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The changing epidemiological pattern of hepatitis A in England and Wales

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SUMMARY

Sera from an age-stratified sample of 4188 individuals, submitted for diagnostic purposes to 15 public health laboratories in England and Wales in 1996, were tested for hepatitis A antibody. The serological profiles were consistent with declining incidence in the past. This hypothesis was tested by comparing the serological profiles of Ashford, Leeds and Preston public health laboratories with those from sera collected during a previous study in the same laboratories in 1986/7. A comparison of equivalent 10 year birth cohorts revealed that significant hepatitis A seroconversion had only continued in Ashford. However, it is probable that most seroconversions are due to vaccination and immigration rather than continuing viral transmission. Further population-based surveys collecting more in-depth social and demographic data are needed to confirm the main factors influencing hepatitis A seroprevalence and to explain the regional differences.

INTRODUCTION

Hepatitis A is a virus with a world-wide distribution that causes a systemic infection attacking the liver. The level of endemicity is related to sanitation and hygiene, inversely related to socio-economic conditions and the pattern of infection is country specific. Within the United Kingdom there are three main patterns of infection: sporadic infection often in travellers to countries of high endemicity; common source outbreaks often caused by contaminated foods and large, slowly evolving community outbreaks associated with oral-faecal transmission that are often centred on primary schools or in economically deprived areas [1].

As clinical hepatitis represents only a small proportion of the total number of infections in the population, notifications and laboratory data underreport the incidence of hepatitis A infection. Seroepidemiological studies overcome this problem by testing for virus-specific IgG antibodies, which are indicative of past infection or vaccination.

Several European countries, including Spain and Italy, have reported a trend of decreasing hepatitis A seroprevalence over time which has been attributed to the control of transmission through improved sanitation and improved access to basic health care [2–7]. It is important to document these changes as the severity of infection increases with age. Decreased transmission in childhood and an increase in the average age of infection could have important consequences for the overall burden of morbidity [5, 8–10]. However, very few of these studies directly compared seroprevalence data collected from the same population at different time points.

We report hepatitis A seroprevalence data collected on over 4000 individuals aged 0–99 years in England

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and Wales in 1996. These were compared with data collected through the same serological surveillance network from a previously reported study from 1986/7 in over 5000 individuals within the same age range from three regions of England [11].

METHODS

Samples

Serum remaining from specimens submitted by patients of all ages for routine diagnostic testing at 15 Public Health Laboratories (PHLs) across England and Wales in 1996 were collected. All sera were anonymized specimen residues collected as part of the routine PHLS serological surveillance programme which has ethical approval from the PHLS ethics committee [12]. A total of 4188 samples, selected to obtain the best approximation to the desired number of samples in each age group and region, were tested. Only 5·1% of these were collected from the London region which was underrepresented as 13·5% of the population of England and Wales live within that region.

In 1986/7 5399 sera had been collected through the same network and had been tested for anti-hepatitis A IgG. However, these had only been collected in four public health laboratories and sera from both years were available only from three laboratories: Ashford, Leeds and Preston.

Laboratory methods

To enable a comparison of results from 1986/7 and 1996 there was a need to ensure that the tests used were equivalent. The 1986/7 sera were tested using an in-house IgG capture enzyme-linked immunosorbent assay (ELISA), described elsewhere [11, 13], with equivocals re-tested using a commercial radio-immunoassay (RIA) (Abbott laboratories, USA). For our study the in-house ELISA was no longer available and given the additional staff time and costs associated with the Abbott RIA it was not possible to use that kit to test all serum samples. Therefore a Sorin ELISA was used as the initial screen with equivocals and low positives re-tested using the Abbott RIA to try to ensure some equivalence of results between the two studies.

The Sorin cut-off criterion for a positive result was a score of $> 50\%$ with the sample ELISA score calculated according to the equation below using the optical densities of the sample, positive and negative controls (OD_{pos} and OD_{neg}) on each ELISA plate:

$$\text{ELISA score} = \left(\frac{OD - OD_{neg}}{OD_{pos} - OD_{neg}} \right) \times 100\%.$$

Samples with a range of ELISA scores were re-tested with the Abbott RIA (see Fig. 1). The positive predictive value of the Sorin test for the ELISA scores 50–98% was poor (only 27·7% when validated against the Abbott RIA, see Fig. 1) and all samples within that range were re-tested by the Abbott RIA which was taken as the final result.

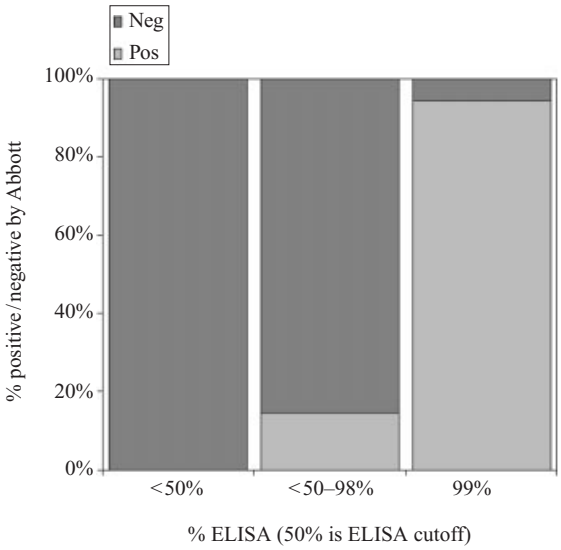

Fig. 1. Abbott results by hepatitis A ELISA% (Sorin).

Statistical methods

Age and area effects in 1996 were investigated using a logistic regression model in Stata 6.0 taking sero-positivity as the dependent variable and age group (in 10-year age bands until age 59, then 60 years and over) and region as explanatory variables. The laboratories were combined into three regions (South-west and Wales, Southeast and East Anglia, North and Midlands) for the analysis, to increase the number of observations within each age group and region category and hence the robustness of the model.

Changes in hepatitis A age-specific seroprevalence over time were investigated by comparing the 1986/7 and 1996 data from the same laboratories of Ashford, Leeds and Preston using a logistic regression model adjusted for age group and laboratory. The comparison assumed that the catchment areas of the laboratories remained the same, which was thought to

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be reasonable as they remained the principal diagnostic laboratories for each area.

As the age-specific seroprevalence in 1996 was dependent upon the seroprevalence in 1986/7 another logistic regression was performed to compare the seroprevalence of hepatitis A in each equivalent 10-year birth cohort in 1986 and 1996. The results were adjusted for laboratory. There were 5399 samples available from Ashford, Leeds and Preston in 1986/7 compared to 1102 in 1996. Assuming that seroconversion is independent of age and given the previously reported hepatitis A seroprevalence of 27% for all ages in 1986/7, the sample numbers gave 80% power to detect an overall increase in seroprevalence of 4·5% over 10 years (from 27% in 1986 to 31·5% 1996) at the 5% statistical level.

The percentage change in seroprevalence over the 10-year period for each laboratory was estimated by applying the odds ratio for the year effect (i.e. 1996 versus 1986) from the best fit logistic regression model for equivalent cohorts (fitted above) to the seroprevalence in 1986. This gave an expected 1996 seroprevalence standardized to the 1986 population (see Appendix A for equation).

RESULTS

Hepatitis A IgG antibody prevalence in 1996

Results were obtained for 4188 sera from individuals aged 0–99 years. The prevalence of hepatitis A IgG antibody by 10-year age group in 1996 for all 15 public health laboratories combined is shown in Table 1. The overall seroprevalence was estimated to be 30·7% (1286/4188) and ranged from 9% among those aged 1–9 to 11% among those aged 10–19 before increasing to 17% among those aged 20–29. After age 30 there was a sharper increase in seroprevalence with age to 73·5% in those aged 60 and over.

As well as the trend of increasing seroprevalence with age group, there was a significantly higher age-adjusted seroprevalence in the North and Midlands compared to the South-West and Wales (35·5% versus 28·0%; OR 1·5 (95% CI 1·3–1·9)) similar to that reported previously for the 1986/7 data [11]. There was a significant interaction between age group and region ($\chi^2 = 27{\cdot}3$, 12 D.F., $P = 0{\cdot}007$) and Figure 2 demonstrates the regional differences in age specific seroprevalence. As the differences do not appear to be large, only the main effects are reported here.

Table 1. *Age specific seroprevalence of hepatitis A in England and Wales in 1996*

Variable	Seroprevalence (%)	Odds ratio	95% CI
Age group			
1–9	8·6 (54/629)	1·0	Baseline
10–19	11·0 (76/694)	1·3	0·9–1·9
20–29	16·9 (122/721)	2·2	1·6–3·1
30–39	32·9 (210/638)	5·3	3·8–7·3
40–49	37·3 (210/563)	6·2	4·5–8·7
50–59	58·1 (254/437)	14·9	10·7–20·6
60+	73·5 (358/487)	30·5	21·6–43·1

There was variation in seroprevalence according to the laboratory that had collected the specimens in 1996. This was especially evident in samples from the 1–14 year olds from Birmingham and Bristol that reported outlying prevalence results of 29% and 31% respectively compared to a range of 3–11% in the other laboratories. Such figures would require very high rates of infections which are not reflected in routine notification and laboratory data (www.phls.co.uk/facts/hepatitis). The small sample sizes and wide 95% confidence intervals involved indicate that sampling variability may account for the unexpected results.

Comparison with 1986/7

The logistic regression model comparing seroprevalence data from Ashford, Preston and Leeds in 1986/7 and 1996 revealed a significant interaction between laboratory and year ($\chi^2 = 7{\cdot}29$, 2 D.F., $P = 0{\cdot}03$). The data were therefore stratified by laboratory and the age-adjusted results are reported in Table 2. There was a significant decline in the age adjusted hepatitis A seroprevalence in Leeds and Preston, but not in the samples collected from Ashford.

Figure 3 shows the seroprevalence data for equivalent birth cohorts in 1986 and 1996 by laboratory. There is little difference between the two lines in Leeds and Preston indicating little seroconversion over time. This was reflected by the logistic regression analysis with no significant difference in seroprevalence between equivalent birth cohorts in 1986 and 1996 after adjustment for age (Leeds OR = 0·93, 95% CI 0·70–1·23; Preston OR 0·96, 95% CI 0·75–1·23). There was however a significant difference between the 2 years for the Ashford data (OR 1·55, 95% CI 1·08–2·23). The estimated annual sero-

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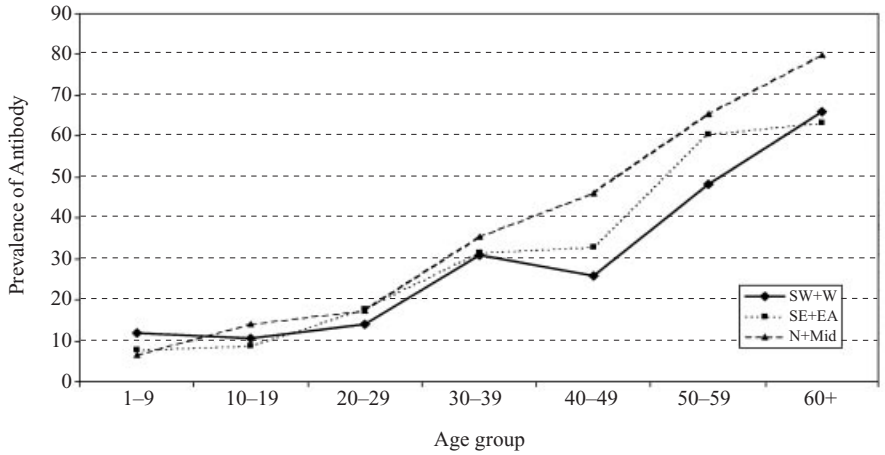

Fig. 2. Age specific prevalence of antibody to hepatitis A in 1996 by region.

Table 2. *Age adjusted comparison of hepatitis A seroprevalence by laboratory in 1986/7 and 1996*

Laboratory	Age adjusted OR*	95% CI
Ashford	0·8	0·6–1·2
Leeds	0·5	0·4–0·7
Preston	0·5	0·4–0·6
Overall	0·5	0·5–0·6

* 1996 compared to 1986/7.

conversion rates, assuming seroconversion to be independent of age, are shown for each laboratory in Table 3.

DISCUSSION

This was a large seroprevalence study conducted across all age groups in England and Wales. The samples were not collected from a random sample of the population, but were from individuals whose serum had been submitted to laboratories for routine diagnostic testing. There is no reason to believe that the study population was not representative in terms of its history of exposure to hepatitis A. The NHS offers free access to health case for all limiting the selection bias. In addition there should be no substantial differences between laboratories in reasons for submission of sera as all offer a comprehensive diagnostic service [14]. Comparisons between the results from each region therefore seem justified.

The comparison of equivalent cohorts in 1986 and 1996 revealed two distinct patterns. In Leeds and Preston there was very little seroconversion over the period of time studied, whereas the data from Ashford showed an increase in seropositivity of 6·3%. This is surprising given the higher age adjusted seroprevalence and notification figures that are commonly reported from the north of England (www.phls.co.uk/facts/hepatitis). The main explanations for seroconversion include natural infection, vaccination and immigration from countries highly endemic for hepatitis A.

If the overall estimated percentage seroconversion (1% between 1986 and 1996 or 0·1% per year, see Table 3) was due to natural infection there would have been 52000 cases each year in England and Wales (assuming a population of 52 million). However, only 43537 were cases notified between 1987 and 1996. Even with significant under-notification it is unlikely that natural infection could account for the majority of seroconversions.

The inactivated hepatitis A vaccine was introduced in 1992 and by 1996 3568034 doses of the adult 770 ELISA unit vaccine, 3305659 doses of the adult 1440 ELISA unit vaccine and 569821 doses of the child 360 ELISA unit vaccine had been sold (data from GlaxoSmithKline). If individuals are assumed to have received only full courses of the relevant vaccine, the doses sold relate to 2·8 million adult vaccinees and 190000 child vaccinees (assuming all persons received a full course of 3 doses of the 720 ELISA unit, 2 doses of the 1440 ELISA unit and 3 doses of the child 360 ELISA unit vaccine). This would have covered approximately 6·5% and 1·7% of the adult and child populations respectively, which would more than explain the 1% increase in seroprevalence estimated for the 10-year period across the three regions.

The final explanation for apparent seroconversion within the population is the immigration of seropositive individuals. Net migration into and out of

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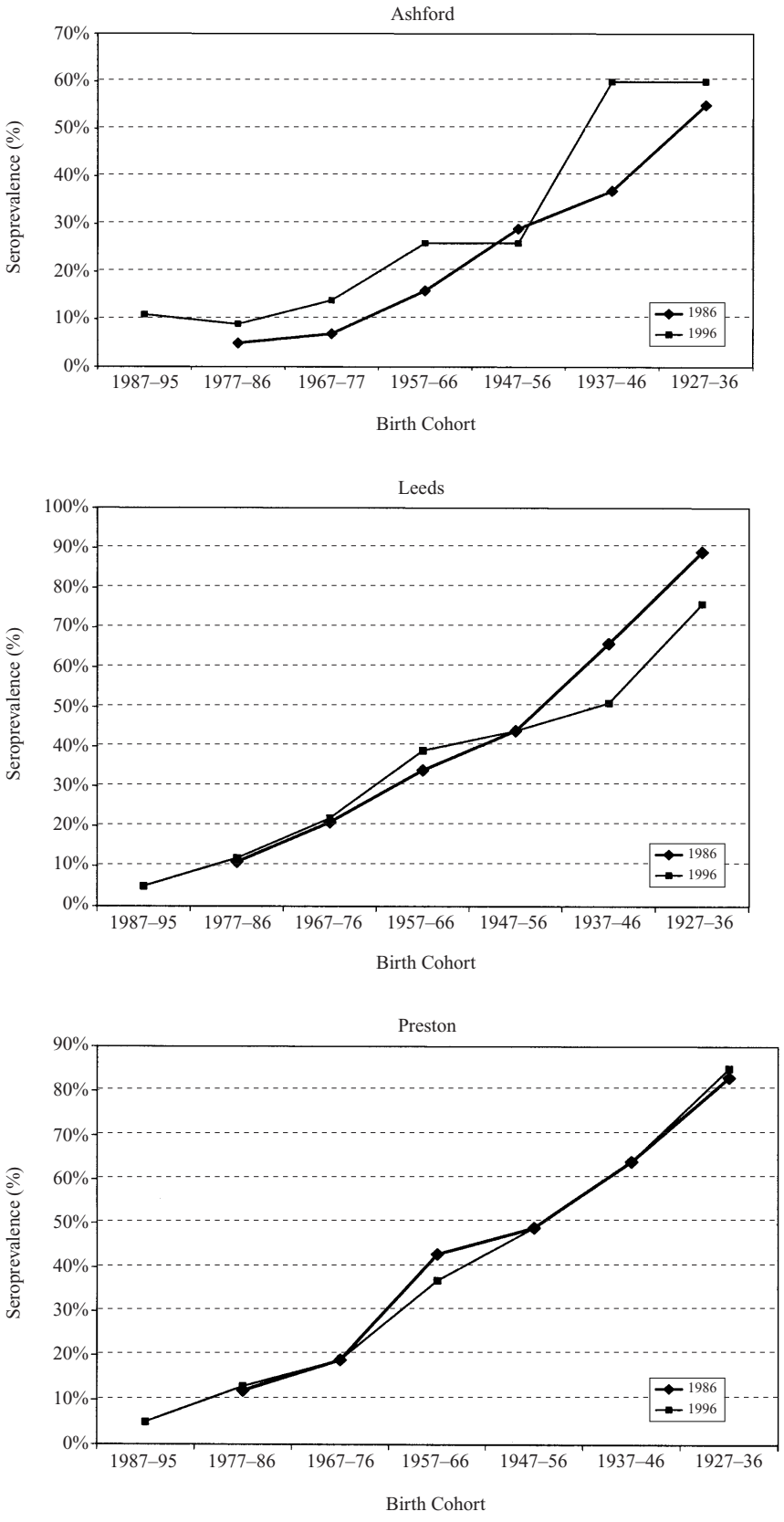

Fig. 3. Prevalence of antibody to hepatitis A by decade of birth in Ashford, Leeds and Preston in 1986 and 1996.

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Table 3. *Estimate of seroconversion to hepatitis A by laboratory between 1986 and 1996*

Laboratory	Ashford	Leeds	Preston	All
Seroconversion (%)	6·3	−1·4	−0·9	1·0
95% CI	1·0–12·9	−6·3–4·2	−6·4–4·9	2·2–4·5

A minus figure relates to a decrease in seroprevalence in equivalent birth cohorts.

England and Wales is estimated through the International Passenger Survey which interviews individuals coming into and leaving the national airports (http://www.statistics.gov.uk/ssd/surveys/international_passenger_survey.asp). Between 1986 and 1995 it was estimated that there was a net migration of 396000 individuals from Africa and South Asia (India, Pakistan and Bangladesh) into England and Wales. These regions are highly endemic for hepatitis A and the vast majority of individuals from those countries are seropositive. Immigration from those regions could therefore have accounted for an increase in seropositivity of approximately 0·76% between 1986 and 1995. Unfortunately, there are no data on where immigrants settle and it is not clear whether immigration makes a larger contribution to hepatitis A seropositivity in the south of England (Ashford), where there was a higher percentage seroconversion over time.

The data indicate that the overall level of hepatitis A seroconversion in the general population of England and Wales is low and that the level of susceptibility is high. It is possible that indigenous transmission may have been interrupted over the past 10 years in many areas with seroconversion explained mainly by vaccination and immigration. However, there are regional differences which could reflect differences in vaccine uptake, travel habits or the presence of certain high risk groups. Population-based surveys collecting more extensive information on ethnicity, socioeconomic status and residence in highly endemic countries are now underway to interpret the data more fully and to accurately assess the risk among certain groups within the population.

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APPENDIX A

The data allowed the calculation of an odds ratio rather than a relative risk. Therefore, in order to calculate the expected 1996 seroprevalence the equation below was necessary (rather than simply multiplying the remaining susceptibles by the relative risk)

$$P_{96} = \frac{OR\left(P_{86}/\left(1-P_{86}\right)\right)}{1+OR\left(P_{86}/\left(1-P_{86}\right)\right)},$$

where P_{96} = expected seroprevalence in 1996 (all ages), P_{86} = 1986 seroprevalence (all ages), OR = odds ratio for effect of year.

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