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Serological study of the epidemiology of mumps virus infection in north-west England

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SUMMARY

Serum samples from individuals of a wide age range, collected in northwest England in 1984 and 1986, provide the basis for an analysis of the epidemiology of mumps virus infection. A radial haemolysis test yielding quantitative antibody measurements was used to screen samples for mumps-specific IgG. Analyses of resultant age-seroprevalence profiles, using statistical models, revealed an age-related pattern in the rate of infection per susceptible similar to that observed for other childhood infections. This rate, or force of infection, was low in young children, high in older children, and low in adults. In addition, the serological surveys provide evidence for time-dependent changes (both epidemic and longer-term) in the rate of mumps virus transmission. The longer-term changes, reflected in the pattern of the age-acquisition of specific antibodies, are supported by evidence from case notification data. The implications of temporal changes in incidence to the interpretation and design of serological surveys are considered.

INTRODUCTION

Changing circumstances surrounding mumps infection in this country provide good reason for further investigations aimed at improving our understanding of the epidemiology of this infection. The recent introduction of a triple measles, mumps and rubella (MMR) vaccine for the immunization of young children [1] has created an urgent need to assess the existing pattern of herd immunity (prior to the introduction of MMR) against which to observe the impact of mass vaccination. This need is augmented by the recent suggestion that, in the UK, mumps is now acquired earlier in life, possibly from changing social and behavioural factors within the general population [2].

Data on mumps epidemiology in this country fall into two categories. Firstly, records provided by the Royal College of General Practitioner's (RCGP) spotter practices and laboratory reports submitted to the Communicable Disease Surveillance Centre (CDSC, Colindale). Unfortunately, these are coarsely stratified

by age and their interpretation is complicated by the non-random nature of notifications and laboratory reports. Such data represent the age-distribution of symptomatic cases rather than a true incidence of infection by age. The second category of data derive from horizontal (i.e. at one point in time), age-stratified serological surveys and provide the most appropriate base for assessing the levels of immunity in a population, and age-related changes in the acquisition of infection [3,4]. However, published surveys from the UK cover only a narrow spectrum of age classes [5], divide the subjects into too few groups by age [6] or lack information on antibody concentrations [5,6]. They are important in providing a qualitative picture of herd immunity, but have insufficient detail for further quantitative analyses.

Theoretical work on the transmission dynamics of childhood infections provides a convenient framework for interpreting age-stratified serological surveys and the estimation of such epidemiological statistics as the average age at infection (A), and the level of immunization coverage required to block transmission given a defined pattern of age-related immunization in childhood (p_c) [3,7–9].

In a recent preliminary investigation of the epidemiology of mumps in the UK the paucity of data, particularly serological, from which to determine key epidemiological parameters, undermined confidence in the predicted impact of mass vaccination against mumps [10]. The present study is an attempt to rectify this situation via the collection of detailed epidemiological data from serological surveys. The paper pays particular attention to age-related changes in the force of infection (i.e. the probability of a susceptible individual being infected over a short period of time, and how this varies with age), and longitudinal trends in the mean age at infection. A future publication based on this work will supply data on the level of mass immunization required to block mumps transmission and the impact of mass immunization on the incidence of serious disease, by age, in the general population.

MATERIALS AND METHODS

Sample collections

Serum samples acquired for investigation by the Department of Virology, Preston Infirmary, during the years of 1984 and 1986 form the basis of this study. Information was obtained for each individual on date of birth, sex and date of sample collection. Samples from individuals suspected of recent mumps infection were specifically excluded. The samples collected for both years comprised sera from males and females over a roughly equivalent age range (Table 1). The 1984 collection included some sera from infants less than 1 year old. These sera were necessary for an analysis of maternally derived mumps antibody. The catchment area for specimens to the Preston laboratory includes Lancashire and south Cumbria, with a population of approximately 1·5 million, and did not alter for the two sample years. Sera collected in 1986 formed part of the countrywide survey of measles, mumps and rubella conducted by the Public Health Laboratory Service, summary results of which have been published [6].

Table 1. *Details of sample sets from NW England 1984 and 1986*

	1984		1986	
Age class	Male	Female	Male	Female
0–	104	76		
1–2	89	73	88	88
3–4	47	36	92	68
5–6	46	25	76	69
7–8	26	16	53	46
9–10	34	26	44	45
11–12	26	18	76	68
13–14	30	35	88	92
15–19	100	151	102	101
20–24	119	160	129	135
25–29	110	125	121	116
30–34	112	120	76	79
35–39	109	96	49	52
40–44	68	62	37	33
45–49	83	60	30	18
50–54	61	57	26	16
55–59	94	50	16	18
60–69	61	65	41	40
70–79	31	44	37	39
80+	7	21	13	34
Total	1357	1316	1194	1157

Serological screening

Mumps-specific antibodies were assayed by a radial haemolysis test, using the method previously described [6,11,12]. Screening of the 1986 samples was conducted at Preston, and the 1984 samples at Imperial College. The protocol was standardized between the two sites, although quantitative measurements [11,12] of antibody concentration were recorded at Imperial College only. Reproducibility of quantitative results was assessed as in previous studies which used the RH tests [11,12].

Analytical techniques

(*a*) Throughout, statistical analyses are based on the assumptions that proportions seropositive (or seronegative) for mumps antibody follow a positive binomial distribution and that the quantitative mumps-antibody levels have a log-normal distribution. Standard procedures have been followed [12,13].

(*b*) A polynomial catalytic infection model [9] was employed for estimating age-related rates or forces of infection (i.e. instantaneous rates of infection of susceptible individuals) from serological data (i.e. age-serological profiles). This model is a mathematical description of the decay, through time, in the susceptible proportion of a population (and, conversely, the rise, through time, in the proportion who have experienced infection). When applied to horizontal age-stratified data the assumption is made that within the study population rates of infection are constant with time (i.e. the infection is at a stable equilibrium). It may then be assumed that a serological profile (which records the change, with age, in antibody prevalence, observed at one point in time) reflects changes, with age (and time), in the susceptible proportion of a cohort followed from birth, as

they experience infection. Any changes detected in the rate of infection of susceptibles from such a profile are then, usually, attributed to age-dependent factors (although other factors, such as genetical differences in susceptibility, may be operating [3]). Within the model these age-dependent changes in the force of infection are described by a polynomial function, the parameters of which are estimated by a method of maximum likelihood. It is further assumed when using horizontal serological data that immunity is indicated by the presence of specific antibodies, and that these antibodies are lifelong. The validity of these assumptions has been discussed in previous publications [3,9,12] and is considered later.

In addition, a logistic regression model [14] was used to describe the changes in seroprevalence levels with age in adults. The best-fit model to the data was determined using a step-wise procedure, estimating parameters by maximum likelihood [15], and calculating the forces of infection from the model estimates of proportions seropositive [7] (see Table 2). Again, it is assumed that mumps infection is at stable equilibrium in the population and that mumps-specific antibodies are durable and indicate past exposure to the virus.

(*c*) The estimation of a number of parameters to summarize the epidemiological properties of mumps infection in the study population follows published methods [7]. The parameters estimated were the mean age of infection, A, the inter-epidemic period, T, the basic reproductive rate, R_0, and the critical proportion to be vaccinated to block transmission, p_c.

RESULTS

Serological test

Sensitivity of the mumps RH test (i.e. the ability to distinguish presence from absence of specific antibody) is assessed from the frequency distribution of antibody levels for the 1984 sample set (ages 1–92 yrs; $n = 2493$) illustrated in Fig. 1. Results of 180 individuals aged between 0 and 1 yr whose antibody levels follow a markedly different distribution (see later) are excluded from the analysis of sensitivity. The approximate logarithmic-normal distribution presented in Fig. 1 (natural logarithmic transformed data: mean {samples > 0·0 au} = 3·45, variance = 1·15, 95% confidence interval = $\pm$0·045, $n = 2199$), with distinct tails at either end, is indicative of a test which will mistake a serum sample with mumps-specific antibody as negative only on rare occasions. However, under routine use in both laboratories, it was established that an antibody level of 5 arbitrary units (au) was the minimum value consistently producing a detectable RH zone of lysis (which is directly comparable with previously published evaluations [6,11]). Fig. 1 suggests that this is a reasonable cut-off level for seropositivity; there are few false negatives (expected probability, $p\{< \ln 5 \text{ au}\} = 0{\cdot}043$). In subsequent analyses the small number of samples which gave visible zones of lysis corresponding to antibody levels of less than the 5 au cutoff (2·8% for 1984 and 1% for 1986) have been treated as negative. However, as discussed in a later section, the inclusion of such samples below the 5 au level, as seropositive, can significantly influence the interpretation of results.

Separate analyses for each sex reveal a significantly lower mean antibody level

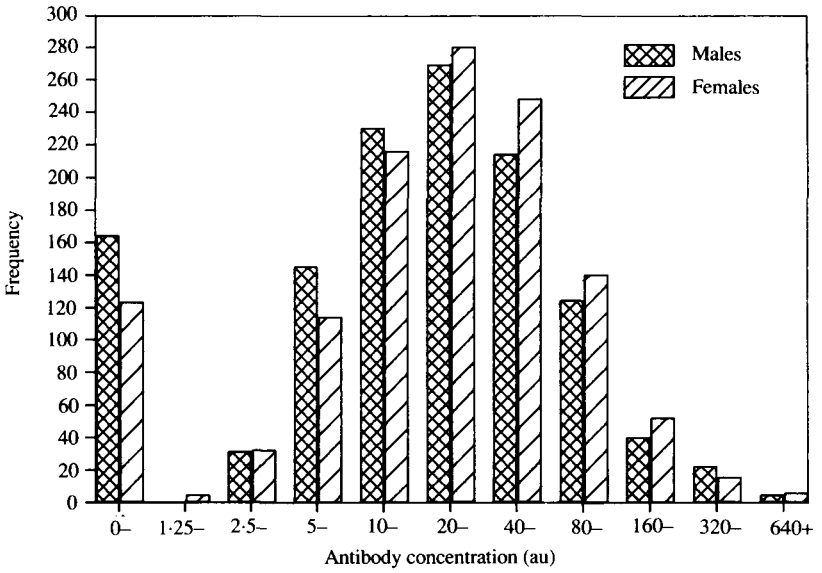

Fig. 1. Frequency distribution of mumps antibody concentrations ($\log_2$ scale) for the survey of NW England, 1984.

for males compared with females (T {pooled variance} $= -2{\cdot}46$, 2-tail, $P = 0{\cdot}014$, D.F. = 2132) (Fig. 1).

Control samples (each pooled from a number of sera with similar antibody levels) covering a wide range of mumps-antibody concentrations were tested in each test series for the 1984 survey (a test series is a set of RH gel plates prepared and run together) [12]. Analysis of the results revealed a degree of inter-test variability in the estimation of antibody concentration similar to other RH tests (CV% = 10·3%) [16,17] and an independence of the variance and the mean antibody concentration (test for homogeneity of variance, $F_{max} = 2{\cdot}13$, $k = 5$, D.F. $= 7$, $P < 0{\cdot}01$). The reader is referred to the work of Nokes, Anderson and Anderson [12] for further details of the methods of standardization and quantification adopted in this study.

Age-related trends in antibody concentrations

Quantitative measurements of mumps antibody acquired from screening the 1984 samples allow an exploration of the variation, with age, in antibody levels.

(i) *Mumps-specific antibody in infants*

Changes in the frequency distribution of mumps-specific IgG (plotted on a $\log_2$ scale) over the age range 0–1 to 10–11 months for 180 infants of both sexes are recorded in Fig. 2. The marked decline in antibody concentrations, as age increases, is assumed to mirror the decay of maternally derived antibody over the first year of life. Individuals with low antibody levels, between 2·5 and 5 au, form a significant proportion of the total sample (12% of all sera with detectable antibody, $n = 118$). As age increases, the proportion with low-level antibody

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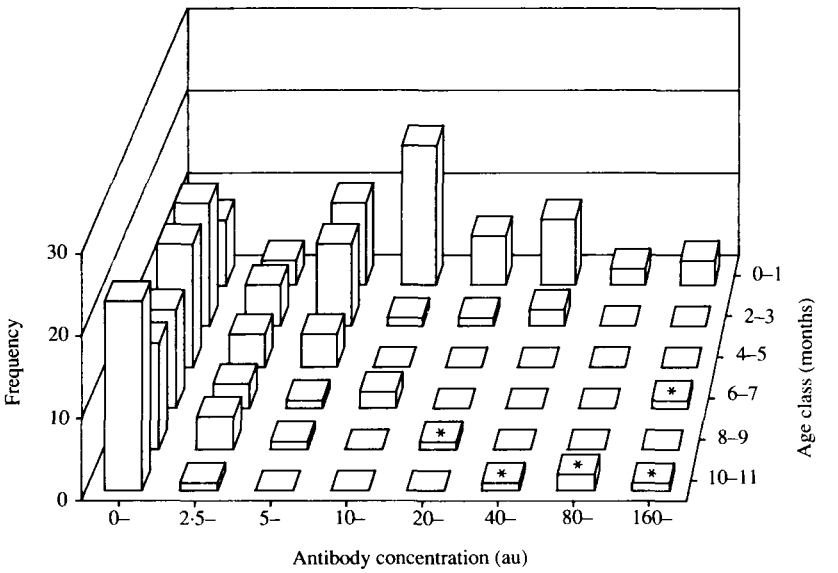

Fig. 2. Changes in the distribution of antibody levels ($\log_2$ scale) for 180 infants from NW England, 1984 over the first year of life. Histogram bars marked with an asterisk were assumed to identify individuals with acquired, in contrast to maternally derived, mumps-specific antibodies.

increases. Sera with high-level antibody (i.e. $\geqslant$ upper quartile of seropositives (26·8 au, $n = 118$)) from individuals over 6 months of age (bars marked with an asterisk in Fig. 2) are clearly outliers to the main trend. These samples are thought to derive from infants who, following the waning of their passive immunity, have acquired antibody as a result of exposure to mumps virus and are, therefore, excluded from further analysis of maternally derived antibody (discussed more fully later).

(ii) *Levels of acquired mumps antibody*

The proportion of individuals possessing detectable mumps-specific antibody, in sequential age classes from 1 to > 90 years, who have antibody levels above various cut-off concentrations, is recorded in Fig. 3. Typically, for the individual, high-level specific IgG from a recent viral infection (or vaccination) rapidly decays over a period of a few months (often at different rates for each individual) to a level which is maintained for many years [18–21]. The profile illustrated in Fig. 3 may be interpreted as the community effect of this process, i.e. the summation of immune responses of a population of individuals who experienced primary infection at various ages (these will be distributed about the average age at attack). It is important to note that only above the age of 15 years do a small proportion of individuals possess antibody levels below the 5 au threshold. This proportion increases in those older than 60 years.

Results from further analysis of age-dependent trends in acquired-antibody concentrations are illustrated in Fig. 4. Fig. 4 (*a*) depicts age-dependent changes in mean (natural logarithm) antibody levels for seropositive sera ($\geqslant 5$ au) in the age range 1–92 years. Antibody is assumed to be acquired as a result of mumps-virus

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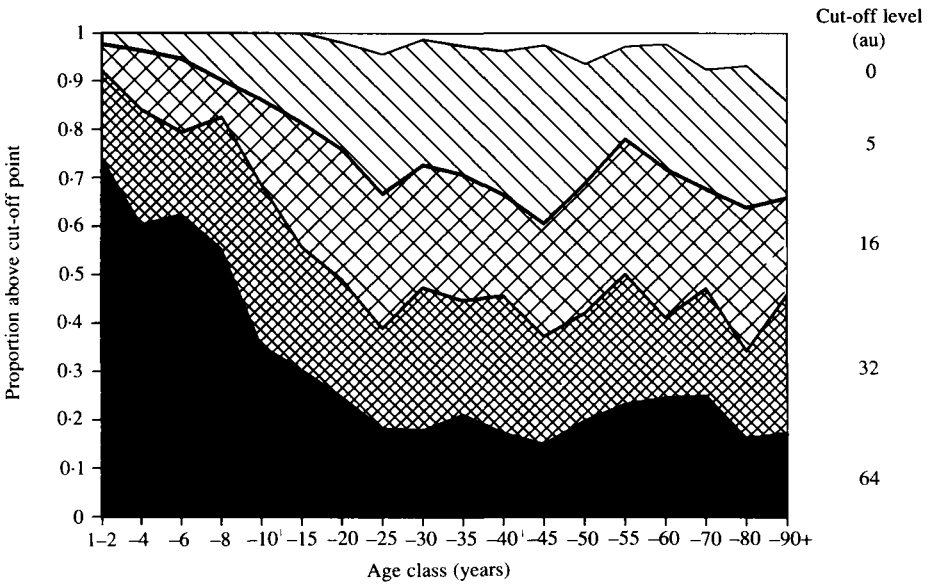

Fig. 3. Changes, with age, in the proportion of seropositive samples (> 0·0 au) with concentrations above various threshold levels, from the survey of mumps antibodies in NW England, 1984 (pooled male and female data, age range 1–92 years). Median (unlogarithmic) antibody level = 32 au, upper quartile = 64, lower quartile = 16.

infection. A rapid decay over the first 20 years (H_0: $b = 0$, significant regression, $F = 107{\cdot}5$, D.F. = 611, $P < 0{\cdot}0001$) is followed by a period of no further decline (H_0: $b = 0$, $F = 0{\cdot}758$, D.F. = 1522, $P > 0{\cdot}05$) over the full range of adult age classes. This trend is similar for males and females, although it was shown earlier in Fig. 1 that when assessed over all ages (1–92 years) the mean antibody level for males was significantly lower than that for females.

A significant rise (H_0: $b = 0$, $F = 5{\cdot}24$, D.F. = 20, $P < 0{\cdot}05$) in antibody-level heterogeneity between individuals (measured as the variance to mean ratio) is detectable with increasing age as shown in Fig. 4(*b*). The combination of declining levels of antibody and increased antibody-level variability with age results in a steady increase in the probability of an individual, who has experienced past mumps infection, having an antibody concentration of less than 5 au (Fig. 4*c*) (H_0: $b = 0$, significant regression, $F = 18{\cdot}74$, D.F. = 20, $P < 0{\cdot}001$). In other words, as age increases there is an increased likelihood of false negatives (compare with Fig. 3). The importance of this observation in relation to loss of protective immunity and to the estimation of epidemiological parameters has previously been emphasized [12] and is considered further in later sections.

Age-serological profiles for mumps antibody

(i) *Passive immunity*

Data presented in Fig. 2 have been used to describe the decay in the proportion of infants with maternally acquired mumps antibody over the first year of life (Fig. 5). Two threshold levels for seropositivity have been used, 2·5 and 5 au, in view of the large proportion of samples with low level (< 5 au) antibody shown in

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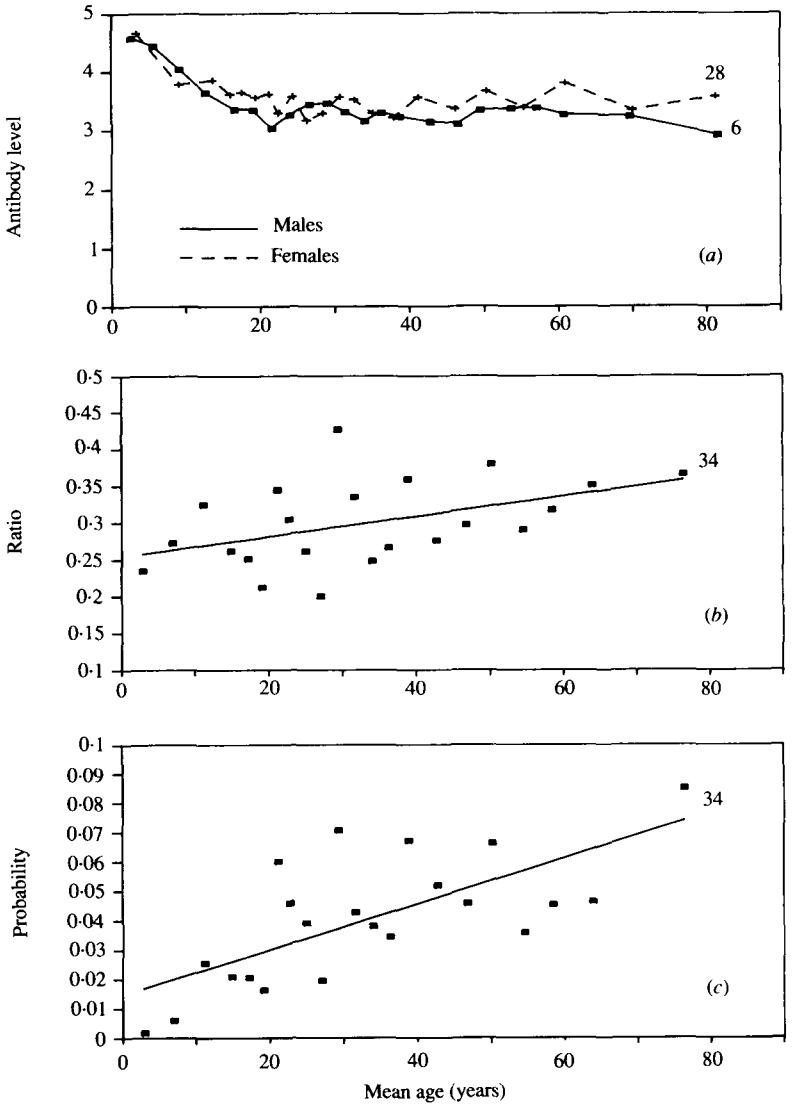

Fig. 4. Analyses of trends in mumps-specific IgG concentrations, NW England 1984. Graph (*a*) records the changes in mean (natural logarithmic) antibody levels (all samples > 5 au, ages 1–92) for males and females, with increasing age. Corresponding trends, for pooled data, in the variance to mean ratio and the probability of false negatives (predicted on basis of normally distributed antibody levels) are shown in graphs (*b*) and (*c*). Each data point represents a sample size of 50 (graph *a*) or 100 (graphs *b* and *c*) unless otherwise indicated. Equations for regression lines in graphs (*b*) and (*c*) are $Y = 0{\cdot}255 + 0{\cdot}0014X$ and $Y = 0{\cdot}0148 + 0{\cdot}008X$ respectively.

Fig. 2. An exponential decay model (solid lines) which assumes a constant rate of decay of maternal antibody has been applied to the observed proportions (symbols) in Fig. 5. The close correlation between observed and predicted values (data points lie within the expected variances [22]) suggests the model provides a good fit to the data.

The rate of decline in proportion of individuals with maternally derived

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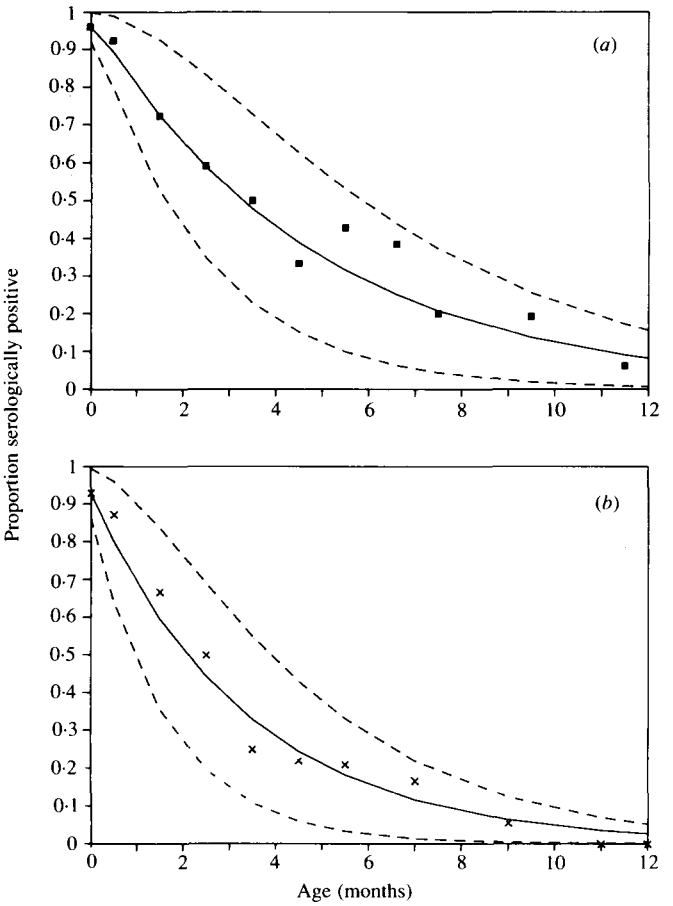

Fig. 5. Decay in the proportion of individuals with maternally derived antibodies, from a survey in NW England, 1984, assuming cut-off points for seropositivity of either 2·5 au (graph *a*) or 5 au (graph *b*). An exponential decay model (——) of the form $Y = ae^{-bX}$, where a is the y axis intercept (estimated to be the proportion of seropositive females of age range 20–30) and b the constant instantaneous decay coefficient, is fitted to the raw data points in graph (*a*) and (*b*). In each case the expected variance (with binomial probability) is given (– – –). Estimates for coefficients are as follows:

graph (*a*) $b = -0{\cdot}2083$ S.E.$_b = 0{\cdot}0207$
$a = 0{\cdot}96$
(*b*) $b = -0{\cdot}2986$ S.E.$_b = 0{\cdot}0234$
$a = 0{\cdot}93$

antibody (Fig. 5) is clearly dependent upon the cut-off in seropositivity adopted (i.e. dependent upon the sensitivity of the serological technique). The predicted rates of decay (see legend to Fig. 5) were found to differ significantly at the 5% level (1-tail test, non-overlapping 95% error bars), and provide a range of estimates for the average duration of maternal antibody of between $3{\cdot}4 \pm 0{\cdot}4$ months and $4{\cdot}8 \pm 0{\cdot}3$ months. The implications of this observation will depend upon the level of antibody that provides protection from infection or prevents

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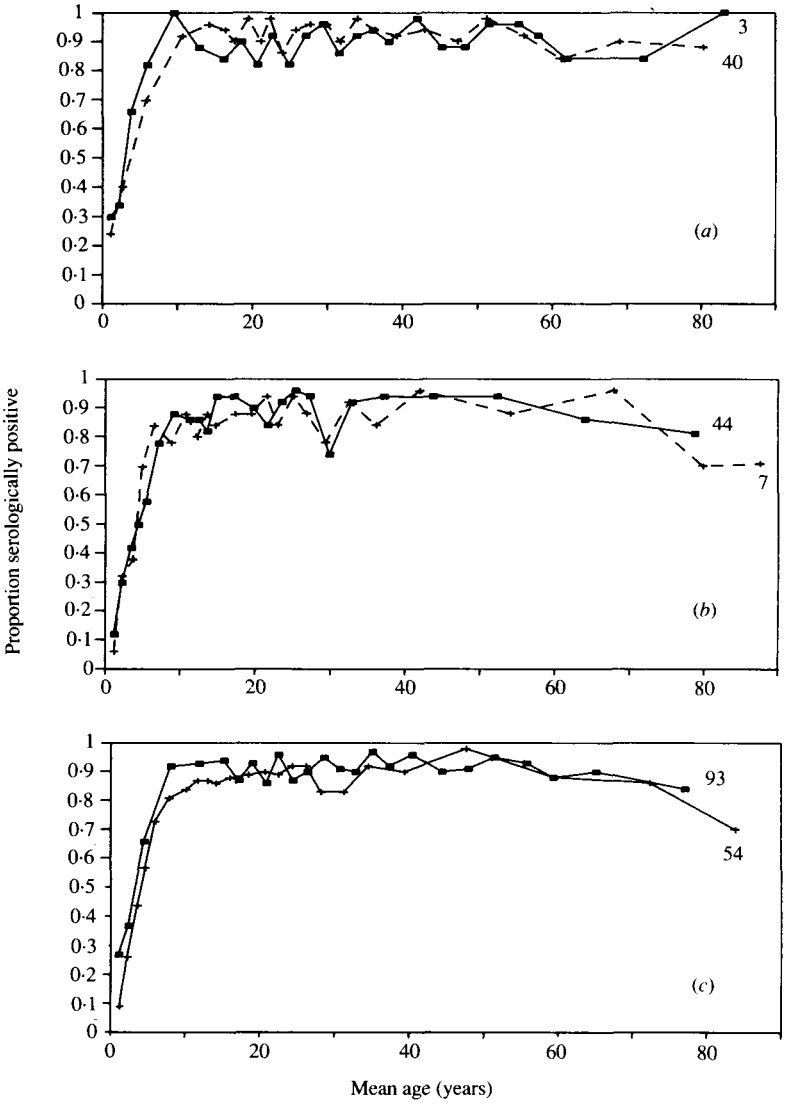

Fig. 6. Age-serological profiles for mumps antibodies in NW England. Comparison of male (■–■) with female (+–+) data sets over the age range 1–92 for 1984 and 1986 are shown in graphs (*a*) and (*b*) respectively. Graph (*c*) compares pooled data for 1984 (■) and 1986 (+). Sample sizes are 50 (graphs *a* and *b*) or 100 (graph *c*) data points. unless otherwise indicated.

seroconversion following immunization [23], and the relationship between serum IgG and other factors involved in immunity. It is evident from Fig. 5 that only a small proportion of individuals will retain passively acquired mumps antibody into their second year of life.

(ii) *Acquired immunity*

Age-related changes in the proportion of males and of females serologically positive for mumps-specific antibody are illustrated for the 1984 and 1986 surveys

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in Fig. 6(*a*) and (*b*) respectively. Samples for individuals under the age of 1 year (1984 only) are excluded to avoid the complication of maternally derived antibodies. Under the premise that production of specific IgG antibody following infection is lifelong, each observation point in Fig. 6(*a*) and (*b*) represents the proportion of individuals who have experienced a past mumps virus infection. Such age-serological profiles are, therefore, a reflection of historical events (i.e. temporal changes) in mumps incidence, as well as events which are related to the age of an individual [9,24].

The profiles in Fig. 6(*a*) and (*b*) each show a rapid rise in the proportion serologically positive over the first 10–15 years to a level of approximately 0·9, succeeded by a gentle rise to a plateau of about 0·95 seropositive over the age-range 20–60 years (for statistical analyses see next section). A slight decline in the proportion positive in those greater than 60 years appears in both profiles. The age-related trends are seen to be broadly similar for both sexes. Closer inspection, however, reveals a more rapid rise in the proportion of seropositive males compared with females over the childhood years in the 1984 survey, with statistically significant differences for age classes 5–6 and 9–10 years (*d*-test, 2-tail, $P < 0{\cdot}05$ [13]). No significant difference between the sexes was detected for the 1986 survey.

Comparison of the profiles for 1984 and 1986 (total samples), shown in Fig. 6(*c*), reveals an earlier acquisition of mumps-specific antibody in 1984 throughout the first 15–20 years (significant differences for age classes 3–4 and 7–8 years, $P < 0{\cdot}05$). No statistical difference between the profiles was detectable over the remaining age distribution.

Estimation of epidemiological parameters

(i) *Age-related transmission rates in children*

Age-specific rates or forces of infection, $\lambda(a)$, were estimated from the serological profiles for northwest England (pooled data for males and females), presented in Fig. 6. Changes in $\lambda(a)$ over the age range 0·5–15 years, determined by a polynomial catalytic infection model [9], are recorded in detail for the years 1984 and 1986 in Figs. 7 and 8 respectively. Below the age of 6 months individuals are assumed to be protected by maternally derived antibody and $\lambda(a)$ is set to zero for age $a \leqslant 0{\cdot}5$ years. Each figure displays the change, with age, in the observed (symbols) and expected (solid lines) proportion of the population assumed to have experienced mumps infection (lower graphs), and the best-fit polynomial function for the forces of infection, $\lambda(a)$ (upper graphs). Average values of $\lambda(a)$ over selected age intervals are represented by histogram bars to facilitate clear description and comparison of results. For both surveys the close correspondence between observed age-prevalence profiles and that expected from the fitted polynomial model (Figs 7 and 8) indicates goodness of fit [9].

Marked variation with age in the predicted $\lambda(a)$ (convex in shape with a maximum at around 5 years of age), is seen for the 1984 and 1986 data (Figs. 7(*a*) and 8(*a*)). Changes in the amount of exposure of susceptibles to infection over the childhood and teenage years has been previously recognized as due to heterogeneity in mixing rates which result from school attendance. Such patterns have been recorded for many childhood viral and bacterial infections [3,4,10].

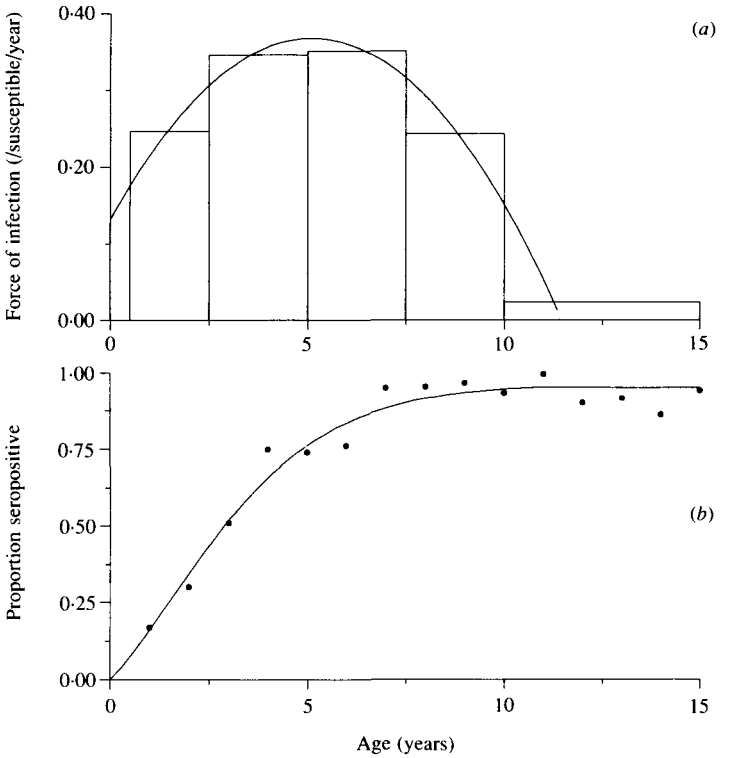

Fig. 7. Force of infection estimates for children (0–15 years) from NW England, 1984. Graph (*a*) records the polynomial form of the force of infection calculated using a catalytic infection model, and corresponding average values over discrete age ranges. The best-fit profile predicted from the force of infection estimates in (*a*) is plotted through the observed data points in graph (*b*).

However, the peak force of infection at around 5 years of age, shown in Figs. 7(*a*) and 8(*a*), is somewhat earlier than that recorded in past studies of a variety of childhood infections, including mumps, where the maximum observed force of infection was within the age range 5–15 years. It is surprising that the rate of infection should fall so rapidly from the maximum level in 5-year-olds to the relatively low levels in the age class 10–15 years (the polynomial function actually falls to zero within this age range), as illustrated in both sets of data (Figs. 7*a* and 8*a*). The case notification data that are available (RCGP, unpublished data from spotter practices) suggest that infection in the teenage classes is more common than this analysis of serological data reveals. Whether the decline to a low rate of infection truly reflects the level of exposure of susceptibles to mumps virus in the population, or is an artifact arising from the method employed in estimating rates of infection from serological data, is discussed later.

From the differences in childhood age-acquisition of mumps between 1984 and 1986 (Fig. 6*c*), the estimated values of $\lambda(a)$ in Figs 7(*a*) and 8(*a*) are consistently higher for 1984 than 1986 over the age range 0·5–10 years. Rates of transmission of many childhood viral infections naturally oscillate on seasonal and longer-term cycles. For mumps there is a clear epidemic pattern to the reported cases with a

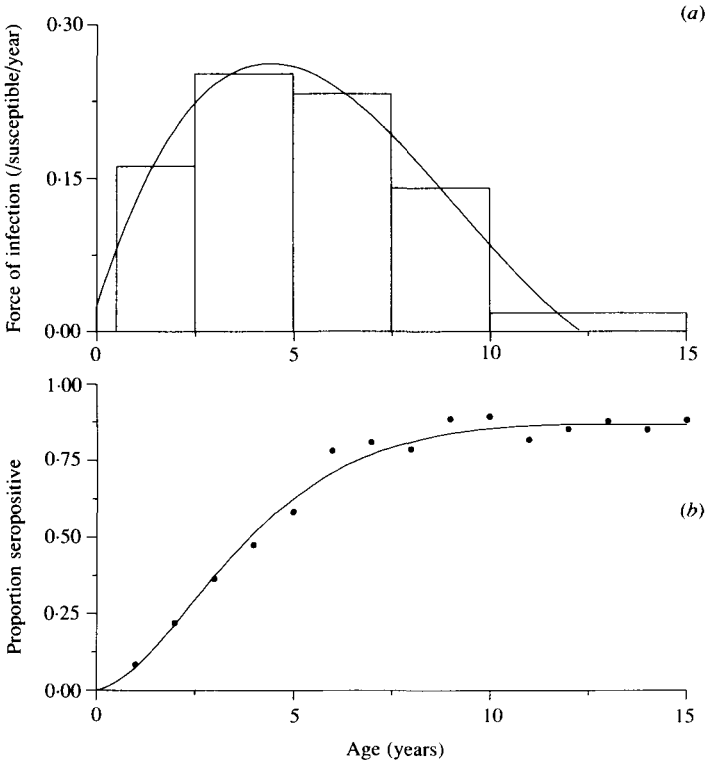

Fig. 8. Force of infection estimates for children, NW England, 1986. Details as for Fig. 7.

period of approximately 3 years (unpublished data from RCGP and CDSC). The observed difference in the rate of childhood mumps infection between 1984 and 1986 (Figs. 7 and 8) might, in part, be attributed to epidemic versus inter-epidemic years of mumps incidence. Unfortunately, case records (RCGP) are not sufficiently detailed to look for temporal trends in incidence of mumps across the country to substantiate this argument. Laboratory records of serodiagnosed mumps for the Preston Infirmary were too few to aid interpretation.

Short-term (over a few years) temporal variability in incidence (seen for many directly transmitted childhood viral or bacterial infections) may be 'averaged out' by pooling data across an epidemic period in order to obtain an estimate of the equilibrium (average) rate of transmission [9]. Results of merging data for the two surveys (1984 and 1986) are presented in Fig. 9 showing the average age-dependent forces of infection. The pattern is similar to that recorded in Figs. 7 and 8.

(ii) *Age-related transmission rates in adults*

One shortcoming of the polynomial maximum-likelihood procedure for the estimation of $\lambda(a)$ is an inability, under certain circumstances, accurately to mirror observed changes in the proportion who have experienced infection in older age classes (15 years and over). In general the method is most able to capture the rapid changes in $\lambda(a)$ over the earlier childhood years. This problem was found to

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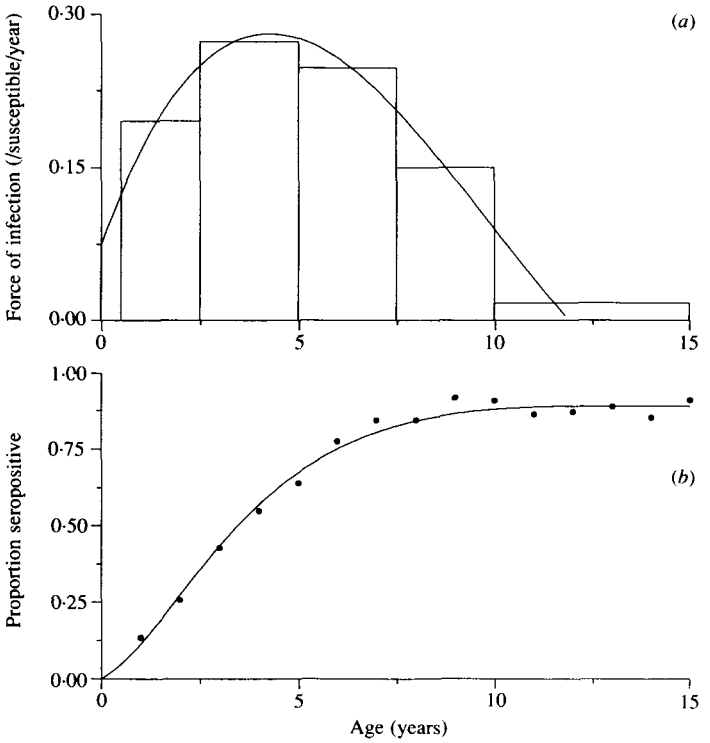

Fig. 9. Force of infection estimates for children, NW England, 1984/1986 (pooled data). Details as for Fig. 7.

Table 2. *Force of infection estimates for adult age classes*

Sample	Age range (years)	Cut-off (au)	P1* (S.E.)	P2* (S.E.)	Test 1† Test 2	Sig† (*P* value)	λ‡
1984	20–40	5	1·3873 (0·5765)	0·0361 (0·0201)	3·30 20·69	0·069 0·354	0·0332
1986	20–50	5	1·3940 (0·4478)	0·0255 (0·0151)	3·01 38·87	0·083 0·066	0·0233
1984/86	15–50	5	1·8439 (0·2183)	0·0161 (0·0074)	4·810 28·81	0·028 0·676	0·0147
1984/86	15–50	0	1·6767 (0·2455)	0·0319 (0·0087)	14·30 33·91	< 0·0001 0·423	0·0298

* Coefficients for the logistic regression model:

$$E(s_a/n_a) = \exp(\mathrm{P1} + \mathrm{P2}a)/(1 + \exp(\mathrm{P1} + \mathrm{P2}a))$$

where $E(s_{(a)}/n_{(a)})$ is the predicted proportion susceptible; $s_{(a)}$ is the number seronegative in age class a, and $n_{(a)}$ the number of samples in age class a. S.E. refers to the standard error of each coefficient.

† *Test 1.* Improvement chi-square and corresponding P value (Sig.) for improvement over model without an age term. A low P value indicates significant improvement [15]. *Test* 2. Goodness-of-Fit chi-square and corresponding P value (Sig.) for the fit of the model to the data. A high P value indicates a good fit [15].

‡ Average force of infection estimate determined using the formula [7]

$$\lambda_{a+0\cdot5\Delta a} = -\ln(x_{a+\Delta a}/x_a)/\Delta a,$$

where $x_a = E(s_a/n_a)$.

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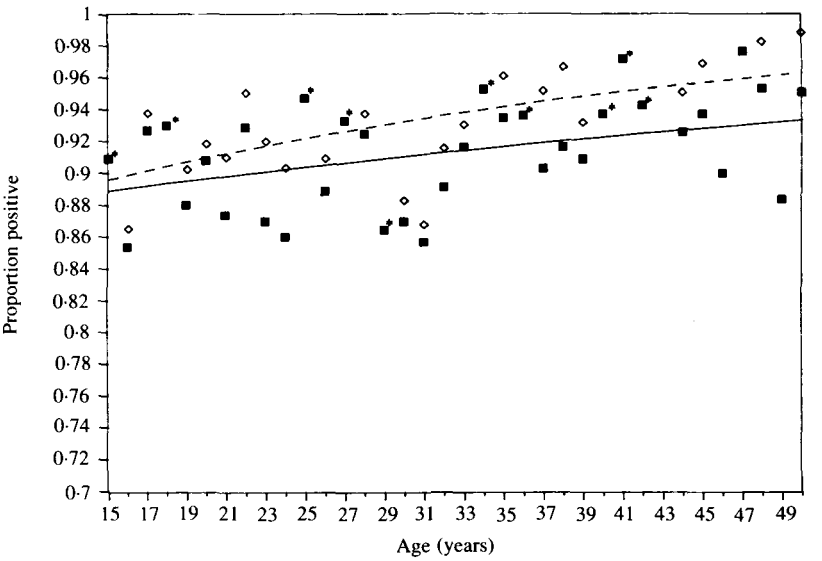

Fig. 10. Fit of a logistic regression model, which assumes a constant force of infection, through the observed adult (15–50 years) age-prevalence profile for NW England, 1984/1986. Observed (■) and predicted (——) proportions using a cut-off for mumps seropositivity of 5 au are compared with observed (◇) and predicted (– – –) proportions using a cut-off point of 0·0 au. An asterisk indicates coincidence of observed proportions for the two cut-off points.

be particularly acute for the mumps age–serological profiles for NW England. In Figs. 7–9 the model identified a period, corresponding to the age class 10–15 years, in which the $\lambda(a)$ estimates fell to negligible levels, appearing to be due to a plateau or slight decline (Figs. 7 and 8*b*) in seropositivity. Subsequent extension of the age range through which the model was applied resulted in a poor fit to the adult age classes because of the apparent low rates of infection in the 10- to 15-year age band.

As a result of these difficulties we have adopted the procedure of stepwise logistic regression to determine, more accurately, the $\lambda(a)$ changes over the wide range of older age classes (15 years upwards). This method provides a suitable alternative for modelling age-related changes in proportions with known sample sizes [25]. Results are summarized in Table 2, and the fit through observed data pooled from both surveys is shown in Fig. 10.

The probability of falsely recording a serum sample as mumps-negative was seen to increase with age (Fig. 4*c*), particularly for the age classes above 60 years, where a decline in seroprevalence was observed (Fig. 6). As previously recognized for rubella [12], this may lead to under-estimation of age-specific forces of infection in these older age classes. To minimize this effect logistic regression was applied within the age range 15–50 years only, and comparison made for cut-off levels in seropositivity of 5 au and 0·0 au (i.e. the latter level includes, as seropositive, samples with any detectable antibody). Over the stated age ranges in Table 2, a constant λ provided a good fit to the observed data (i.e. a significant goodness-of-fit chi-square [15]), and was a significant improvement over the model

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Table 3. *Summary epidemiological statistics estimated from the serological surveys of mumps in NW England, 1984 and 1986*

Sample set	Cut-off (au)	A* (yrs)	R_0†	p_c‡	T§ (yrs)
1984	5	5·43	15·2	0·934	3·34
1986	5	8·24	9·7	0·897	4·11
1984/86	5	6·94	11·6	0·914	3·77
1984/86	0	7·54	10·7	0·907	3·93

* Average age at infection (see text for method of deviation)

† Basic reproductive rate

$$R_0 = L/(A-D),$$

where L is life expectancy (75 years), and D is the average duration of maternal antibody (set at 0·5 year).

‡ Critical proportion of population requiring immunization to block transmission

$$p_c = 1-1/R_0,$$

§ Inter-epidemic period

$$T = 2\pi(Ak)^{0.5},$$

where k is the sum of the latent and infectious periods (0·052 year) [7].

in which the age term was omitted (i.e. a significant improvement chi-square [15]). Thus with a constant λ over this age range the profiles clearly indicate a rising trend in the proportion of immunes in the adult age classes. The magnitude of the estimated λ values for the adult age classes is considerably lower than for the childhood age classes in general, excepting the 10 to 15-year age class which recorded a decline to zero (Figs. 7–9). A more rapid rise, with age, in the immune proportion using a cut-off of 0·0 au rather than 5 au, shown for the pooled 1984 and 1986 data (Fig. 10), indicates that decaying antibody levels may be a source of under-estimation of λ values in the adult age classes (Table 2). This observation is of practical significance and should be borne in mind when predicting the impact of mass mumps immunization on the incidence of disease related to mumps-virus infection.

(iii) *Summary epidemiological parameters*

Estimates for four summary epidemiological parameters (A, R_0, T and p_c) derived from the surveys of NW England are presented in Table 3. In general, calculations follow the methods of past studies. However, the estimation of the average age at infection is complicated by a possible long-term change in incidence of infection suggested by the serological profiles recorded in Figs. 6–9. In order to obtain an approximation for A we divide the serological profiles into two age zones, 0–15 years and over 15 years, on the premise that the former age range corresponds to current levels of infection and the latter to past levels. The assumption remains that within each zone there are no time-dependent changes in transmission rates, but now also that adult age classes (> 15 years) are not influenced by the factors which have brought about an increase in rate of infection

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in the younger class (0–15 years). Some evidence to endorse this last assumption is provided by RCGP data.

Thus the average age at infection, A, has been estimated from

$$A = D + \frac{\int_D^{t_2} a\lambda(a)x(a)da}{\int_D^{t_2} \lambda(a)x(a)da}, \quad (1)$$

where D is the duration of maternal antibody protection (set to 0·5 years), t_1 is age 15 and t_2 is age 75 (life expectancy) [7]. Over the range 0 to t_1 age-dependent forces of infection derived from the polynomial method were used (see Figs. 7–9), while over the range t_1 to t_2 a constant force of infection was assumed (as discussed earlier) (see Table 2).

DISCUSSION

Analysis of age–serological profiles provides two main types of information on the dynamics of an infection in a population, namely age-related and time-dependent processes. It is usual to assume one of these processes to be unchanging (stable or at equilibrium) in order to make inferences about the other [9]. However, evidence from the surveys presented here suggests that both age- and time-dependent factors are determining observed patterns of mumps transmission in NW England.

Each survey (1984 and 1986) revealed the familiar convex change (low–high–low) in the force of infection with increasing age previously observed in surveys of other common childhood infections [3,11,12]. These changes are thought to be due to age-related heterogeneity (particularly as a result of school attendance) in rates of mixing in a population ('who mixes with whom' by age class) [3]. The implications of such variation to the predicted impact of mass-immunization schedules are well documented [4,8,10].

The evidence for time-dependent effects is twofold. It may be argued that the significantly higher rates of transmission for 1984 compared with 1986 (seen in Figs. 7 and 8) are the consequence of short-term (2- to 4-year) cycles in mumps incidence created by the rise and fall in herd immunity in conjunction with seasonality in transmission. Where such periodicity is of short duration compared with the age span of the host, the effects may be countered by amalgamating data from different periods over an epidemic cycle [9]. Alternatively, increasing sample sizes and widening the catchment area from which sera are collected (ideally to a national level) will lessen the influence of this periodicity. The countrywide programme of serological surveillance of measles, mumps and rubella in England, initiated by the Public Health Laboratory Service [6], illustrates this approach, which should be adopted where resources permit.

Long-term temporal changes in the incidence of mumps infection are suggested by the low rate of transmission in the 10 to 15-year age class (relative to the adult age classes) shown in both survey years (Figs. 7 and 8). This low transmission force is puzzling in view of expected high rates of mixing. The shape of the age-prevalence profiles may simply be an artifact of chance variability in serological

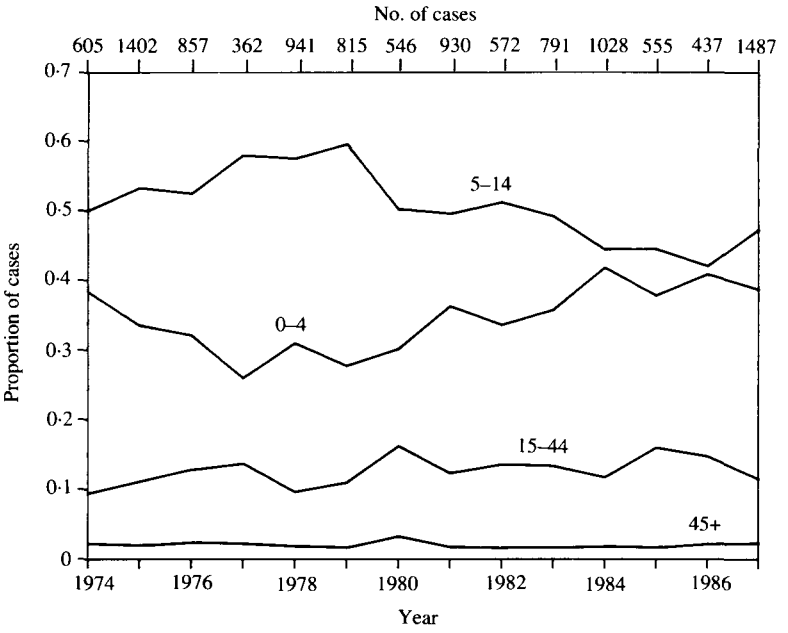

Fig. 11. Trends in the proportion of mumps consultations collated by RCGP (unpublished data) in various age classes over the period 1974–87. Absolute numbers of consultations are also provided.

data. However, it is equally plausible that in recent years there has been an increase in the rate of mumps transmission in the very young, which has had little effect on seroprevalence in older age classes (> 15 years). Thus the low $\lambda(a)$ in the 10 to 15-year-olds may mark a transition period between two transmission intensities (present (high) in young and past (low) in adult); and the peak rate of transmission at around 5 years of age, which is lower than observed (5–15 years) in previous studies, may be a manifestation of higher mixing intensities in the very young due, for example, to increasing use of playgroups, day-care nurseries and creche facilities by working parents [26]. This finding may be repeated with other childhood infections.

A longer-term change in infection rates in the young would be reflected by; (1) a lower average age at infection; (2) a reduction in the period between epidemics [4], and (3) coupled with a change in the age-distribution of cases in the general population, an increase in subclinical cases and, accordingly, a decrease in the number of cases of serious complications.

Limited evidence corroborates this hypotheses. Serology from NW England is difficult to interpret as a result of temporal changes, but the rough estimates of the average age at infection of between 5 and 8 years are not appreciably different from previous reports. However, past estimates have been based either upon case notifications (and, therefore, fall prey to problems of age-related disease severity) or poorly age-stratified serological surveys over a narrow age range. The serology from NW England does, however, reveal a reduction in the age at which the highest intensity of mumps virus infection occurs.

Analysis of available RCGP data (Fig. 11) indicates an increasing proportion of mumps cases in the 0 to 4-year age range over the last decade, predominantly at the expense of cases in 5 to 15-year-olds. Average RCGP consultation rates per 100000 for the period 1961–7 to 1969–71 show a similar trend [2]. Changes, through time, in the proportion of cases reported to RCGP (Fig. 11) appear to be limited to the age range 0–15 years, providing circumstantial evidence that adults have been unaffected by any increase in transmission rates in children. The paper by Galbraith and colleagues [2] also points to a reduction in frequency of severe mumps cases in recent decades. Mumps incidence data have not been collected for a long enough period for time series analysis to detect, with any reliability, changes in the inter-epidemic period. These points serve to highlight the usefulness of collecting long-term, finely age-stratified incidence data for childhood infections.

It is interesting to note that changes in the epidemiology of mumps in this country may influence the potential benefit from mass-immunization. For example, a younger age at infection would necessitate a higher vaccination coverage required to block transmission [27]. Rough estimates, based on simple theory [7], of the critical proportion of the population requiring vaccination in order to interrupt transmission shown in Table 2 suggest values in the region of 90% as soon after birth as possible. In addition, the relative magnitude of the force of infection in the older age classes and in the young, which from these surveys presented seems to have been altered, is of crucial importance to the predicted outcome of a vaccination programme on the incidence of serious complications arising from mumps infection. Such programmes may shift upwards the age-distribution of the remaining cases [4]. Quantitative analyses based on a mathematical model of mumps infection would help to resolve this issue.

Although serological data do not have the serious disadvantages of case notifications [9], the accurate estimation of $\lambda(a)$ in older age classes presents a number of problems. First, serological data are inherently sensitive to past changes in incidence, and may fluctuate as a consequence of chance variation (affected by sample size). Secondly, as for any childhood infection, the proportion seronegative in the older age classes is only a small fraction, and, therefore, absolute changes in the proportion seropositive from infection will be small, relative to those in childhood. Hence, small amounts of variability, arising from random processes or, as clearly illustrated in this study, the decline, with age, in mean antibody levels, may mask or alter any age-related trends in the data. Previous studies have demonstrated the importance of accuracy in estimating the force of infection in older age classes to calculations of p_c and to predictions of the likely impact of mass immunization on the incidence of infection and disease [3,11]. Thus in designing serological surveys it is important to attempt to minimize these problems. Careful attention should be paid to antibody test sensitivity, and to covering a wide range of age classes, including large samples in the adult age groups and, ideally, for a number of years through one or more epidemic cycles. The surveys for NW England satisfy these requirements to some extent, although undoubtedly significant improvement could be achieved with larger sample sizes. Estimates of the force of infection in adulthood derived from

these surveys (similar in magnitude for 1986 and 1984) are likely to be the most accurate available to date and will be of value in further studies of the likely effects of the recent introduction of mumps immunization in this country.

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