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Seroepidemiological study of the transmission of the mumps virus in St Lucia, West Indies

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SUMMARY

A seroepidemiological study of the prevalence of mumps virus specific antibodies reveals a pattern of endemic peristence on the island of St Lucia in the West Indies. In the unvaccinated population the proportion seropositive rose rapidly in the child age classes to attain a stable plateau close to unity in value in the teenage and adult age groups. The average age at infection was estimated to be between 3 and 4 years of age and the average duration of detectable levels of maternally derived antibodies was approximately 3 months. Analyses based on mathematical models of the transmission dynamics of the virus suggest that in excess of 75% of each cohort of 1- to 2-year-old children must be effectively immunized to eliminate mumps virus transmission. A mumps radial haemolysis test, developed for quantitative measurements of antibody, is discussed.

INTRODUCTION

Age-stratified serological surveys for the presence or absence of antibodies specific to defined viral antigens are an important component of the epidemiological data required for the effective design of mass immunization programmes for the control of common childhood viral infections such as measles, mumps and rubella (Anderson & May, 1983, 1985*a*; Nokes, Anderson & Anderson, 1986; Anderson & Grenfell, 1986; McLean & Anderson, 1988*a*, *b*). In this paper we report the results of a recent study of the transmission dynamics of the mumps virus in the small island community of St Lucia in the Caribbean. The research forms part of a seroepidemiological study of three common childhood viral infections (measles, mumps and rubella) on the island. The overall objective was to provide empirical data necessary for the development of a mass immunization programme, based on the use of MMR (measles, mumps and rubella) vaccine, which has recently been introduced by the Government of St Lucia.

Prior to the introduction of mass immunization, the proportion of individuals seropositive for a specific viral antigen and the distribution of this quantity with respect to age defines the level of 'herd immunity' within the population to the infection (Black, 1959; Fox *et al.* 1971). A measure of the rapidity with which the proportion seropositive rises as host age increases will provide an estimate of the average age at infection, A, and the basic reproductive rate of the infection, R_0 (defined as the average number of secondary cases generated by one primary case in a susceptible population, Anderson & May, 1983). In turn, these statistics enable rough estimates to be obtained of the level of vaccination coverage required in a given population to interrupt viral transmission sufficient to eradicate the infection (Dietz, 1976; Anderson & May, 1985*a*). To a good approximation, the critical level of vaccination coverage, p_c, is given by the simple relationship $p_c > 1\text{-}\bar{x}$, where $\bar{x}$ is the proportion of the total population susceptible to infection prior to the introduction of control measures ($R_0 \sim 1/\bar{x}$; Anderson & May, 1983).

The importance of seroprevalence data (finely stratified by age) to the design of community-based control programmes has resulted in a growing body of seroepidemiological data from both developed and developing countries (Kenny *et al.* 1976; Mortimer, 1978; Wagenvoort *et al.* 1980; McLean & Anderson, 1988*a*; Nokes, Anderson & Anderson, 1986; Anderson, Crombie & Grenfell, 1987). In a few instances, surveys have been both horizontal and longitudinal in design (e.g. Nokes, Jennings & Anderson, 1987).

Viral transmission in small isolated communities has been the focus of some attention in the past as a consequence of the theoretical prediction that there is a critical human community size for the endemic persistence of viruses that induce lifelong immunity in those who recover from infection (Bartlett, 1957; 1960; Black, 1966; Yorke *et al.* 1979; Anderson & May, 1985*a*). The study of measles persistence in small islands by Black (1966) suggested a critical population size of approximately 500000 people. The earlier studies of Bartlett (1957, 1960) of measles persistence (measured by reference to the frequency of 'fade out', defined as weeks or months in which no cases were reported) in cities in the United States suggested a critical community size of around 200000–300000 people. Since these early studies patterns of human movement between cities and between islands and mainlands have changed dramatically due to factors such as more frequent air travel and increased rates of immigration and emigration. In addition, there have been changes in demography such as net birth rates. Both factors are important determinants of the transmission of viral infections in small isolated communities.

St Lucia is a small island (238 sq. miles) with a population size in 1984 of 134066. The annual population growth rate at present is close to 3% per annum (World Bank and United Nations statistics) when based on crude birth and death rates, but is closer to 1·6% per annum once emigration is taken into account. Roughly 38% of the population live in or around the largest town, Castries. The dependency ratio of the population, defined as the number of children in the age range 0–14 years plus the number of elderly people over 65 years, all divided by the number of adults in the age range 15–65 years, is close to unity in value. Before the introduction of the MMR immunization programme, limited immunization against measles and rubella had taken place but none against mumps prior to the seroepidemiological survey reported in this paper. Previous studies of viral and

bacterial infections in St Lucia have included those by Cooper & Fitch (1983) and Evans *et al.* (1979).

MATERIALS AND METHODS

Serum samples

A total of 1608 sera from individuals in the age range of 0 to 81 years were collected, by the staff of the Parasite Epidemiology Project (St Lucia), over a 7-month period between 1985 and 1986, within 5 kilometres of Castries. The large sample (1·35% of the resident (1984) population) was designed to mimic the age distribution of the population (Table 1) and represent all socioeconomic classes. Cord bloods were obtained from the major delivery facilities for the city. Children and students were sampled on an area-wide basis in schools, colleges, clinics and nurseries. Adults were also sampled on an area-wide basis in places of employment. An additional 202 sera, taken in 1985 by the same team, from a variety of areas in St Lucia, were obtained from the Immunology Department, The London Hospital. The sera were stored at −20 °C and heat inactivated at 56 °C for 30 min prior to antibody screening.

This study was conducted with the agreement of the Ministry of Health. Permission was received from all subjects recruited to the study, or in the case of children, their guardians.

The mumps radial haemolysis test

The method used for the detection of mumps specific IgG antibody was developed from that described by Mortimer (1978). This relies, as with other radial haemolysis (RH) methods, on complement mediated lysis by anti-virus antibody of antigen-sensitized erythrocytes. Details on the quantification and reproducibility of the assay closely follow from the technique for detecting rubella-specific antibody developed by Nokes, Anderson & Anderson (1986).

Basic procedure for the RH test

(*a*) *Chick red blood cells* (*CRBC*). These were obtained from day-old male chicks bled into alsevers solution. For use, cells were washed three times in complement fixation buffer (CFB) (Oxoid, BR16) and made up to 10% packed cell volume in the buffer.

(*b*) *Mumps virus*. Enders strain (provided by Dr R. Jennings, Sheffield University Medical School), grown in the allantoic cavity of chicken eggs, was used as antigen. Purification consisted of a single centrifugation to remove cell debris and storage was at −80 °C. The titre of the haemagglutinating (HA) antigen was determined by titration using 0·5% CRBC. The optimal titre of HA antigen for use in the test was determined by preparing a series of RH plates differing only in antigen concentration (diluted in CFB) and selecting the one which provided both well-defined zones of haemolysis and a high degree of sensitivity to specific antibody. A preparation with an HA antigen titre of 2048 was elected for use in the test.

(*c*) *Preparation and running of gels*. 0·05 ml of diluted antigen was incubated with 1 ml 10% CRBC for 10 min with regular mixing. The sensitized cells were

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Table 1. *Age specific sample sizes for males and females (No record of sex for some samples.)*

Age (years)	Total (% of 1984 pop.)	Male	Female
0–4	660 (3·2)	276	309
5–9	257 (1·3)	136	120
10–14	181 (0·95)	91	89
15–19	190 (1·14)	92	98
20–24	112 (0·92)	42	70
25–29	79 (0·95)	29	50
30–34	74 (1·21)	35	38
35–39	53 (1·1)	17	36
40–44	41 (0·96)	17	24
45–49	45 (1·11)	28	17
50–54	34 (0·88)	16	18
55–59	21 (0·60)	11	10
60–64	24 (0·76)	8	16
65–69	8 (0·3)	3	5
70–74	5 (0·25)	1	4
75+	5 (0·17)	2	3
Total	1789	804	907

then washed with CFB and resuspended in 0·5 ml buffer. 15 ml of 1% agarose (ICN Immunobiologicals), sensitized cells and guinea-pig complement (Richardson's Preserved, L.I.P.), were all equilibrated at a temperature of 41 °C. It was found that the stability of the CRBC (and hence the quality of plates) was reduced by temperature stress and by direct contact with a high concentration of complement. Therefore throughout gel preparation, reagents were equilibrated (usually to room temperature, RT) and the complement (0·5 ml) was initially added to the agarose before addition to the cells and immediate pouring into RH plates (10 × 10 cm plates, Sterilin 109). Control gels were made up by the same procedure except that mumps HA antigen was replaced by CFB. After a period of at least 30 min, but invariably the same day, 49 wells, each 3 mm in diameter were cut into each gel. 7 μl of each test serum were added to test and control gels. Plates were then incubated at 37 °C for 18 h. Resultant zones of haemolysis were measured to the nearest 0·1 mm using a graticuled eyepiece magnifier.

Quantification of results

An internal standard of pooled sera, having a high antibody concentration, was used to create a series of double dilutions in negative serum. The highest dilution consistently detectable in the assay (found to be a 1/128 dilution of the neat standard) was deemed to be the cut-off point between positive and negative and given the arbitrary value of 5 units antibody per ml. No international or national anti-mumps serum was available.

Standards from undiluted to 1/128 and a negative serum were added, at random locations, to wells in each plate. Any test sera with an antibody concentration greater than or equal to 5 units/ml, calculated by linear regression, were regarded as positive. The typical bell-shaped frequency distribution of logged antibody concentration which was observed for the sample set suggested that a

good sensitivity had been attained by the mumps RH test in which few samples would be considered falsely negative using 5 units/ml as the cut-off point for seropositivity. Although dilutions of the standard serum higher than 1/128 (corresponding to 5 units/ml) were not always detectable by the test, zones of haemolysis were produced by a small number of samples, which gave antibody levels of between 2·5 and 5 units/ml. Repeated testing by RH and re-testing following adsorption with CRBC to remove anti-CRBC antibodies (see Nokes, Anderson & Anderson 1986 for details) confirmed these results. A disproportionate number of these samples (43%) were from the 0–1-year-old age class and in accordance with the findings of Wagenvoort *et al.* (1980), that any detectable level of mumps specific antibody confers immunity, have been included in the analysis of maternally-derived antibodies. The remainder of these samples were evenly distributed throughout the older age-classes and as such would not significantly alter analysis of the data.

Reproducibility and specificity

In addition to the standards, five control sera were used in each test series to record test-to-test variation. The test for homogeneity of variance (Sokal & Rohlf, 1981) showed no significant inhomogeneity at the 5% level ($F_{\max} = 2{\cdot}44$, D.F. = 7, $k = 5$).

Specificity of a mumps RH assay with regard to cross-reactivity with other paramyxoviruses has been examined by Grillner & Blomberg (1976). On testing paired sera (with complement fixation titre rises to parainfluenza types 1, 2 and 3), no mumps antibody titre rises were detected in the haemolysis-in-gel (HIG) test.

RESULTS

Herd immunity and mean antibody concentrations in sample population

Figure 1 shows the proportions of males and females seropositive for mumps antibodies in each age class. There are no significant differences between the sexes at the 5% level (assuming a binomial distribution for seropositivity). All seropositivity is presumed to be due to natural infection by mumps virus as no immunization had taken place in St Lucia prior to the serum samples being collected. Acquisition of immunity is rapid in the young age classes (1–10 yrs) such that 70% are seropositive at 4 years of age. From the 8-year age class, right through adulthood, the proportion seropositive is generally between 90 and 100%.

The decay through time (=age) of the proportion of infants with detectable levels of maternally derived antibody is recorded in Fig. 2. The rate of decay as infants age is somewhat dependent on the concentration of antibody that is chosen to delineate seropositive from seronegative individuals. The results from two different assumptions concerning this critical 'cut-off' point (2·5 and 5·0 units/ml, as indicated in the method) are recorded. The mean duration of detectable levels of maternally derived antibodies from birth is approximately 1–3 months, and less than that recorded previously for mumps (Wagenvoort *et al.* 1980), rubella (Nokes, Anderson & Anderson 1986) and measles (Anderson & May, 1983). The

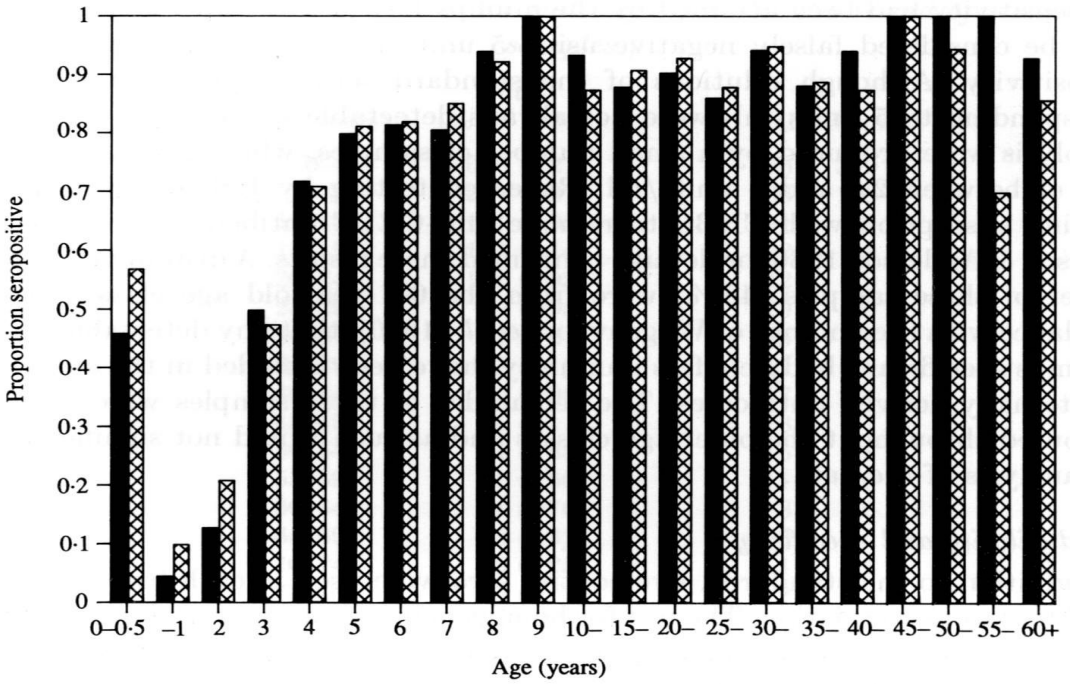

Fig. 1. Age stratified serological profile of mumps specific immunity in males (■) and females (xx). (Sample sizes – age, male, female: 0–0·5, 63, 86; −1, 43, 50; 2, 70, 62; 3, 44, 40; 4, 57, 59; 5, 46, 33; 6, 27, 28; 7, 26, 27; 8, 17, 13; 9, 19, 19; 60+, 14, 28; see Table 1.)

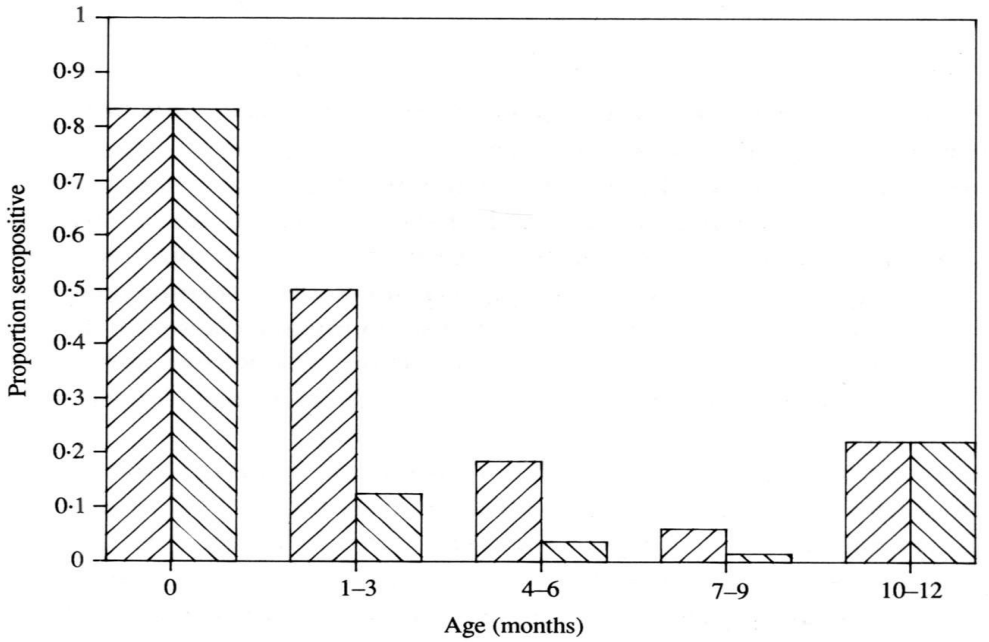

Fig. 2. The decay of maternally derived antibody for all infants from birth to 1 year of age. The graph represents results obtained using cut-off points in the radial haemolysis test of 2·5 units/ml (▨) and 5 units/ml (▨). (Sample sizes, 0, 161; 1–3, 8; 4–6, 54; 7–9, 66; 10–12, 27.)

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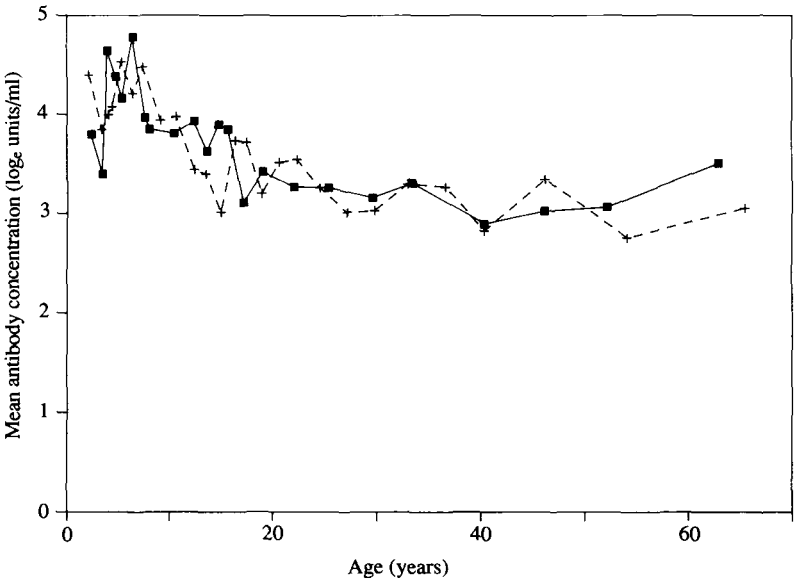

Fig. 3. Age specific mean antibody levels of seropositive males (■) and females (+). Each point represents a sample size of 25 except males at mean age 63 ($n = 20$).

average concentration of antibody in those infants recorded seropositive also decayed rapidly over the first 10 months of life, although the sample sizes were small. The mean concentration in the 10–12-month age class showed a slight increase over the previous age group presumably as a result of natural infection in some individuals within the sample. In the 7–9-month age class a single serum sample showed a high antibody level (again, presumably due to acquired antibody). Sample sizes, for those seropositive between 1 and 11 months of age, are small and as such the results are tentative.

Over the full age range of the sample the mean antibody concentration in serum samples for each age class decline with age for both males and females (Fig. 3). Regression analysis on the combined male and female samples showed a significant decay in antibody concentration with age ($F = 123{\cdot}1$, $P < 0{\cdot}001$). However, no significant differences between males and females within age classes were observed ($P > 0{\cdot}05$). The average antibody level declines fairly rapidly after infection in the child age classes and then remains relatively constant in value throughout adult life. There was no significant decay in average concentrations between 20 and 80 years of age ($F = 2{\cdot}86$, $P > 0{\cdot}05$). Previous studies have recorded a decline with age in average antibody concentrations specific to rubella (Nokes, Anderson & Anderson 1986), measles (Black, 1959) and mumps (Wagenvoort *et al.* 1980) antigens. In the study of Nokes, Anderson & Anderson (1986) of rubella the decay in average antibody concentration continued through the adult age class. The pattern of decay recorded by Wagenvoort *et al.* (1980) for mumps in the Netherlands was broadly similar to that depicted in Fig. 3.

Age-dependent changes in the rate of acquisition of infection

The age-stratified profile may be used to calculate age-dependent rates of acquisition of mumps infection. The per capita rates or forces of infection, denoted by the symbol λ, in a series of age classes were estimated using the maximum-likelihood method described by Grenfell & Anderson (1985). The following age ranges were employed to group the data into a series of age classes; 0·5–2·4 yrs, 2·5–4·9 yrs, 5·0–7·4 yrs, 7·5–9·9 yrs, 10+ yrs. Figure 4 records the estimates of the force of infection $\lambda(\text{yr}^{-1})$ as a function of age.

The pattern of change with age from a low rate in the youngest age class (0·5–2·4 yrs), to a peak in children (5–7·4 yrs), to low again in teenagers and adults (10+ yrs) is similar to those recorded in a variety of published studies of the transmission of rubella, mumps and measles in developed and developing countries (Grenfell & Anderson, 1985; Anderson & May, 1985*b*; Nokes, Anderson & Anderson, 1986; Anderson, Crombie & Grenfell, 1987; McLean & Anderson, 1988*a*).

The average age at infection, A, in the St Lucia population was calculated to be 3·6 years. This figure is much lower than those derived from seroepidemiological studies of the transmission dynamics of mumps in developed countries (see Table 2). Lower average ages at infection in developing countries when compared with developed countries have been observed in epidemiological studies of other viral infections such as measles (McLean & Anderson, 1988*a*) and rubella (Clarke *et al* 1980; Anderson & May, 1983). Such differences are thought to arise as a consequence of higher birth rates and greater degrees of intimate contact likely to promote transmission both within and between child age classes in developing countries by comparison with developed countries.

Immunization coverage required to interrupt transmission

Observed patterns of change in the force of infection, λ, with respect to age in an unvaccinated community can be used to derive estimates of the critical level of vaccination coverage, p_c, required to totally interrupt transmission (Anderson & May 1983, 1985*a*, *b*). The value of p_c is somewhat dependent on the estimate of force of infection in the older age classes (i.e. 10- to 70-year-olds). A discussion of this problem plus details of the method of estimation of p_c is given in Anderson & May (1985*b*). An illustration of varying the magnitude of the force of infection in the 10–70-year age class on the estimate of p_c is presented in Fig. 5. In broad terms the value of λ in the 10–70-year-olds derived from the observed serological profile in St Lucia suggests a value of p_c in the range 75–80% vaccination coverage of a cohort of children immediately after the wane of maternally derived protection.

Uncertainties surrounding estimates of the force of infection in teenage and adult age classes centre on the sensitivity of serological tests to detect specific antibodies in individuals who experienced infection many years prior to the collection of sera and subsequently the distinction between presence and absence of antibodies to viral antigens. Following infection, antibody concentration may decay at different rates in different individuals depending on genetic or other factors (Anderson & May, 1985*b*). A crude test for variability in the rate of decay in antibody concentration is provided by an inspection of the variance to mean

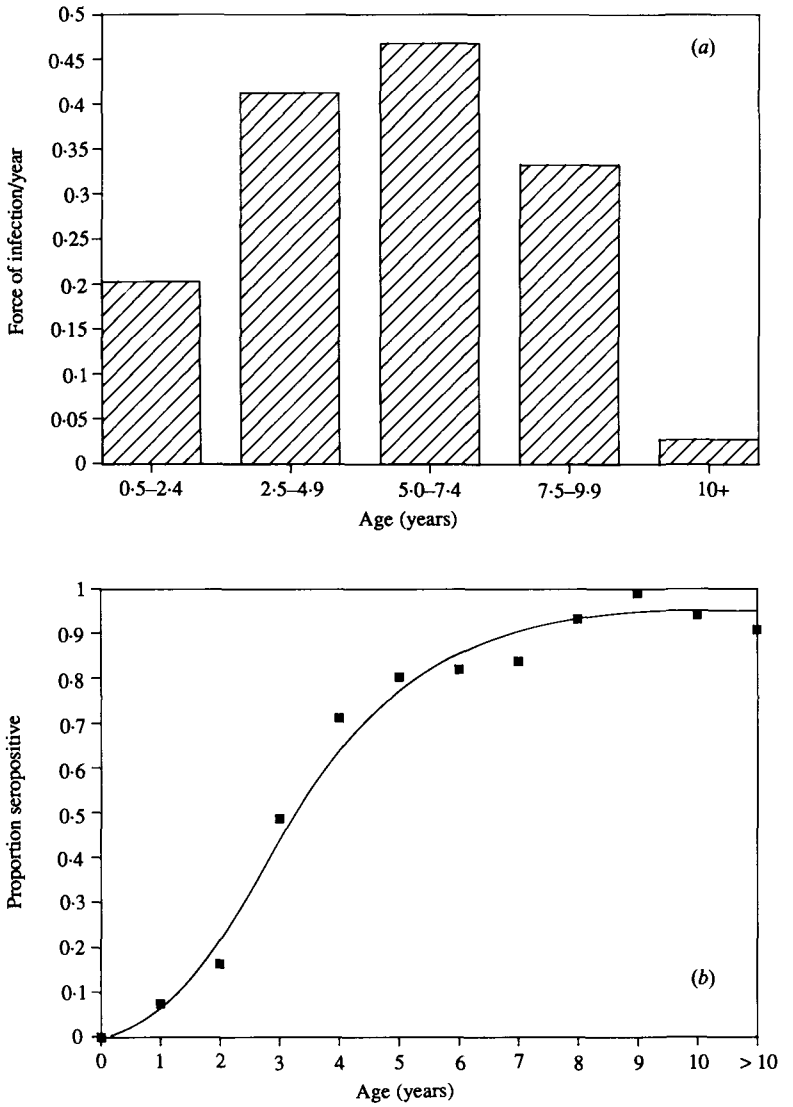

Fig. 4. Age-dependent changes in the force of infection, estimated for combined male and female data. (*a*) Force of infection, $\lambda(a)$ yr^{-1}, estimates for various age classes, calculated by the maximum-likelihood technique of Grenfell & Anderson (1985). (*b*) A comparison of the predicted changes in the proportion seropositive (—), based on the $\lambda(a)$ estimates in graph (*a*), with the observed data (■).

ratio of antibody concentrations in samples of sera drawn from people of roughly the same age. Any increase in the variance to mean ratio as individuals age might suggest variability between individuals in the rate of decay of detectable levels of antibody. Analysis of the St Lucia serum samples shows no significant trend for an increase in the degree of variability as people age.

The impact of a mass immunization programme on the level of herd immunity within a population can be examined with the use of age-stratified mathematical

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Table 2. *Average age at infection A, interepidemic period T and reproductive rate R_0 for mumps in various countries (See Anderson & May (1985), for details.)*

Country	Year	A (yr)	T (yr)	R_0	Ref.
England	1975–7	6–7	3·65	11·2	Mortimer (1978) Anderson, Crombie & Grenfell (1987)
Netherlands	1977–9	6–7	3·65	11·2	Wagenvoort *et al.* (1980) Anderson, Crombie & Grenfell (1987)
St Lucia	1986	3–7	2·73	20·6	Present study

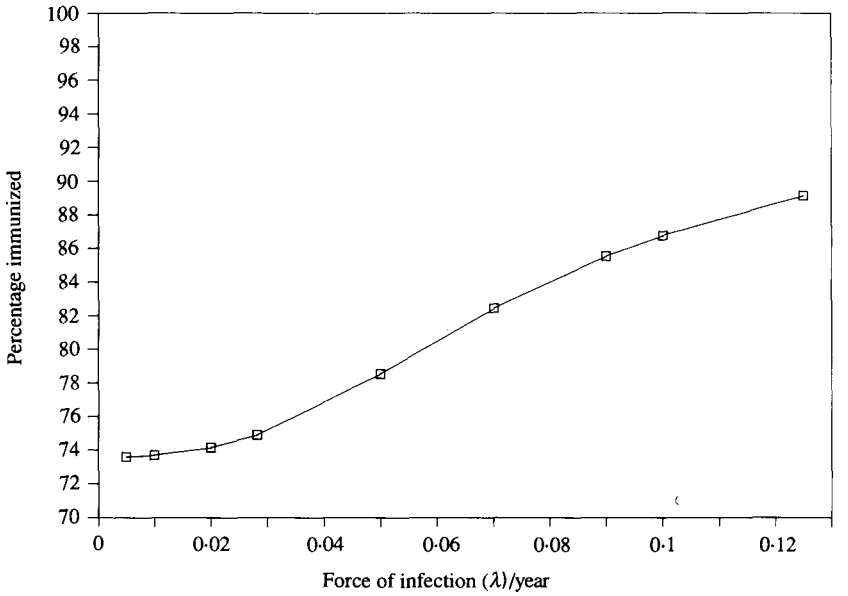

Fig. 5. The effect of small changes in the force of infection in the 10–70-year-old age class, on estimates of the critical vaccination coverage for eradication of the infection (p_c). (Anderson & May, 1985*b*).

models that mimic the transmission dynamics of the virus. In the case of mumps virus, Anderson, Crombie & Grenfell (1987) have recently published the details of a model to aid in the assessment of mass immunization. The predictions of this model, with the appropriate estimates of the age-specific forces of infection, latent plus infectious periods, community size and birth plus death rates are recorded in Fig. 6. The numerical simulation records changes in the age distribution of immunity to mumps (proportion seropositive) whether acquired by natural infection or vaccination, through time and after the introduction of a mass vaccination programme that immunizes 75% of each 1- to 2-year-old age cohort each year. Note that after the introduction of a cohort immunization programme targeted each year at a specific age class, it will take a number of decades of cohort immunization before transmission of the virus is eliminated. The slow increase in

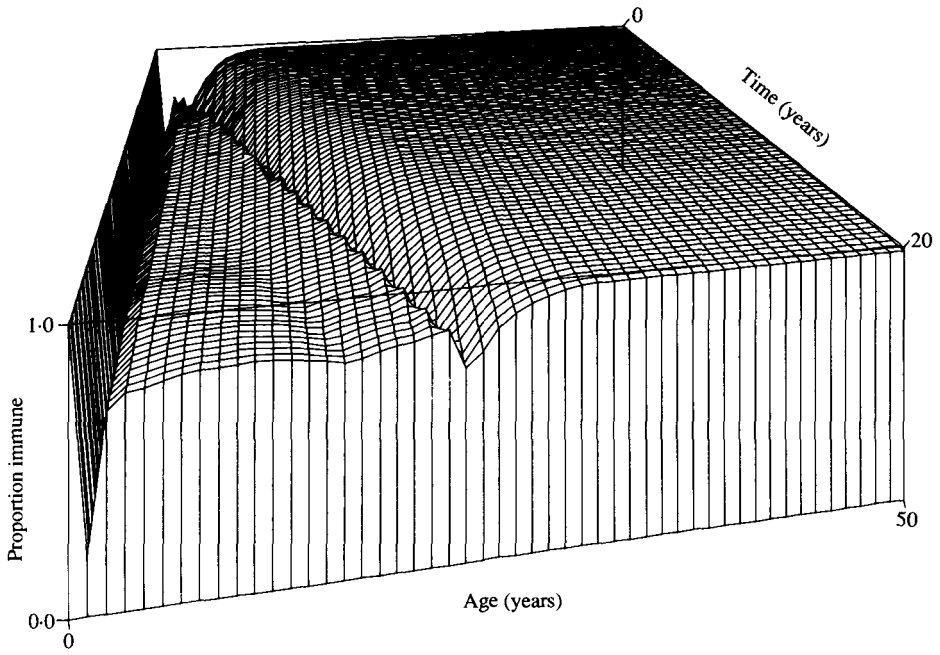

Fig. 6. The predicted changes over a time-span of 20 years in seropositivity to mumps virus, stratified according to age, when an immunization programme covering 75% of each yearly cohort of 1–2-year-old boys and girls is introduced.

the number of cohorts immunized (one per year) acts to raise the level of herd immunity in the younger age classes over that pertaining prior to the introduction of control, and decrease that in the older age classes due to the reduction in viral transmission induced by mass vaccination (see Anderson & May, 1985*a*; Nokes & Anderson, 1988). The reduction in the rate of viral transmission results in an increase in the average age at infection within the vaccinated population. This trend can have important consequences if the likelihood of serious complications resulting from infection (e.g. orchitis) increases with age (as is the case for mumps and rubella infection). In the case of mumps, however, a detailed analysis of the manner in which the incidence of case complications change with age suggests that moderate to high levels of mass vaccination will, in general, act to decrease both the incidence of infection and the incidence of disease (Anderson, Crombie & Grenfell, 1987). The important issue, however, is to ensure that a high level of vaccination of each yearly cohort (75%) is achieved in the second year of life (as soon as possible after the wane of maternally derived protection).

DISCUSSION

The radial haemolysis test proved to be a sensitive and reproducible assay for the rapid detection and quantification of mumps specific IgG antibodies in serum samples. However, the quality of haemolysis was sensitive to small variations in technique and to batches of reagents. Thus the test is most suitable, in its present

form, for research purposes, such as large-scale serosurveillance studies. A small percentage (~1%) of samples gave equivocal results due to faint or fuzzy zones which persisted on re-testing and were therefore excluded from the analysis. This problem is not normally encountered in the radial haemolysis test for rubella specific antibodies (Nokes, Anderson & Anderson, 1986).

The serological profile suggests that the mumps virus is endemic in the St Lucia population. There is no hint of epidemic years followed by the 'fadeout' of viral transmission. This observation is somewhat surprising given the small size of the population (134000) and the observations of Black (1966) that island populations of 200000 to 300000 are required for endemic persistence of measles (see also Cliff *et al.* 1981). A number of factors may contribute to the endemic persistence of mumps on St Lucia including (i) the high birth rate of the population (30 live births per annum per 1000 head of population) providing a steady recruitment of susceptible infants, (ii) behavioural attributes that promote transmission in infants and children and (iii) a high immigration rate into the population. With respect to the latter factor, statistics from the island (Government of Saint Lucia; Annual Statistical Digest, 1984) reveal high rates of emigration and immigration (particularly from tourism). In 1984 the total number of arrivals and departures was approximately 86% of the estimated size of the resident population. Twenty-three per cent of these were St Lucia nationals. These levels of population movement may promote the endemic maintenance of the virus via the influx of susceptible and infectious individuals.

The predicted level of vaccination coverage required for the elimination of viral transmission (75–80%) does not take account of high levels of population inflow and outflow. As such the predicted figure of 75–80% must be interpreted as a lower bound. Ideally, any community-based programme should aim at levels in excess of 90% (see Nokes & Anderson, 1988). We believe such a figure would take account of the problem associated with the immigration of susceptible children. An additional factor in such calculations concerns the use of the triple vaccine MMR (measles, mumps and rubella). The desired level of effective vaccination coverage of child cohorts must be deduced from serological data for all three viral infections. The virus with the greatest transmission potential (i.e. the lowest average age at infection prior to mass vaccination) will determine the target level of vaccination coverage to interrupt the transmission of all three infectious agents. The seroepidemiology of measles and rubella will be examined in a subsequent publication.

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