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Rubella epidemiology in South East England

BY D. J. NOKES, R. M. ANDERSON,

Parasite Epidemiology Research Group, Department of Pure and Applied Biology, Imperial College, London University, London SW7 2BB

AND M. J. ANDERSON

Department of Medical Microbiology, University College London and the Middlesex Hospital Medical School, London University, London WC1E 6JJ

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SUMMARY

Analyses of data collected in a large survey (sample size > 3000) of rubella antibody in South East England, finely stratified according to age, reveal age-dependent changes in the pattern of virus transmission. The rate or force of infection changes from low in the young children to high in the 5 - to 15-year-olds and back to low again in the adult age classes (there is a 50% reduction between the 5- to 15-year-olds and the 20+-year-olds). Raised levels of immunity are recorded in the teenage and young adult female segments of the population as a consequence of the UK rubella immunization programme. Mean antibody concentrations show a decline with age and are, on average, lower in vaccinated females when compared with unvaccinated males of the same age. The interpretation of horizontal cross-sectional serological data and future research needs are discussed.

INTRODUCTION

Recent studies of the transmission dynamics of rubella virus have highlighted the importance of quantitative information concerning age-specific rates of infection to any detailed assessment of the impact of mass immunization on the incidences of rubella and congenital rubella syndrome (CRS) (Anderson & May, 1982*a*, 1983*a*, 1984, 1985; Schenzle, 1984; Anderson, Grenfell & May, 1984; Anderson & Grenfell, 1986; Grenfell & Anderson, 1985). Advances in the development of a mathematical framework to aid in the design of immunization programmes have, to some extent, outstripped the acquisition of the relevant epidemiological data needed to compare prediction with observation. The combination of these theoretical and empirical components is required to assess the likely impact of different immunization policies.

Changes in the force of infection (the per capita rate at which susceptibles acquire infection per unit of time) with respect to age are of particular significance in this respect (Anderson & Grenfell, 1986; Grenfell & Anderson, 1985). Past attempts to assess the level of vaccine coverage required either to eliminate rubella, or to reduce the incidence of CRS to a defined level, have been based on the

assumption that the force of infection, λ, is constant and independent of age (Knox, 1980; Dietz, 1981; Anderson & May, 1982*a*, *b*; 1983*b*;Hethcote, 1983). Recent research has begun to explore ways of modifying this assumption in the light of data compiled from case notification records and horizontal serological surveys (Anderson & May, 1985). These studies suggest that the force of infection adopts low values in young children, rises to a peak value in teenagers, and then declines to a low value in adult age classes (Anderson & May, 1983*a*, 1985; Anderson & Grenfell, 1986). Heterogeneity in mixing of individuals, both within and between age classes, is thought to be responsible for observed trends.

This paper reports the results of a horizontal cross-sectional seroepidemiological survey of rubella antibodies in samples of sera collected from males and females in a wide range of age classes between 1980 and 1984 in South East England. The survey was motivated by (i) the paucity of published serological data on rubella infection in male and female populations finely stratified according to age, (ii) the need to assess the impact of the current UK vaccination policy on the prevailing levels of herd immunity to infection, and (iii) the need to assess whether the force of infection varies systematically with age.

METHODS AND MATERIALS

Serum samples

Serum samples were collected from two sources. The Department of Virology, King's College Hospital, London, provided aliquots of 1556 sera (age range of patients, 0–93 years) that had been submitted for diagnostic tests and stored at −20 °C since 1980. The Blood Transfusion Centre for South East England provided 1822 serum specimens from blood donors (age range of donors 18–65 years) collected during 1984. The catchment area for both sources of material is, in broad terms, South East England.

Radial haemolysis (RH) test

The RH test for rubella-specific IgG antibody described by Kurtz *et al.* (1980) was used with the following modifications:

Reproducibility of results. Wells of 3 mm diameter and capacity of 7–8 μl were filled with test sera dispensed from haematocrit tubes. Gels were incubated for 24 h. Test to test variation was monitored by determining the antibody concentration of five control sera in each test series.

Quantification of antibody concentration. A local standard serum specimen was calibrated by parallel line assay (Finney, 1978) with a British Standard Serum containing 360 international units (i.u.) of rubella antibody (obtained from the National Institute of Biological Standards and Control, Holly Hill, London). For each gel in a test series, serial two-fold dilutions of the local standard in antibody-negative serum, from undiluted to 1 in 128, were tested in randomly located wells, and the equation of the linear relationship between haemolysis zone diameter and logarithm of antibody concentration (i.u./ml) calculated by least-squares regression. All zones of haemolysis were measured to the nearest 0·1 mm using an eyepiece lens with graticule. The antibody concentration of each test serum was derived from the linear equation of standard serum dilutions. Sera with

concentration of rubella-specific antibody equal to or greater than 3·3 i.u./ml were regarded as positive.

Inter-serum interference. The incidence of overlapping zones of haemolysis was reduced by cutting only 49 wells, in hexagonal configuration, per plate. Where haemolysis zones overlapped preventing accurate measurement the sera were retested.

Sera containing anti-sheep red blood cell antibody. A serum producing zones of haemolysis of equal diameter with both antigen coated and uncoated sheep red blood cells (SRBC) and greater than the test zone for the 3·3 i.u./ml standard may contain rubella-specific antibody, the detection of which is obscured by the lysis caused by anti-SRBC antibody. Sera falling into this category were incubated in SRBC for 1 h and retested.

Validation of negative and equivocal RH results. All sera giving negative results on initial testing were retested by RH. Two separate, randomly selected samples of antibody-negative sera each comprising some 10% of the total number of negative sera, were tested by haemaglutination inhibition (HI) (PHLS Monograph No. 16) and by the Rubazyme enzyme-linked immunosorbent assay (ELISA) (used according to the instructions of the manufacturer, Abbott Diagnostics, UK) to determine the incidence of 'false negative' RH results. All sera giving zones of atypical lysis were tested by HI or ELISA.

Quantitative methods

Age-specific forces or rates of infection ($\lambda(a)$) were estimated from the age-stratified serological data (proportions seropositive in each age class) by the method recently described by Grenfell & Anderson (1985). The technique is based on a 'polynomial catalytic infection model' of the rate at which the proportion seropositive changes with age, and employs maximum-likelihood methods in estimating the age-specific forces of infection (Griffiths, 1974; Grenfell & Anderson, 1985). In the model, the proportion who have experienced infection by age a, $F(a)$, is defined as

$$F(a) = 1 - \exp\left[-\int_0^a \lambda(\alpha) d\alpha\right]. \tag{1}$$

Here $\lambda(a)$ denotes the age-specific rate of infection. The parameter $\lambda(a)$ may be set at zero below some lower age limit to denote the duration of protection against infection induced by maternally derived antibody. The function $\lambda(a)$ is expressed as a polynomial of order k, where

$$\left.\begin{aligned} \lambda(a) &= \sum_{i=0}^{k} b_i a^i \quad (D < a \leqslant U), \\ \lambda(a) &= 0 \qquad (a \leqslant D). \end{aligned}\right\} \tag{2}$$

Here U denotes the upper age limit of the data, D the duration of maternal antibody protection, and the b_i's represent the coefficients of the polynomial function. A number of assumptions are incorporated in the model which influence the accuracy of the estimation method for the age-specific forces of infection. They are as follows: (i) the infection is assumed to be endemic and at some quasi-equilibrium state within the population (this state may be oscillatory in nature); (ii) the infection is assumed to induce lifelong immunity to reinfection and not to

Table 1. *Reproducibility of the radial haemolysis test*

	Controls				
	1 (High)	2	3	4	5 (Low)
Mean (ln(i.u./ml))	6·98	6·23	4·43	3·97	3·17
n	7	7	10	11	10
$*s^2$	0·007	0·017	0·014	0·017	0·024
CL	0·080	0·118	0·086	0·088	0·110
CV %	1·23	2·09	2·71	3·31	4·90

* Test for homogeneity of variance – no significant inhomogeneity at 1 % level.
n, sample size, s^2, variance, CL, confidence limit (95 %) and CV %, coefficient of variation.

increase the mortality of infected individuals; (iii) it is assumed that horizontal changes in the proportion seropositive mirror longitudinal changes for specific cohorts of individuals. Assumptions (i), (ii) and (iii) broadly hold for developed countries provided the inter-epidemic period of the oscillations in disease incidence (4–5 years for rubella, see Anderson & May, 1983*a*; Anderson, Grenfell & May, 1984) is short in relation to the age span over which serum samples are collected (0–75+ years in this study).

The mean age, A, at which susceptibles acquire infection can be estimated directly from eqns. (1) and (2), where

$$A = D + \int_D^\infty [1 - F_{(a)}]da, \tag{3}$$

and D denotes the average duration of protection provided by maternal antibodies. The inter-epidemic period, T, of directly transmitted viral and bacterial infections that induce lifelong immunity, is related to the average age at infection (see Anderson & May, 1982*a*, 1983*a*), where

$$T \simeq 2\pi(AK)^{\frac{1}{2}}. \tag{4}$$

Here, K is the sum of the latent and infectious periods of the infection. For rubella, the period T is approximately 4–5 years.

Oscillatory fluctuations in the incidence of infection may well be reflected in horizontal age-stratified serological profiles, both with respect to the proportions seropositive and to the mean antibody concentrations in each yearly cohort of people. Time series analyses (auto-correlation and spectral analysis) were employed to examine the data for regular oscillatory fluctuations in seropositivity and mean antibody concentrations within the male segment of the sample population (for a discussion of the statistical techniques, see Anderson, Grenfell & May, 1984). No significant correlations were found.

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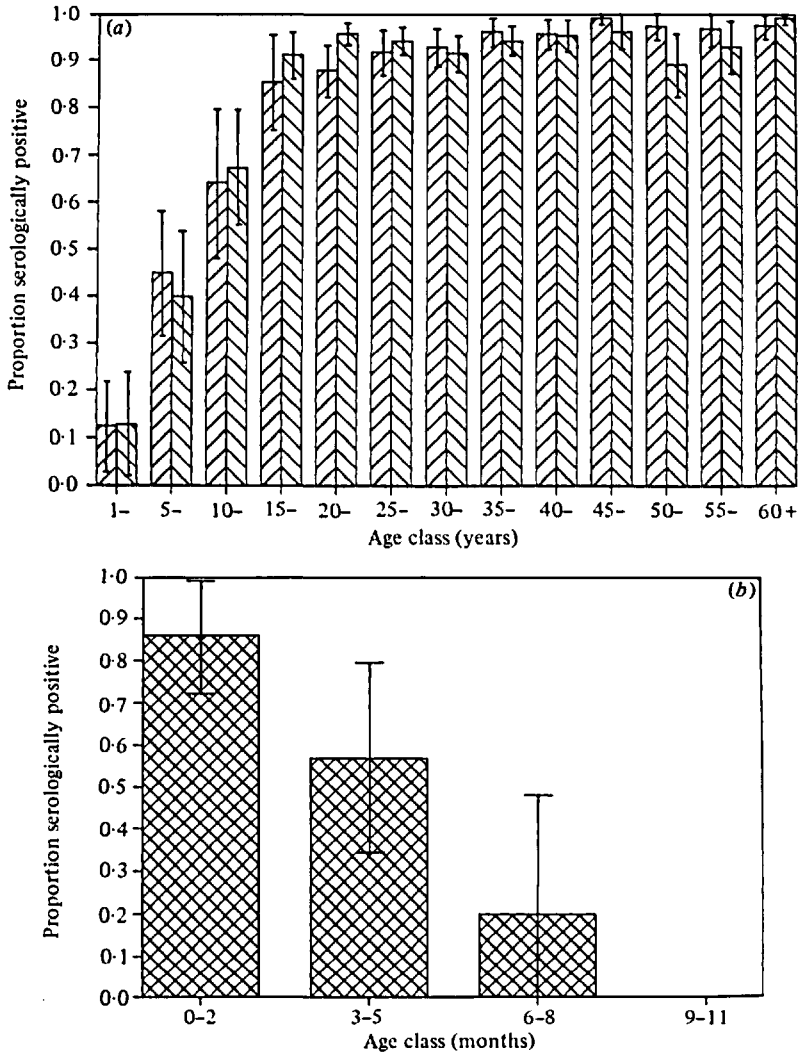

Fig. 1. Graph (*a*). Serological profile for males (▨) and females (▧) stratified according to age. The vertical lines at the top of the bars denote 95% confidence limits (based on the positive binomial distribution). (Sample sizes, for males and females respectively, are as follows: 1–4, 48, 39; 5–9, 60, 50; 10–14, 39, 61; 15–19, 48, 137; 20–24, 141, 310; 25–29, 146, 259; 30–34, 169, 235; 35–39, 163, 207; 40–44, 138, 151; 45–49, 126, 103; 50–54, 110, 100; 55–59, 93, 84; 60+, 124, 127).

Graph (*b*). The decay in maternally derived antibody (+95% confidence limits) over the period from birth to 11 months of age. (Sample sizes, 0–2, 28; 3–5, 21; 6–8, 10; 9–11, 7.)

RESULTS

Sensitivity and reproducibility of the RH test

The local standard serum when diluted 1 in 64 in antibody-negative serum to give a preparation containing 3·3 i.u./ml was the highest dilution that consistently gave a visible zone of lysis. This degree of sensitivity is in accordance with previous reports (Neumann & Weber, 1983; Morgan-Capner, 1984). Inter-test variation in results is shown in Table 1. The variance in antibody concentration was found to

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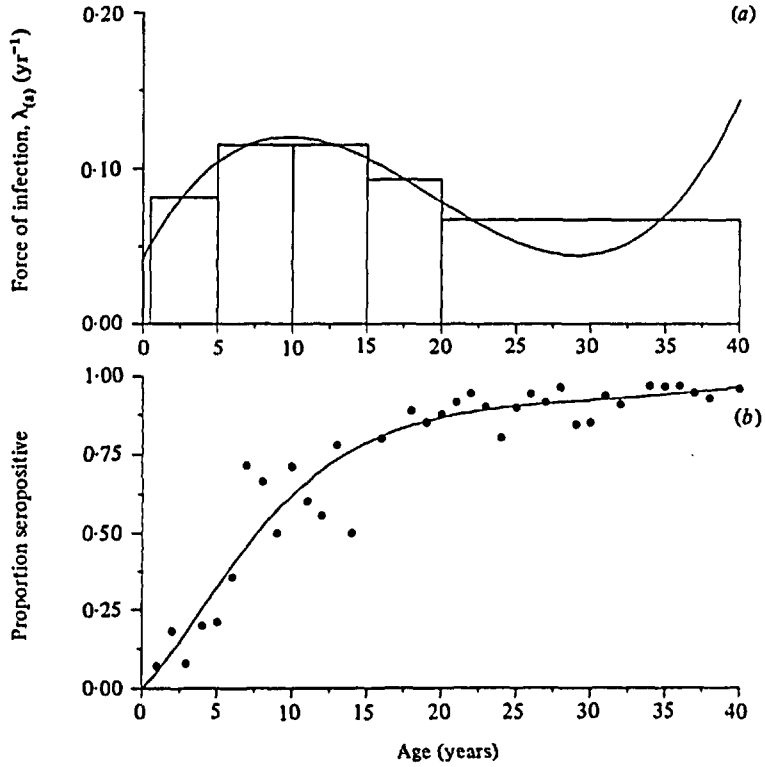

Fig. 2. Estimates of the age-dependent forces of infection derived from the serological data for males in SE England (1980–4). Graph (*a*) records the (maximum likelihood method) estimated values of the force of infection, $\lambda(a)$ (yr^{-1}) based on the polynomial catalytic model of Grenfell & Anderson (1985). The polynomial fit derived from the data is shown as a curved line while the histogram bars denote the average values (derived from the polynomial) for various age classes. Graph (*b*) compares the predicted change in the proportion serologically positive with age (——) based on the $\lambda(a)$ estimates defined in graph (*a*), with observed data (●).

be constant and independent of the mean antibody level. Consequently, th coefficient of variation (CV%) was inversely related to the mean antibod concentration. The mean CV% (weighted by sample size) is 3·0, which is simila to that found by Neumann and Weber (1983) in their evaluation of the RH test

The retesting of 20% of the RH negative sera by HI and ELISA gave n discrepant results, reinforcing the general observation that false negatives ar rarely encountered in RH screening (Morgan-Capner, 1984). However, from th total 3378 sera tested, two were found which inhibited haemolysis by sera teste in adjacent wells; in both these sera rubella-specific IgG was detected by ELISA

Prevalence of rubella antibody

The proportions of males and females seropositive for rubella in each five-yea age class are shown in Fig. 1 (*a*). The slower rate of acquisition of antibody by male between the ages of 10 and 29 years is indicated by the lower proportions o seropositive males than females. For the age class 20–24 years the difference significant at the 5% level (assuming binomial distribution of seropositivity

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Table 2. *Estimates of various epidemiological parameters of rubella infection derived from a serological survey of SE England*

Data	Average age at infection* A (years)	Basic reproductive† rate of infection, R_0	Inter-epidemic‡ period, T (years)
Males	10·83	6·78	5·10

* Estimated by a maximum likelihood method (see Grenfell & Anderson, 1985).

† R_0, $L/(A-D)$ where L, life expectancy; A, average age at infection; and D, average duration of maternal antibody protection (= 0·5 yr) (see Anderson & May, 1983*a*).

‡ $T = 2\pi(AK)^{\frac{1}{2}}$ where K = sum of latent plus infectious periods (= 22 days) (see text).

Seropositivity in females between 10 and 29 years old reflects antibody acquired by both natural infection and immunization; the contribution of vaccine-induced antibody raises the proportion seropositive in the 20–24 years age class to 95%, a level not attained in males until the 35–39 years age class.

Fig. 1(*b*) shows the decline of maternally derived antibody. The average persistence of detectable maternal antibody levels is between 3 and 6 months; antibody was not detectable in any of the seven sera from infants aged 9–11 months.

Age-dependent changes in the force of infection

Changes in the true force of infection (λ) with respect to age can be estimated from the serological profile only within the male segment of the sample population since the relative contributions of vaccination and natural infection to female immunity cannot be determined. Changes in λ with respect to age, estimated from the serological data by the maximum-likelihood method described by Grenfell & Anderson (1985), are recorded in Fig. 2. Mean values of the force of infection over selected age intervals (0·5–5·0, 5–10, 10–15, 15–20, 20–40 years) and the best fit polynomial catalytic model (to the observed serological data) are displayed in Fig. 2(*a*). Using the data from male subjects, and assuming the duration of maternally-derived protection to be 6 months (Fig. 1(*b*)), the mean age at infection, A, is estimated to be 10·8 years (Table 2). This estimate is somewhat higher than that quoted previously (see Anderson & May, 1985) from smaller studies and indicates that immunization of 10- to 15-year-old girls in the period 1970–1984 may have caused a slight reduction in the net force of infection.

Rubella antibody concentrations

The frequency distribution of antibody concentrations (i.u./ml) for seropositive individuals of all ages was found to exhibit a marked positive skew. A logarithm ($\log_e$) transformation of the raw data was therefore employed in the parametric statistical tests used to examine changes in mean concentrations with age and sex.

Mean antibody levels show a significant decline with age (regressions of mean concentration (both males and females) against age gave negative slopes ($P < 0{\cdot}005$)) as recorded in Fig. 3. Similar trends have been noted in age-stratified serological surveys for measles (Black, 1959) and mumps (Wagenvoort *et al.* 1980) antibodies. Over the age range, 13–27 years, influenced by the UK rubella vaccination policy started in 1970, there is a statistically significant difference (*t*-test

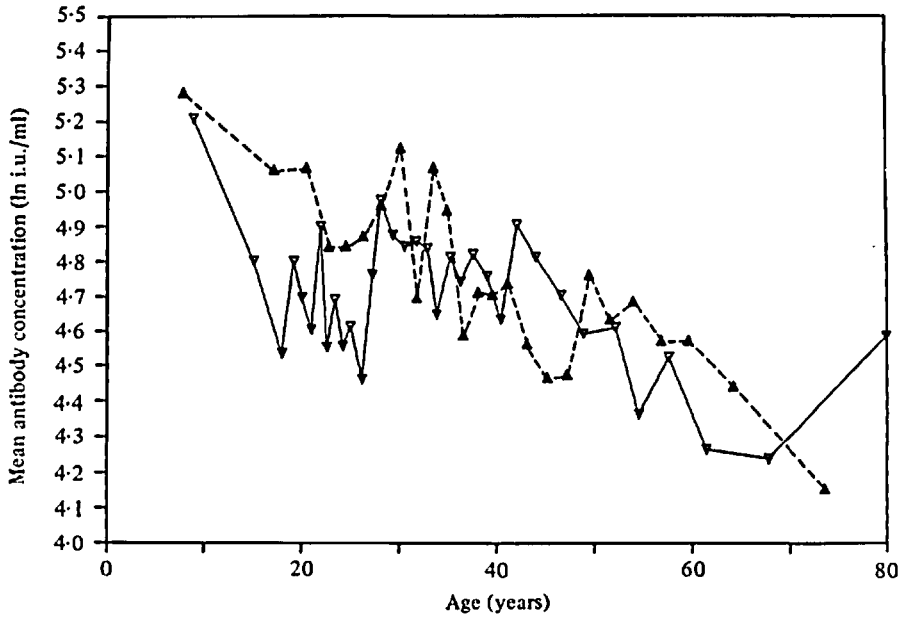

Fig. 3. The decay in mean antibody concentration with the age and sex of the individual from whom the serum sample was collected ▲---▲, males; ▽—▽, females). (Each point denotes an average value for 50 samples excepting females of age 80 ($n = 29$) and males of age 74 ($n = 46$).)

on $\log_e$-transformed data $P < 0{\cdot}005$) in the mean antibody levels in males an females. The latter have a lower average antibody level (that could not b attributed to haemodilution in the samples obtained from pregnant women), whic suggests that vaccination induces lower levels of antibody production than thos stimulated by natural infection. This hypothesis is supported by a recent comparisoı of antenatal patients in 1975–6 with those in 1978–9 (CDR, 1984) which shows a overall decrease in the number of females with high antibody levels over the tim interval between the two sample points (see also Enders, 1985).

The variability in antibody concentration within a given age group shows a overall tendency to increase with age (Fig. 4). This increase suggests that th probability of falsely identifying an individual who has experienced infection a seronegative (i.e. < 3·3 i.u./ml) increases with age (Fig. 5). As such, the estimate force of infection in the older adult age classes is likely to be an underestimate.

DISCUSSION

In the absence of mass immunization, age-stratified serological profiles provid important information on the force or rate of infectious disease transmission withi large communities of people. Differences in seropositivity between two age classe provide quantitative information on the per capita rate at which susceptible acquire infection over a defined interval of time. If the proportion seropositive rise rapidly with age, the force of transmission is high and the converse also applies Within a population in which the infection is endemic, and at a quasi-steady stat (which may be oscillatory in nature), age-related changes reflect time-dependen

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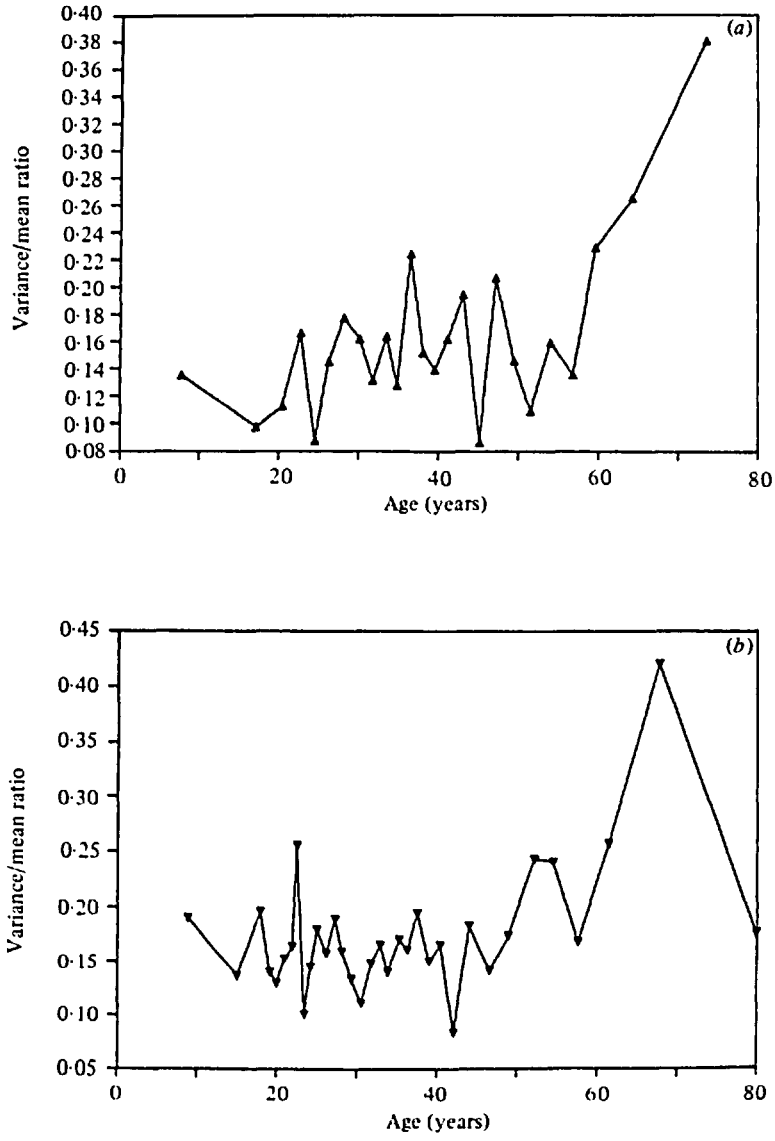

Fig. 4. Change in the variance of antibody concentration per samples of sera collected from patients in different age and sex classes. The change is recorded by the variance to mean antibody concentration ratio. Note how the ratio increases in the older adult age classes. Graphs (*a*) and (*b*) record changes in the male and female segments of the population sample respectively. (Sample sizes as for Fig. 4.)

rates of transmission (Muench, 1959; Anderson & May, 1982*a*, 1983*a*; Grenfell & Anderson, 1985). In other words, horizontal changes reflect longitudinal trends.

The present study was undertaken to provide a reliable data base for the study of rubella transmission in the UK prior to immunization (by surveying seropositivity levels in children less than 10 years old, and male subjects) and to examine the impact of the current vaccination policy. Previous studies have sought to obtain this information, either from case notification records or from small scale serological surveys of restricted age groups (e.g. Field, 1967). Serological data are likely to

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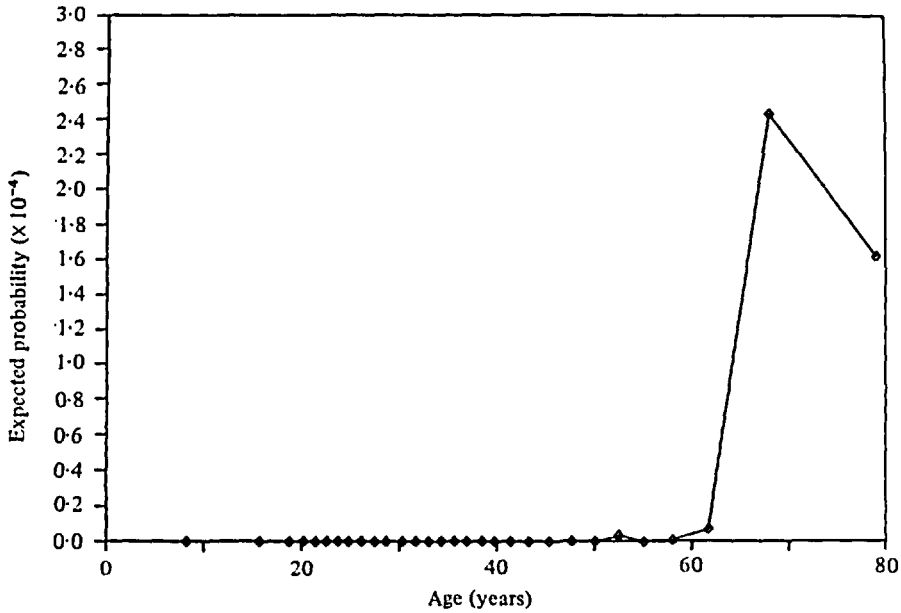

Fig. 5. Changes in the probability of falsely identifying a seropositive individual as seronegative (given a test sensitivity of $\geqslant 3{\cdot}3$ i.u./ml of antibody) with age. The calculations are based on the assumption that antibody concentrations within an age class are normally distributed in seropositive individuals with means as defined in Fig. 4. Sample sizes are 100 sera (males and females) per average excepting for age 78 where sample size was 50.

provide a truer reflection of rubella epidemiology for two reasons: first the clinical diagnosis of rubella is notoriously difficult (see for example Anderson, Kidd & Morgan-Capner, 1985; Cohen & Shirley, 1985) and second there is considerable age-dependent bias in reporting of cases. However, serological data must also be interpreted with care.

The serological profiles recorded in Fig. 1 (*a*) show that levels of immunity in the older adults (50+-year-olds) never attain 100%. In part this is a consequence of the low force of infection in the adult classes (see Fig. 2). If an individual escapes infection during the child and teenage years, the probability of acquiring rubella infection in the adult years appears to be low (probably as a consequence of behavioural factors). However, this observation is based on the estimates of the forces of infection which are derived from the serology itself. If the serological data is not a true picture of past experience of infection in those where the interval between infection and serological testing is long, then the estimates of the force of infection are inaccurate. Seronegativity in adults could be due to other factors such as genetic determination of antibody production following infection (and perhaps susceptibility to infection) or the inability to detect low antibody levels in individuals where the interval between infection and test is long (many decades). Some evidence in support of the latter conjecture is provided in Fig. 3, which records a decay in the mean antibody concentration of seropositives with an increase in age. The rate of decay itself may be determined by genetic factors since the variance in antibody concentration among seropositive individuals also rises with age (Fig. 4). This issue requires further research. Preliminary studies could

profitably focus on assessing the degree of association between HLA type and antibody titre in adult age classes. Evidence for an association between rubella antibody titres and HLA type in vaccinated individuals provides some support for this line of enquiry (Spencer *et al.* 1977; Kato *et al.* 1982). However, it is important to note that although serum antibodies are highly correlated with immunity they may not necessarily be the major mediators of acquired immunity to viral infection (Roitt, 1984). Cell-mediated factors are thought also to be important.There are recorded instances of seronegative individuals resisting infection or reinfection with mumps virus, for example in the Netherlands (Wagenvoort *et al.* 1980). This may be genetically linked and implies either that low antibody titres (undetectable by current methodology) provide adequate protection against infection, or more likely that cellular immunity is of greater importance in suppressing infections.

The present study suggests, in accord with others (O'Shea *et al.* 1982, 1984, 1985), that antibody levels in vaccinated individuals are on average lower than those in naturally infected individuals; the mean concentrations in teenage and young adult females are lower than in males of the same age (Fig. 3). The degree of immunity to rubella infection provided by low concentrations of antibody is unclear. In the present study a low threshold (3·3 i.u./ml) was regarded as indicative of immunity since challenge studies have revealed that low levels of naturally acquired antibody confer immunity to reinfection (Mortimer *et al.* 1981; O'Shea *et al.* 1982, 1983, 1984, 1985). However, it must be remembered that RH does not distinguish between antibody produced in response to natural infection and that produced in response to vaccination, and similar challenge studies suggest low levels of vaccine-induced antibody do not correlate well with protection from reinfection (Balfour *et al.* 1981; Harcourt *et al.* 1980). Thus the value of long-past vaccination in preventing rubella infection must be in doubt. If vaccine-induced immunity is not life-long it will be of advantage to continue the present UK policy since to protect the unborn child the vaccine needs only to be effective for a maximum of a few decades.

The selective rubella immunization policy practised at present in the UK, vaccinating only girls between the ages of 10 and 15 years, and adult women found to be seronegative during pregnancy in the postpartum period, was designed to have little impact on the net force of virus transmission within the younger segments of the population. A small but discernable effect was, however, detected in the present study where the mean age at infection calculated was slightly higher than has previously been recorded (see Anderson & May, 1985). This slight reduction in the force of infection consequent upon immunization means that the use of serological data from male subjects to examine the dynamics of rubella transmission prior to immunization may be slightly inaccurate, underestimating the true natural force of infection.

The general pattern of change in the rate of antibody acquisition with age (low in young children, high in older children and early teenagers, falling to low again in adults), recorded in this survey (Fig. 2(*a*)) is similar to that observed for other predominantly childhood infections such as measles, mumps and chickenpox (see Anderson & May, 1985). The factors inducing age-related changes in transmission are not fully understood although heterogeneity in the degrees of contact and mixing between different age classes are likely to be important (Schenzle, 1984;

Anderson & May, 1983*a*, 1984, 1985). The high forces of infection in the 5- to 15-year-olds may be assumed to be due to high contact rates among children attending school. An observed value of the force of infection within a given age class is a composite measure of the rate at which susceptibles in that age class acquire infection from infectious individuals in all age classes. Patterns of contact and mixing between age classes are likely to vary in different societies and this in part explains the observed differences in the rate at which antibody is acquired in different age classes in the developed and developing world. For example, the proportion seropositive rises more rapidly with age in large urban communities in areas such as Russia (Kantarovich *et al.* 1983) and The Gambia (Clarke *et al.* 1980) than is seen in the UK and USA (Anderson & May, 1983*a*). In addition to these behavioural factors it should be noted however that demographic parameters such as the net birth rate, which determines the input of new susceptibles into a community, are also important (Anderson & May, 1985).

Our estimation of age-dependent changes in the force of infection is based on horizontal serological data. As such it provides no information on short term longitudinal changes such as those induced by seasonality in virus transmission. Seasonal changes in the incidence of childhood viral and bacterial infections may arise as a direct consequence of the influence of climatic factors on virus transmission or, more significantly, as a consequence of changes in human behaviour related to season (Anderson, Grenfell & May, 1984; Schenzle, 1984; Fine & Clarkson, 1982; Yorke & London, 1973). It is possible that the latter factor, particularly with respect to school children, alters the pattern of infection within and between age classes. Investigation of this problem would require detailed age-stratified serological data based on sequential serum sampling at intervals throughout a year. Such samples are not available at present but this problem deserves further attention in future research.

The differences between the male and female segments of the population observed in the present study illustrate the impact of immunization of females between the ages of 10 and 15 years, and are in agreement with a recent study conducted in the Manchester area in England (Miller *et al.* 1985), and the longitudinal studies by Clarke *et al.* (1983). In the present study the degree of herd immunity in adult women was not detectably increased by the 'second arm' of the UK vaccination policy, the postpartum immunization of women found to be seronegative at antenatal booking. Recent research has revealed that predictions of the levels of vaccination coverage required to eradicate common infections which are based on mathematical models assuming the force of infection to be constant, tend to produce higher estimates than models which take account of the observed patterns of change in λ with age (Schenzle, 1984; Anderson & May, 1984, 1985). In other words, predictions based on homogeneous mixing models give too pessimistic a picture of the levels of vaccination coverage required for elimination of a virus from large populations. The results obtained in the present study do not entirely support this view since the observed decline in λ between the teenage and adult age groups is relatively small. Certainly the decline in λ in the adult (20- to 40-year-olds) age classes is less marked than has been reported for measles and pertussis.

However, the observed decay in the force of infection from a value of 0·115 per year in the 5- to 15-year-olds to 0·067 per year in the 20+ age group, a reduction

of almost 50%, is still likely to have a substantial impact on predictions of the changes in the incidence of rubella infection compared with those obtained from models assuming transmission to be constant and independent of age. The impact of these data upon design of vaccination programmes for the control of rubella and prevention of congenital rubella infection are the subject of an accompanying paper (Anderson & Grenfell, 1986).

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