48] Ichida F, Suzuki S, Furuta S *et al*. Age specific prevalence of anti HA in Japan: from multi-institutional analysis. *Gastroenterol Jpn* 1981;**16:**384–88.

[49] 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.

[50] Kashiwagi S, Hayashi J, Ikematsu H *et al*. Prevalence of antibody to hepatitis A virus in Okinawa and Kyushu, Japan. *Am J Epidemiol* 1983;**117:**55–59.

[51] Kiyohara T, Satoh T, Yamamoto H, Totsuka A, Moritsugu Y. The latest seroepidemiological pattern of hepatitis A in Japan. *Jpn J Med Sci Biol* 1997;**50:**123–31.

[52] Sohn YM, Rho HO, Park MS *et al*. The changing epidemiology of hepatitis A in children and the consideration of active immunization in Korea. *Yonsei Med J* 2000;**41:**34–39.

[53] Tan DSK, Fang R, Collett D, Ooi BG. Seroepidemiologic study of hepatitis A in Malaysia. *Southeast Asian J Trop Med Public Health* 1986;**17:**201–04.

[54] Sawayama Y, Hayashi J, Ariyama I *et al*. A ten year serological survey of hepatitis A, B and C viruses infections in Nepal. *J Epidemiol* 1999;**9:**350–54.

[55] Goh KT, Wong LY, Oon CJ, Kumarapathy S. The prevalence of antibody to hepatitis A in Singapore. *Asia Pac J Public Health* 1987;**1:**9–11.

[56] Vitarana T, Kanapathipillai M, Gunasekera HDN, Lehmann NI, Dimitrikakis M, Gust ID. A seroepidemiological study of hepatitis A and hepatitis B infection in Sri Lanka. *Asian J Infect Dis* 1978;**2:**247–52.

[57] Wu JS, Chen CH, Chiang YH *et al*. Seroepidemiology of hepatitis A infection in children in Taiwan. *J Formos Med Assoc* 1980;**79:**694–99.

[58] Burke DS, Snitbhan R, Johnson DE, Scott R McN. Age specific prevalence of hepatitis A virus antibody in Thailand. *Am J Epidemiol* 1981;**113:**245–49.

[59] Kalayanarooj S, Vaughn DW, Snitbhan R, Ariyasriwatana C. Age-specific prevalence of hepatitis A antibody in Thai children. *Southeast Asian J Trop Med Public Health* 1995;**26:**709–11.

[60] Poovorawan Y, Paiboonkasemsuthi S, Theamboonlers A, Kamolratanakul P, Chumdermpadetsuk S. Seroepidemiology of antibody to hepatitis A in the rural eastern part of Thailand. *Southeast Asian J Trop Med Public Health* 1991;**22:**35–38.

[61] Viranuvatti V, Hemindra P, Chainuvati T. Anti-HAV in Thai population. *J Med Assoc Thai* 1982;**65:**379–82.

[62] Hau CH, Hien TT, Tien NT *et al*. Prevalence of enteric hepatitis A and E viruses in the Mekong River delta region of Vietnam. *Am J Trop Med Hyg* 1999;**60:**277–80.

[63] Prodinger WM, Larcher C, Solder BM, Geissler D, Dietrich MP. Hepatitis A in western Austria: the epidemiologic situation before the introduction of active immunisation. *Infection* 1994;**22:**53–55.

[64] Vranckx R, Muylle L. Hepatitis A virus antibodies in Belgium: relationship between prevalence and age. *Infection* 1990;**18:**364–66.

[65] Beran J, Douda P, Rychly R. Seroprevalence of viral hepatitis A in the Czech Republic. *Eur J Epidemiol* 1999;**15:**805–08.

[66] Linneberg A, Østergaard C, Tvede M *et al*. IgG antibodies against microorganisms and atopic disease in Danish adults: the Copenhagen Allergy Study. *J Allergy Clin Immunol* 2003;**111:**847–53.

[67] 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.

[68] Frösner G, Willers H, Müller R, Schenzle D, Deinhardt F, Höpken W. Decrease in incidence of hepatitis A infections in Germany. *Infection* 1978;**6:**259–60.

[69] Thierfelder W, Hellenbrand W, Meisel H, Schreier E, Dortschy R. Prevalence of markers for hepatitis A, B and C in the German population: results of the German National Health Interview and Examination Survey 1998. *Eur J Epidemiol* 2001;**17:**429–35.

[70] Kremastinou J, Kalapothaki V, Trichopoulos D. The changing epidemiologic pattern of hepatitis A infection in urban Greece. *Am J Epidemiol* 1984;**120:**703–06.

[71] Papaevangelou G. Epidemiology of hepatitis A in Mediterranean countries. *Vaccine* 1992;**10:**S63–66.

[72] Langer BCA, Frösner GG, von Brunn A. Epidemiological study of viral hepatitis types A, B, C, D and E among Inuits in West Greenland. *J Viral Hepat* 1997;**4:**339–49.

[73] Briem H. Declining prevalence of antibodies to hepatitis A virus infection in Iceland. *Scand J Infect Dis* 1991;**23:**135–38.

[74] Briem H, Weiland O, Friorikssson I, Berg R. Prevalence of antibody to hepatitis A in Iceland in relation to age, sex, and number of notified cases of hepatitis. *Am J Epidemiol* 1982;**116:**451–55.

[75] Chiaramonte M, Floreani A, Silvan C *et al*. Hepatitis A and hepatitis B virus infection in children and adolescents in North-East Italy. *J Med Virol* 1983;**12:**179–86.

[76] Chiaramonte M, Moschen ME, Stroffolini T *et al*. Changing epidemiology of hepatitis A virus (HAV) infection: a comparative seroepidemiological study (1979 vs 1989) in north-east Italy. *Ital J Gastroenterol* 1991;**23:**344–46.

[77] D'Argenio P, Esposito D, Mele A *et al*. Decline in the exposure to hepatitis A and B virus infection in children in Naples, Italy. *Public Health* 1989;**103:**385–89.

[78] La Rosa G, Guli V, Terrana B. First results of anti HAV antibodies assay in Western Sicily. *Boll Ist Sieroterapico Milan* 1978;**57:**682–83.

[79] Moschen ME, Floreani A, Zamparo E *et al*. Hepatitis A infection: a seroepidemiological study in young adults in North-East Italy. *Eur J Epidemiol* 1997;**13:**875–78.

[80] Stroffolini T, Franco E, Romano G *et al*. Hepatitis A virus infection in children in Sardinia, Italy. *Community Med* 1989;**11:**336–41.

[81] Stroffolini T, Chiaramonte M, Franco E *et al*. Baseline seroepidemiology of hepatitis A virus infection among children and teenagers in Italy. *Infection* 1991;**19:**97–100.

[82] Stroffolini T, De Crescenzo L, Giammanco A *et al*. Changing pattern of hepatitis A infection in children in Palermo, Italy. *Eur J Epidemiol* 1990;**6:**84–87.

[83] Zanetti AR, Ferroni P, Bastia A. Decline in incidence of hepatitis A infection in Milan: a serologic study. *Boll Ist Sieroterapico Milan* 1978;**57:**816–20.

[84] Zanetti AR, Romano L, Tanzi E *et al*. Decline in anti-HAV prevalence in the Milan area between 1958–1992. *Eur J Epidemiol* 1994;**10:**633–35.

[85] Termorshuizen F, Dorigo-Zetsma JW, de Melker HE, van den Hof S, Conyn-Van Spaendonck MAE. The prevalence of antibodies to hepatitis A virus and its determinants in The Netherlands: a population-based survey. *Epidemiol Infect* 2000;**134:**459–66.

[86] Cianciara J. Hepatitis A shifting epidemiology in Poland and Eastern Europe. *Vaccine* 2000;**18:**S68–70.

[87] Polz-Dacewicz MA, Policzkiewicz P, Badach Z. Changing epidemiology of hepatitis A virus infection: a comparative study in Central Eastern Poland (1990–1999). *Med Sci Monit* 2000;**6:**989–93.

[88] Barros H, Oliveira F, Miranda H. A survey on hepatitis A in Portuguese children and adolescents. *J Viral Hepat* 1999;**6:**249–53.

[89] Lecour H, Ribeiro AT, Amaral I, Rodrigues MA. Prevalence of viral hepatitis in the population of Portugal. *Bull World Health Organ* 1984;62:743–47.

[90] Stroffolini T, Pretolani S, Miglio F *et al*. Population-based survey of hepatitis A virus infection in the Republic of San Marino. *Eur J Epidemiol* 1997;**13:**687–89.

[91] Amela C, Pachón I, Bueno R, de Miguel C, Martinez-Navarro F. Trends in hepatitis A virus infection with reference to the process of urbanization in the greater Madrid area (Spain). *Eur J Epidemol* 1995;**11:**569–73.

[92] Bolumar F, Giner-Duran R, Hernandez-Aguado I, Serra-Desfilis MA, Rebagliato M, Rodrigo JM. Epidemiology of hepatitis A in Valencia, Spain: public health implications. *J Viral Hepat* 1995;**2:**145–49.

[93] Bruguera M, Salleras L, Plans P *et al*. Changes in seroepidemiology of hepatitis A virus infection in Catalonia in the period 1989–1996: implications for new vaccination strategy. *Med Clin (Barc)* 1999;**112:**406–08.

[94] Cilla G, Perez-Trallero E, Marimon JM, Erdozain S, Gutierrez C. Prevalence of hepatitis A antibody among disadvantaged gypsy children in northern Spain. *Epidemiol Infect* 1995;**115:**157–61.

[95] Dal-Ré R, García-Corbeira P, García-de-Lomas J. A large percentage of the Spanish population under 30 years of age is not protected against hepatitis A. *J Med Virol* 2000;**6:**363–66.

[96] Garcia-Fulgueiras A, Rodriguez T, Tormo MJ, Perez-Flores D, Chirlaque D, Navarro C. Prevalence of hepatitis A antibodies in southeastern Spain: a population-based study. *Eur J Epidemiol* 1997;**13:**481–83.

[97] González A, Bruguera M, Calbo Torrecillas F, Monge V, Dal-Ré R, Costa J. Encuestra seroepidemiologica de prevalencia de anticuerpos antihepatitis A en la poblacion adulta joven Española. *Med Clin (Barc)* 1994;**103:**445–48.

[98] Montes I, Agulla A. Prevalencia de marcadores de hepatitis viricas en niños del norte de Extremadura. *An Pediatr (Barc)* 1996; **45:**133–36.

[99] Perez-Trallero E, Cilla G, Urbieta M, Dorronsoro M, Otero F, Marimon JM. Falling incidence and prevalence of hepatitis A in northern Spain. *Scand J Infect Dis* 1994;**26:**133–36.

[100] Rodriguez-Iglesias MA, Perez-Garcia MT, Garcia-Valdivia MS, Perez-Ramos S. Seroprevalence of hepatitis A virus antibodies in a pediatric population of southern Spain. *Infection* 1995;**23:**309.

[101] Salleras L, Bruguera M, Vidal J *et al*. A change in the epidemiologic pattern of hepatitis A in Spain. *Med Clin (Barc)* 1992;**99:**87–89.

[102] Vargas V, Buti M, Hernandez-Sanchez JM, Jardi R, Portell A, Esteban R, Guardia J. Prevalencia de los anticuerpos contra el virus de la

hepatitis A en la poblacion general: studio comparative 1977–85. *Med Clin (Barc)* 1987;**88:**144–46.

[103] Böttiger M, Christenson B, Grillner L. Hepatitis A immunity in the Swedish population: a study of the prevalence of markers in the Swedish population. *Scand J Infect Dis* 1997;**29:**99–102.

[104] Iwarson S, Frösner G, Lindholm A, Norkrans G. The changed epidemiology of hepatitis A infection in Scandinavia. *Scand J Infect Dis* 1978;**10:**155–56.

[105] Weiland O, Berg R, Böttiger M, Lundberge P. Prevalence of antibody against hepatitis A in Sweden in relation to age and type of community. *Scand J Infect Dis* 1980;**12:**171–74.

[106] Damjanovic V, Ross M, Brumfitt W. Studies on antibody to hepatitis A virus in children and adults in London. *Infection* 1979;**7:**267–72.

[107] Gay NJ, Morgan-Capner P, Wright J, Farrington CP, Miller E. Age-specific antibody prevalence to hepatitis A in England: implications for disease control. *Epidemiol Infect* 1994;**113:**113–20.

[108] Morris MC, Gay NJ, Hesketh LM, Morgan-Capner P, Miller E. The changing epidemiological pattern of hepatitis A in England and Wales. *Epidemiol Infect* 2002;**128:**457–63.

[109] Khalfa S, Ardjoun H. Epidemiologie des hepatitis virales en Algerie. *Med Trop (Mars)* 1984;**44:**247–52.

[110] Farzadegan H, Shamszad M, Noori-Arya K. Epidemiology of viral hepatitis among Iranian populations: a viral marker study. *Ann Acad Med Singap* 1980;**9:**144–48.

[111] Chironna M, Germinario C, Lopalco PL, Carrozzini F, Barbuti S, Quarto M. Prevalence rates of viral hepatitis infections in refugee Kurds from Iraq and Turkey. *Infection* 2003;**31:**70–74.

[112] Shamma'a MH, Abu-Samra S, Salameh V, Nassar NT. The significance of anti-HAV in different population sectors in Lebanon: a comparative seroepidemiologic study. *Int J Epidemiol* 1982;**11:**406–09.

[113] Nejmi S, Coursaget P, D'Khissy D, Barres JL, Chiron P. Prévalence des infections par les virus des hépatitis A et B au Maroc. *Presse Med* 1984;**13:**1786–87.

[114] Agboatwalla M, Isomura S, Miyake K, Yamashita T, Morishita T, Akram DS. Hepatitis A, B and C seroprevalence in Pakistan. *Indian J Pediatr* 1994;**61:**545–49.

[115] El-Hamzi MAF. Hepatitis A antibodies: prevalence in Saudi Arabia. *J Trop Med Hyg* 1989;**92:**427–30.

[116] Khalil M, Al-Mazrou Y, Al-Jeffri M, Al-Howasi M. Childhood epidemiology of hepatitis A virus in Riyadh, Saudi Arabia. *Ann Saudi Med* 1998;**18:**18–21.

[117] Ramia S. Antibody against hepatitis A in Saudi Arabians and in expatriates from various parts of the world working in Saudi Arabia. *J Infect* 1986;**12:**153–55.

[118] Shobokshi O, Serebour F, Abdul-Rahim SM. The prevalence and pattern of hepatitis A viral infection in the western region of Saudi Arabia. *Saudi Med J* 1986;**7:**402–08.

[119] Tufenkeji H. Hepatitis A shifting epidemiology in the Middle East and Africa. *Vaccine* 2000;**18:**S65–67.

[120] Antaki N, Kamel Kebbewar M. Hepatitis A seroprevalence rate in Syria. *Trop Doct* 2000;**30:**99–101.

[121] Baki A, Aynaci M, Koksal I. Prevalence of antibody to hepatitis A virus among children in Trabzon, Turkey. *Infection* 1993;**21:**132–33.

[122] Kanra G, Tezcan S, Badur S. Hepatitis A seroprevalence in a random sample of the Turkish population by simultaneous EPI cluster and comparison with surveys in Turkey. *Turk J Pediatr* 2002;**44:**204–10.

[123] Sidal M, Unuvar E, Oguz F, Cihan C, Onel D, Badur S. Age-specific seroepidemiology of hepatitis A, B, and E infections among children in Istanbul, Turkey. *Eur J Epidemiol* 2001;**17:**141–44.

[124] Yapicioglu H, Alhan E, Yildizdas D, Yaman A, Bozdemir N. Prevalence of hepatitis A in children and adolescents in Adana, Turkey. *Indian Pediatr* 2002;**39:**936–41.

[125] WHO/UNICEF Joint Monitoring Programme for Water Supply and Sanitation. Global Water Supply and Sanitation Assessment 2000 Report.

[126] United Nations Development Programme. Human Development Report 2003. Available at: http://hdr.undp.org/reports/global/2003/indicator/index_indicators.html.

[127] World Bank. GNI per capita 2002. World Development Indicators Database, July 2003.

[128] Schenzle D, Dietz K, Frösner GG. Antibody against hepatitis A in seven European countries: statistical analysis of cross-sectional surveys. *Am J Epidemiol* 1979;**110:**70–76.

[129] Hu M, Schenzle D, Deinhardt F, Scheid R. Epidemiology of hepatitis A and B in the Shanghai area: prevalence of serum markers. *Am J Epidemiol* 1984;**120:**404–14.

[130] Struchiner CJ, Alameida LM, Azevedo RS, Massad E. Hepatitis A incidence rate estimates from a pilot seroprevalence survey in Rio de Janeiro, Brazil. *Int J Epidemiol* 1999;**28:**776–81.

[131] Alameida LM, Amaku M, Azevedo RS, Cairncross S, Massad E. The intensity of transmission of hepatitis A and heterogeneities in socio-environmental risk factors in Rio de Janeiro, Brazil. *Trans R Soc Trop Med Hyg* 2002;**96:**605–10.

[132] Gay NJ. A model of long-term decline in the transmissibility of an infectious disease: implications for the incidence of hepatitis A. *Int J Epidemiol* 1996;**25:**854–61.

[133] Farrington CP, Kanaan MN, Gay NJ. Estimation of the basic reproduction number for infectious diseases from age-stratified serological survey data. *Appl Stat* 2001;**50:**251–92.

[134] Poorvorawan Y, Vimolkej T, Chongsrisawat V, Theamboonlers A, Chumdermpadetsuk S. The declining pattern of seroepidemiology of hepatitis A virus infection among adolescents in Bangkok, Thailand. *Southeast Asian J Trop Med Public Health* 1997;**28:**154–57.