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Age-specific antibody prevalence to hepatitis A in England: implications for disease control

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SUMMARY

Sera from an age-stratified sample of 7196 individuals, submitted for diagnostic purposes to four public health laboratories in England in 1986/7, were tested for hepatitis A antibody. The serological profiles, which showed marked regional differences, were consistent with declining incidence in the past. The decline in the incidence of hepatitis A has resulted in an increase in susceptibility in adults. This has three main consequences: an increase in the average age of infection may be leading to an increase in morbidity; normal immunoglobulin may become less protective against hepatitis A; the risk of transmission through blood products contaminated by viraemic blood donors may rise.

Current average annual incidence in 5–14-year olds was estimated to vary between regions from 0·5–1·9%. This supports the view that, in the absence of a vaccination programme, hepatitis A will remain endemic unless there are further improvements in living conditions and standards of hygiene. A vaccine giving long-lasting protection could eliminate hepatitis A transmission with modest coverage at a young age. Targeting childhood vaccination on economically deprived areas or using vaccine to control outbreaks might be more effective policies.

INTRODUCTION

Hepatitis A is endemic in the United Kingdom, with approximately 7000 cases notified in England and Wales in each of the years 1990–2. The disease is often asymptomatic in children but can be severe in adults and is occasionally fatal. Many cases are the result of community outbreaks, often centred on a primary school [1, 2] and usually in economically deprived areas [2, 3]. Others may arise from common source outbreaks caused by contaminated food or drinking water, while a small proportion of infections are contracted abroad.

Short term protection against hepatitis A can be conferred by the administration of normal immunoglobulin [4]. If given soon after contact, this can prevent or

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attenuate a clinical attack, but has often proved unsuccessful in controlling community outbreaks [1, 3, 5]. An inactivated hepatitis A vaccine is now available, but doubt about its ability to confer long term protection without the need for booster doses has so far restricted its use to those likely to be at increased risk of infection. Live attenuated vaccines are being developed and are expected to provide long term immunity, so leading to consideration for widespread use [6].

Before any assessment of the likely impact of a mass vaccination programme can be made, information on the age-specific prevalence of immunity to hepatitis A and on the current incidence (the rate at which susceptible persons acquire infection) is essential. This is best obtained through sero-epidemiological studies. The serological data currently available for hepatitis A in the UK is limited to small samples of adults. We report hepatitis A antibody prevalence data on over 7000 individuals aged 1–99 years collected from four areas of the UK during 1986/7.

METHODS

Laboratory materials and methods

Serum remaining from samples submitted in 1986/7 for routine diagnostic examination to Ashford, Manchester, Leeds and Preston Public Health Laboratories was saved from patients aged 1–99 years. Together, the four laboratories receive serum samples from 32 districts in four NHS Regions of England – South East Thames (4/8 districts), North Western (13/19 districts), Yorkshire (13/17 districts) and Mersey (2/10 districts). Samples from immunocompromised patients and samples sent for testing for hepatitis B and antibody to the human immunodeficiency virus were excluded. It was not possible to exclude samples submitted for testing for hepatitis A, but these comprise only a minute proportion of the total.

All serological tests were performed at Preston Public Health Laboratory. Sera were first tested for total hepatitis A antibody by an IgG capture enzyme-linked immunosorbent assay (Division of Microbiological Reagents and Quality Control. Central Public Health Laboratory, Colindale, UK) [7]. Results were compared with a dilution series (100, 50, 20, 10, 5, 1 and 0·5 international units (i.u.)) of the World Health Organisation 1st Reference Preparation for hepatitis A antibody. Sera giving less than 0·5 i.u. were ascribed negative and those greater than 5·0 i.u. positive. Sera with low levels of reactivity equivalent to 0·5 to 5·0 i.u. were retested by competition radioimmunoassay (HAVAB, Abbott Laboratories, USA) and this result used for analysis. HAVAB was shown to have a cut-off of 0·5 i.u. on repeatedly testing the dilution series of the international control.

Statistical methods

Age, sex and area effects were investigated using 10 age groups (1–4, 5-year age groups to age 29, 10-year age groups to age 59, and 60+ years). The data were analysed by modelling the numbers seropositive as binomial with complementary log–log link function [8]. The prevalence at age a is equal to $1-\exp(-\Lambda(a))$, where $\Lambda(a)$ is the integrated incidence to age a. The exponentiated parameter estimates therefore represent relative integrated incidences, from which average incidence estimates may be derived.

Table 1. *Number tested and proportion with antibody to hepatitis A by age group*

Age group (years)	Tested	Antibody positive	
		No.	(%)
1–4	1198	78	(6·5)
5–9	1140	120	(10·5)
10–14	1184	165	(13·9)
15–19	689	135	(19·6)
20–24	765	224	(29·3)
25–29	726	265	(36·5)
30–34	454	193	(42·5)
35–39	287	123	(42·5)
40–44	188	104	(55·3)
45–49	149	110	(73·9)
50–54	105	85	(81·0)
55–59	91	69	(75·8)
60+	220	197	(89·5)

Estimation of R_0

Under the assumption of homogeneous mixing (i.e. that incidence is independent of age etc), the basic reproduction number of a directly transmitted disease, R_0, is defined as the average number of secondary infections caused by a single infectious individual in a totally susceptible population. If the disease is established at an endemic equilibrium R_0 is related to the proportion of the population who are susceptible, x, by the equation, $R_0 = 1/x$ [9]. Making the assumption that hepatitis A has reached a new equilibrium level (following a period of declining R_0) enables this relationship to be used to estimate R_0. The proportion susceptible in the catchment area of each laboratory was calculated from published demographic data [10] together with the serological data, using five age groups (four 15-year age groups and 60+ years).

RESULTS

Antibody prevalence

Results were obtained for 7196 sera in persons aged 1–99 years. These comprised 1170 from Ashford, 1798 from Manchester, 2352 from Leeds and 1876 from Preston Public Health Laboratories. A total of 3723 sera (51·7%) were from males. Antibody prevalence by age is given in Table 1 for all laboratories combined, with results for individual laboratories shown in Fig. 1. The integrated incidences estimated by the statistical model are consistent with incidence either declining over time or increasing with age. This effect can be seen in the steepening of the prevalence profiles after age 40 years (Fig. 1). Above the age of 5 years, the serological profiles are consistent with incidence being lowest in Ashford followed by Manchester, Leeds and Preston. The pattern is significantly different ($P < 0{\cdot}001$) for the 1–4-year age group for which the prevalences were 8·6% in Ashford, 2·2% in Manchester, 6·6% in Leeds and 10·6% in Preston. There were no significant differences in antibody prevalence between males and females.

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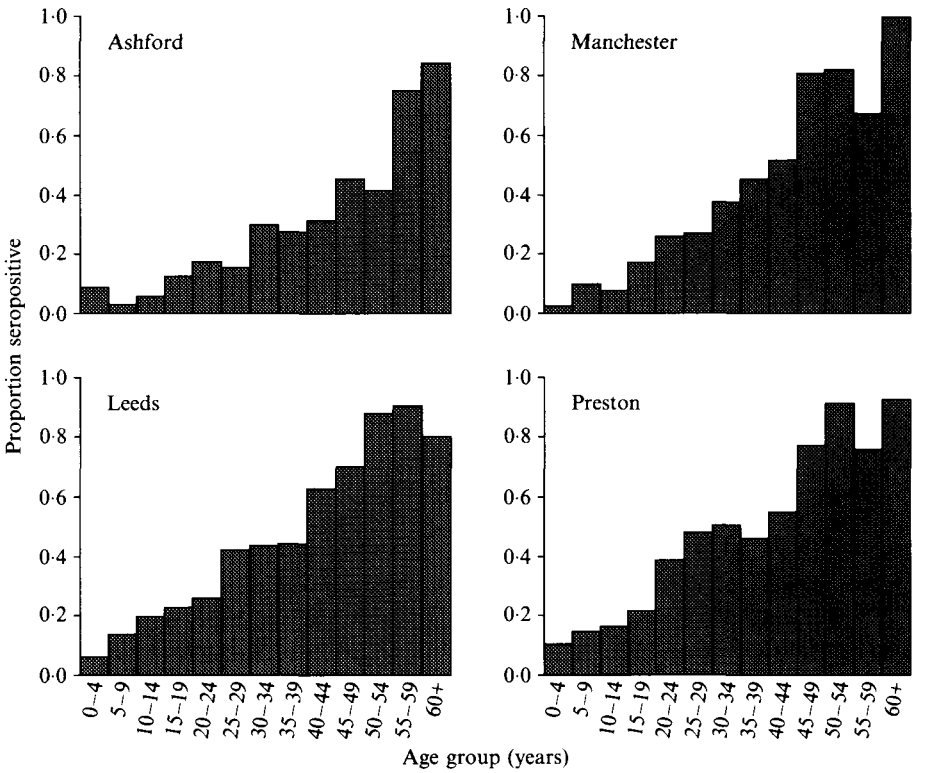

Fig. 1. Proportion with antibody to hepatitis A by age group according to laboratory.

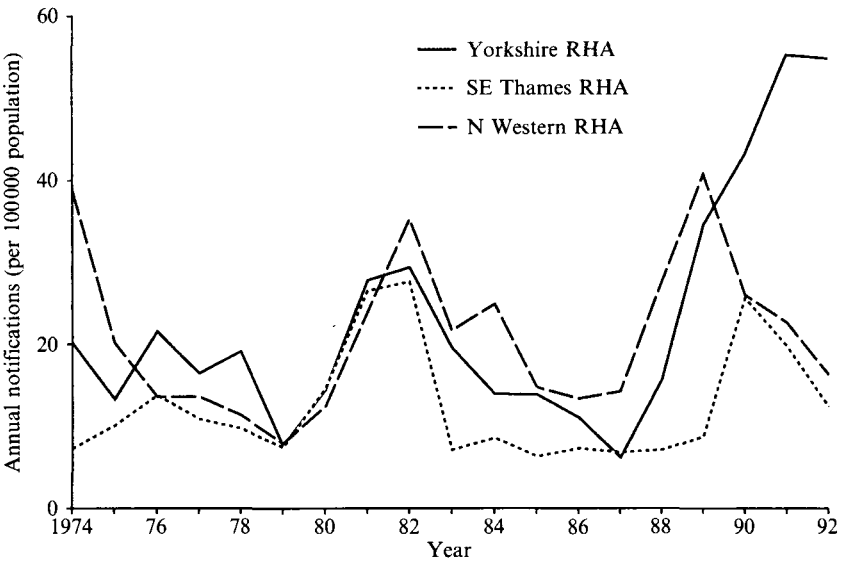

Fig. 2. Annual notifications of infective jaundice per 100000 population in three NHS Regions of England 1974–92 (1992 totals are provisional).

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Table 2. *Estimated annual incidence in 5–14-year olds and basic reproduction number for hepatitis A infection according to laboratory*

Laboratory	Ashford	Manchester	Leeds	Preston
Annual incidence (%)	0·5	0·9	1·9	1·8
(95% CI)	(0·3–0·8)	(0·7–1·4)	(1·6–2·3)	(1·3–2·4)
R_0	1·6	1·9	2·0	2·2

Incidence and R_0

Notifications of infective jaundice (the vast majority of which are hepatitis A) by study Regions were available from 1974 (Fig. 2) and show a 9–10 year epidemic cycle with no overall downward trend. Average annual incidences estimated from prevalence in 5–14-year olds (Table 2) are therefore a good indication of the current rates of infection in this age group. The estimate of the basic reproduction number, R_0, was lowest in Ashford, followed by Manchester, Leeds and highest in Preston (Table 2).

DISCUSSION

This is the largest study of the prevalence of antibody to hepatitis A virus across the whole age range to be reported in the United Kingdom. The subjects tested were not a random sample of the population, but were persons whose serum was submitted to laboratories for routine diagnostic examination. However, there is no reason to believe that the study population is not representative in terms of its history of exposure to hepatitis A. Substantial differences between laboratories in the reasons for which sera were submitted are unlikely in view of the comprehensive diagnostic service that each offers. Comparisons between the results from each region therefore seem justified.

This study shows that there are marked geographical variations in the age-specific antibody prevalence and current incidence of hepatitis A in England. Such differences are likely to result from variation in socioeconomic status, existing both now and in the past. Immigration from highly endemic areas might also influence seroprevalence to varying extents. The incidence estimated from serological data was lower in South East Thames region (Ashford laboratory) than in Yorkshire and the North West, a trend which was reflected in the notification rates in these regions (Fig. 2). Applying these incidences to all age groups, it is estimated that the average annual number of infections per 100000 population ranges from 330 in Ashford to 950 in Leeds. These estimates are 10–20-fold higher than the actual numbers notified, reflecting the under-reporting of cases and the occurrence of asymptomatic infections. The 1–4-year olds are the exception to the regional pattern with prevalence being highest in Ashford. These children were born after the 1981–2 epidemic and infection will have been determined primarily by isolated outbreaks. The calculations of the basic reproduction number, R_0, should be treated as a rough estimate because of heterogeneities in the population (e.g. geographical variations in susceptibility, possible age dependence in transmission, the localized nature of outbreaks). Collection of sera at the trough

of the epidemic cycle may result in a slight overestimate of the susceptibility of the population and therefore cause a small underestimate of R_0. However the values obtained show the same regional trend as incidence, with R_0 lowest in Ashford. They range from 1·6–2·2, all greater than the threshold, $R_0 = 1$, below which the disease can no longer remain endemic.

A decline over time in the incidence of hepatitis A has been noted in the UK [11] and in other European countries [12, 13]. Although the prevalence data from a single survey cannot distinguish between rising incidence with age and a decline in incidence over time, the observed pattern is most readily explained by a drop in incidence in the past. This is most probably associated with improvements in socioeconomic and hygienic conditions. Incidence does not appear to have declined since 1974, the average annual rate in 5–14-year olds being in the range 0·5–1·9% per year. The decline in incidence to current levels has potential adverse consequences since it has resulted in an increase in susceptibility in adults and therefore in the average age of infection. Because the disease is more severe in older persons the overall morbidity attributable to hepatitis A may have increased. Some European countries, such as those in Scandinavia, have succeeded in improving conditions sufficiently that hepatitis A is no longer endemic. Until this is achieved in the UK the disease will continue to cause significant morbidity.

The changing epidemiology of hepatitis A has implications for the efficacy and safety of blood products. First, the ability of normal immunoglobulin to protect against hepatitis A infection may be compromised as a result of reduced antibody prevalence in the blood donor population. Regional variations may accentuate the problem, such as in East Anglia where the prevalence in blood donors is only 17% [14]. In future, normal immunoglobulin may need to be prepared using selected donations, chosen on the basis of age or region. Second, there are concerns about the increased risk of transmission of hepatitis A by blood products. Separate outbreaks among haemophiliacs in Italy [15], Germany [16], Ireland [17] and Belgium [18] have been linked to solvent/detergent processed factor VIII concentrates. Contamination of donated blood can occur as there are 2–3 weeks of viraemia before the onset of symptoms [19]. Assuming a 1% annual incidence in the 50% of 18–65-year olds who are susceptible, it is estimated that as many as 1 in 5000 blood donations in the UK may be infected. One such case has been reported recently [20]. Antibody from other donors plays a role in neutralizing the virus, but the fall in prevalence in adults may result in levels in the pool being insufficient to prevent contamination of the final product. Although mathematical models suggest that current levels of infection will prevent prevalence falling much further, the very low prevalence in some regions means that the possibility of contamination will remain.

With the prospect of a live attenuated vaccine, the effect of a mass vaccination programme requires consideration. A value of R_0 in the range 1·6–2·2 suggests that hepatitis A could be eliminated with a vaccine coverage of only 40–60% at a young age [9]. However, such a vaccination programme would need to be long term, given the large numbers of susceptible young adults. If insufficient coverage were achieved morbidity might be increased, as a result of increasing the average age of infection of a disease that is more severe in adults [9]. This risk would be heightened should the vaccine fail to confer lifelong immunity. An alternative to

blanket mass immunization would be to target economically deprived areas, as this is where most outbreaks occur. Targeting could be at a district level, or even focus on individual general practices. A third possible strategy is to use vaccine to help control community outbreaks, as the long latent period causes these to build up gradually, allowing time for interventions. In order to target vaccination effectively within a community the principal chains of transmission must be identified. If, for example, transmission between households occurs principally through school-acquired infection, vaccination of the school population might be sufficient to control a community outbreak. Sero-epidemiological studies to measure age-specific antibody prevalence and incidence during the course of a community outbreak are planned.

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