Infections with varying contact rates: application to varicella

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Summary.

We develop methods for the analysis of infectious disease data when age-specific contact rates vary over time. Our methods are valid when contact rates vary slowly on the time scale of the infection process, and are applicable to a variety of data types including serial seroprevalence surveys and case reports. The methods exploit approximate endemic equilibria, and require numerical solution of an associated integral equation in age and time. We also estimate summary statistics such as time-dependent analogues of the basic reproduction number and critical immunization threshold. We illustrate the methods with data on varicella (chickenpox) in the UK.

Key words: infectious disease; reproduction number; contact rates; serological survey.

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1. Introduction

Survival models have been used to analyze infectious disease data ever since Bernoulli (1766). They are commonly employed with cross-sectional data on case reports or population immunity, so as to take account of age-related heterogeneities in transmission (Grenfell and Anderson, 1985; Farrington, 1990). Widespread availability of serological survey data has encouraged their use to estimate key parameters such as age-specific contact rates, reproduction numbers, and critical vaccination coverage (Anderson and May, 1991; Farrington, Kanaan and Gay, 2001).

A common assumption is that the infection is in endemic equilibrium, implying that age-specific infection rates are constant over time. However, in a single cross-sectional survey, age and time effects are confounded; hence the endemic equilibrium assumption is unverifiable. Some authors have taken the alternative perspective of assuming the infection hazard varies with time but not with age (Schenzle, Dietz and Frosner, 1979; Hu et al., 1984; Ferguson, Donnelly and Anderson, 1999). In many situations, however, both age and time effects are likely to be important. To disentangle age and time, additional information is required, for example from sequential cross-sectional samples or longitudinal time series. Ades and Nokes (1993), Marschner, (1996, 1997) and Nagelkerke et al. (1999) have jointly modelled infectious disease data from several sequential serological surveys, using both parametric and non-parametric methods.

Most work on jointly modelling age and time effects in infectious diseases from cross-sectional data has concentrated on estimating infection hazards. For example, Ades and Nokes (1993) modelled the age and time-dependent

hazard of infection as a separable function $\lambda(a,t) = \mu(a)\gamma(t)$, where $\mu(a)$ is an age component and $\gamma(t)$ a temporal component. However, for infections transmitted directly from person to person, the infection hazard $\lambda(a,t)$ is derived from contact rates. Gay (1996) argued that the focus of the models should be the key transmission parameters rather than the infection rates. In general, if a realistic model is assumed for the contact rates, then the derived model for the age and time specific infection rates is unlikely to be separable.

Direct modelling of time-varying transmission parameters is commonly employed in time series analyses of infectious disease data. For example, much work has been done on modelling the seasonal variation in transmission probabilities of measles from case reports data (Deguen, Thomas and Chau, 2000; Wallinga, Teunis and Kretzschmar, 2003). In particular, the time series susceptible infected recovered (TSIR) model (Finkenstadt and Grenfell, 2000) can be used to estimate reproduction numbers and other important quantities, and has provided new insights into the dynamics of measles transmission.

In the present paper we adapt methods suitable for endemic infections in equilibrium to allow for secular changes in contact rates. We seek to model long-term, gradual changes in the contact structure. Such changes might be described as societal shifts in mixing patterns, in contrast to changes occurring on shorter time scales, such as seasonal variation.

We illustrate our methods with an analysis of data on varicella infection in the UK. In section 2 we describe this application. The models are introduced in section 3. In section 4 we describe estimation methods. In section 5 we give the results of applying these models to the data. Finally in section 6 we

discuss the models and the results.

2. Motivation: varicella in the UK

2.1 *Epidemiology of varicella*

Varicella, commonly known as chickenpox, results from primary infection with varicella zoster virus (VZV). Infection occurs primarily by direct contact with infected persons and by airborne transmission. Most infections occur in childhood and young adulthood, and confer lasting immunity. Following a primary infection, VZV may persist in a latent state for many years, eventually reappearing as herpes zoster, commonly known as shingles. Here we follow Garnett and Grenfell (1992) and ignore varicella cases resulting from contact with persons with shingles; such infections account for only a small proportion of varicella cases (Ferguson, Anderson and Garnett, 1996). There is no vaccination against VZV in the UK.

The recent epidemiology of varicella in England and Wales has been described by Ross and Fleming (2000) and by Brisson et al. (2001). Both presented consultation rates for varicella from the Royal College of General Practitioners (RCGP). These data showed an increase in consultations among pre-school children. The authors suggested that the change is due to an increase in contact rates between pre-school children resulting from a secular increase in pre-school and nursery school provision. We shall investigate this hypothesis in an analysis based on the RCGP data and a serological survey.

2.2 *Data*

The RCGP data comprise consultation rates for varicella, per 100,000 person weeks, for the period 1969 to 1998, stratified in 5 age bands: 0-4, 5-14, 15-44, 45-64 and 65+ years. However, consultations for varicella represent

only a proportion of all primary VZV infections. The proportion of infections reported may vary with age. We assume that these age-specific proportions remain constant over time, so that the consultation rates are proportional to incidence rates. We allow for under-reporting by calibrating the consultation data against the results of a large serological survey conducted by the Public Health Laboratory Service (PHLS) in England and Wales in 1996. The survey only included the 1-20 age group, and was stratified in 1-year age bands. This is not a serious restriction since most VZV infections occur before age 20.

The model predictions were checked against seven small serological surveys (52 to 262 individuals) carried out in Sheffield during 1966, 1970, 1974, 1978, 1984, 1988 and 1992. These data have been published in Kudesia et al. (2002).

3. Models for varying contact rates

We consider endemic immunizing infections of childhood directly spread from person to person in a large population, with short latency and infectious periods. Let $M(y)$ denote the probability of surviving to age y; for simplicity we assume that $M(y)$ does not vary over time, and that infection-associated mortality is negligible. L is the life expectancy, and so $L^{-1}M(y)$ is the age density of the population. Transmission of the infection depends on the age- and time- specific contact function $\beta(x, y, t)$, which is the average per capita rate at which an individual of age y makes effective contacts with individuals of age x at time t. An effective contact between persons A and B is a contact such that, if A is infectious and B susceptible, then A infects B.

The hazard (or force) of infection $\lambda(x, t)$ is the rate at which susceptible

individuals of age x acquire infection, at time t. The corresponding survivor function for an individual of age y at time t is:

$$S(y,t) = \exp\left\{-\int_0^y \lambda(u, t-y+u)du\right\}.$$

In the next subsection we derive the local equilibrium condition which relates the contact function $\beta(x,y,t)$ to the force of infection $\lambda(x,t)$.

3.1 *Local equilibria*

Let N denote the population size. Denote the latency and infectious periods by Z_L and Z_I respectively. Write

$$\pi(u) = P(Z_L \leq u < Z_L + Z_I).$$

Then

$$\lambda(x,t) = \frac{N}{L}\int_0^\infty\int_0^\infty \beta(x, y+u, t)\pi(u)\lambda(y, t-u)S(y, t-u)M(y+u)dudy. \quad (1)$$

Suppose now that the expectations D_L and D_I of Z_L and Z_I and their standard deviations are very short compared to the time scales over which $\beta(x,y,t)$ and $M(y)$ change. Then

$$\lambda(x,t) \simeq \frac{ND_I}{L}\int_0^\infty \beta(x,y,t)\lambda(y,t)S(y,t)M(y)dy. \quad (2)$$

This is an approximate local equilibrium condition which holds at each time point t, provided that the contact rates change little during the generation time of the infection process. For varicella $D_L + D_I$ is about 21 days while in our application contact rates only change appreciably over a time scale measured in years, reflecting changes in attendance at nursery schools. Equation (2) makes sense intuitively: over short time scales there is very little variation in average hazards of infection since contact rates remain practically constant.

3.2 *Numerical solution*

Our strategy is to specify a parametric model for $\beta(x, y, t)$, then solve the non-linear integral equation (2) to find its nonzero solution $\lambda(x, t)$. A unique non-zero solution exists at each t by virtue of Inaba (1990), provided that the leading eigenvalue of $\frac{ND_I}{L}\beta(x, y, t)$, considered as a bivariate function of x and y, is greater than 1 for each t.

We assume type I mortality, that is, all individuals live to age L then die. This assumption has very little bearing on the results since most infections are acquired in childhood. Thus $M(y) = 1$ for $y \in [0, L]$, and $M(y) = 0$ for $y > L$. We solve the local equilibrium equation (2) by first discretizing the problem. We assume that $ND_IL^{-1}\beta(x, y, t)$ is a $K \times K$ matrix with non-negative time-varying entries $\beta_{ij}(t)$, $x \in (a_{i-1}, a_i]$, $y \in (a_{j-1}, a_j]$, $i, j = 1...K$, where $a_0 = 0$, and $a_K = L$. It follows from (2) that the force of infection $\lambda(x, t)$ is piecewise constant within age groups. Thus a solution of (2) involves K functions $\lambda_i(t)$. We further discretize the problem by assuming that the process occurs in discrete time with steps of 1 year. The survivor function $S(y, t)$ is then a step function and the equilibrium equation (2) can be written:

$$\lambda_i(t) = \sum_{j=1}^{K} \sum_{r=a_{j-1}+1}^{a_j} \beta_{ij}(t)\lambda_j(t)S(r, t) \tag{3}$$

where, for $a_{j-1} < r \leq a_j$,

$$\begin{aligned} S(r, t) \;=\; & \exp -\{\lambda_1(t - r + 1) + ... + \lambda_1(t - r + a_1) \\ & +\lambda_2(t - r + a_1 + 1) + ... + \lambda_2(t - r + a_2) \\ & +... \\ & +\lambda_j(t - r + a_{j-1} + 1) + ... + \lambda_j(t)\}. \end{aligned}$$

The time variable t spans the available data, from year t_1 to year t_2, say. However, evaluation of $S(r,t)$ at time t requires knowledge of the forces of infection $\lambda_i(s)$ at times s between $t-r+1$ and t, for all $r = 1, ..., L$. In consequence, we need to know the values of the contact rates $\beta_{ij}(t)$ and forces of infection $\lambda_i(t)$ prior to the period when data are available. We make the assumption that, prior to some time $t_0 \in [t_1, t_2]$, the contact rates were constant: thus $\beta_{ij}(t) = \beta_{ij}(t_0)$ for all $t \leq t_0$. In other words, we observe the point at which contact rates began to change. Other assumptions about the distant past are of course possible.

With these assumptions, given the contact functions $\beta_{ij}(t)$, we solve the local equilibrium equation (2) iteratively using the scheme:

$$\lambda_i^{(m+1)}(t) = \sum_{j=1}^{K} \sum_{r=a_{j-1}+1}^{a_j} \beta_{ij}(t) \lambda_j^{(m)}(t) S^{(m)}(r,t) \tag{4}$$

starting from suitable functions $\lambda_j^{(0)}(t) > 0$. We stop iterating once the expression

$$\sum_{i=1}^{K} \sum_{t=t_1}^{t_2} \left\{ \lambda_i^{(m+1)}(t) - \lambda_i^{(m)}(t) \right\}^2$$

becomes negligibly small.

3.3 *Epidemiological parameters*

The basic reproduction number $R_0(t)$ at time t is the average number of individuals infected by a single typical infective introduced at time t into the population, if everyone were susceptible at time t. This definition extends the standard time-independent definition of R_0 in an obvious manner. It makes sense by virtue of the fact that contact rates are assumed to change slowly: thus an epidemic would have the time to take off or not at time t before the contact rates changed appreciably. Following standard theory $R_0(t)$ is the

leading eigenvalue of

$$\frac{ND_I}{L}\beta(x,y,t)$$

considered as a bivariate function of x and y.

We also aim to estimate the critical immunization threshold $v_c(t)$ at time t. We define this as the minimum proportion of the population that must be immunized to eliminate the infection from the population, if the contact rates at time t were to remain constant thereafter. We consider a vaccination programme in which a constant proportion v of children aged 15 months are immunized. The probability $\sigma(x)$ that an individual of age x is not protected by vaccination is:

$$\sigma(x) = \begin{cases} 1 & 0 \leq x < 1.25 \\ 1-v & 1.25 \leq x < L \end{cases}$$

The projected reproduction number $R_v(t)$ is the expected number of cases produced when one typical infective individual is introduced into the population at time t, assuming that all immunity in the population at time t is vaccine-derived. $R_v(t)$ is the leading eigenvalue of $L^{-1}ND_I\sigma(x)\beta(x,y,t)$. The critical immunization threshold $v_c(t)$ at time t is the value of the proportion immunized v for which $R_v(t) = 1$.

4. Estimation

4.1 *Models for varicella*

Since the RCGP data are stratified in broad age groups, we model $\beta(x,y,t)$ as a 5×5 matrix. Such models are commonly used for infectious diseases (Anderson and May, 1991). For our age group cut-offs we used $a_0 = 0$, $a_1 = 5$, $a_2 = 15$, $a_3 = 45$, $a_4 = 65$, $a_5 = L = 75$, which represent epidemiologically relevant categories: pre-school, school, adult, and two older categories.

We used four contact matrices, labeled B_A to B_D (figure 1). To resolve the unidentifiability inherent in the equilibrium equation (2), we followed standard practice by restricting the numbers of distinct entries in the 5×5 contact matrix at each time point. Matrices B_A, B_B and B_D are time-dependent versions of models previously used for varicella data (Garnett and Grenfell, 1992, Halloran et al., 1994, Brisson et al., 2000). In matrix B_A most contacts occur within age groups. In matrix B_C the contact rate between two age groups is determined by the oldest age group. Matrices B_B and B_D are variants of B_C, with a dedicated parameter β_2 for contacts between school children.

For matrices B_A, B_B and B_C, only contact rates between individuals in the youngest age groups (pre-school children under 5 years) were allowed to vary with time, in line with the hypothesis that changes in pre-school and nursery-school provision are responsible for observed trends. Thus we assumed that

$$\beta_{ij}(t) = \begin{cases} \beta_1(t) & \text{if } i = j = 1 \\ \beta_{ij} & \text{otherwise.} \end{cases}$$

In contrast, for matrix B_D we assumed that only the contact rates between 0-4 and 5-14 year olds were allowed to change. This is to investigate the alternative hypothesis that the observed incidence pattern is due to increased contacts between children of pre-school age and older children, contact rates within each age group remaining constant.

We took the time-specific contact rate $\beta_1(t)$ in year t to be of the form

$$\beta_1(t) = \begin{cases} b_1 + (b_2 - b_1)\frac{\exp\{\alpha(t_0-\tau)\}}{1+\exp\{\alpha(t_0-\tau)\}} & t < t_0 \\ b_1 + (b_2 - b_1)\frac{\exp\{\alpha(t-\tau)\}}{1+\exp\{\alpha(t-\tau)\}} & t \geq t_0 \end{cases}$$

with b_1, $b_2 \geq 0$, and $t_0 \leq \tau \leq 1998$. We assumed that there had been no

change in contact rates before the year t_0, which was fixed at 1970, chosen to ensure that for $t \leq t_0$, $\beta_1(t) \simeq b_1$. $\beta_1(t)$ is an S-shaped function; τ marks the year corresponding to its centre of symmetry; b_1 and b_2 determine the minimum (pre-1970) and maximum contact rates; and α shapes the rate of change.

4.2 *Likelihoods*

We denote the vector of contact model parameters (b_1, b_2, α, β_2, β_3, β_4, β_5, τ) by β. All parameters except α and τ are constrained to be non-negative.

We begin with the likelihood for serological survey data collected in year t. Let $\mathrm{BB}(p, n, \phi)$ denote the beta-binomial distribution with mean np and variance $np(1-p)\{1+\phi(n-1)\}$, $\phi > 0$. If r_a out of n_a individuals of age a were seropositive in this survey, we modelled

$$r_a \sim \mathrm{BB}(1 - S(a, t; \beta), n_a, \phi).$$

The beta-binomial likelihood allows for extra-binomial over-dispersion. The log likelihood kernel l_S^t for a serological survey at time t is

$$\begin{aligned} l_S^t(\beta, \phi) &= \sum_a \{\log\Gamma(\gamma_{at} + r_a) + \log\Gamma(\delta_{at} + n_a - r_a) + \log\Gamma(\gamma_{at} + \delta_{at}) \\ &\qquad - \log\Gamma(\gamma_{at} + \delta_{at} + n_a) - \log\Gamma(\gamma_{at}) - \log\Gamma(\delta_{at})\} \end{aligned}$$

where $\gamma_{at} = \{1 - S(a, t; \beta)\}(\frac{1-\phi}{\phi})$, $\delta_{at} = S(a, t; \beta)(\frac{1-\phi}{\phi})$.

We now turn to the RCGP data. Denoting the observed age-specific varicella consultation rate within age group i in year t as I_{it}, we modelled

$$I_{it} \sim \mathrm{Gamma}(\theta_i \mu_i(t; \beta), \nu)$$

with density

$$\frac{\nu^\nu}{\Gamma(\nu)} \left\{ \frac{I_{it}}{\theta_i \mu_i(t; \beta)} \right\}^{\nu-1} \frac{1}{\theta_i \mu_i(t; \beta)} \exp\left(-\frac{\nu I_{it}}{\theta_i \mu_i(t; \beta)} \right).$$

Here ν is a shape parameter ($\nu > 0$), $\mu_i(t;\beta)$ is the expected incidence rate of new VZV infections in age group i during year t, namely

$$\mu_i(t;\beta) = \lambda_i(t;\beta) \int_{a_{i-1}}^{a_i} S(x,t;\beta)dx$$

and θ_i is an age-specific scaling factor included to adjust $\mu_i(t;\beta)$ to the RCGP consultation rates ($\theta_i > 0$). Thus I_{it} has mean $\theta_i\mu_i(t;\beta)$ and variance $\nu^{-1}\{\theta_i\mu_i(t;\beta)\}^2$. Since the 1996 serological survey stops at age 20, we assumed that $\theta_2 = \theta_3 = \theta_4 = \theta_5$. The log likelihood kernel l_C for the RCGP data is

$$\begin{aligned} l_C(\beta,\theta_1,\theta_2,\nu) &= \sum_i \sum_t \Big\{ \nu\log\nu - \log\Gamma(\nu) - \nu\log(\theta_i\mu_i(t;\beta)) \\ &\qquad +(\nu-1)\log(I_{it}) - \frac{\nu I_{it}}{\theta_i\mu_i(t;\beta)} \Big\}. \end{aligned}$$

It is necessary to use at least one serological survey in conjunction with the RCGP data to ensure that $\mu_i(t;\beta)$ is estimated correctly, owing to the fact that not all infections produce clinical symptoms, and reporting rates are likely to vary with age. Thus we combined the RCGP data with the 1996 serological survey, and maximised the joint log likelihood kernel $l_C + l_S^{1996}$. Because the model is essentially parametric in form, standard likelihood theory (with constrained parameters) applies.

The Pearson χ^2 was used to assess goodness of fit. Model predictions were also tested, by calculating the Pearson χ^2 for the Sheffield serological survey data.

4.3 *Convergence*

The estimation procedure is time consuming because the integral equation (2) is solved at each iteration of the maximization algorithm. Ten iterations

of (4) sufficed to find the forces of infection $\lambda_i(t)$. In initial experiments, we found that the iteration diverged if $\beta_1(t)$ was allowed to change too rapidly (α too large or τ too close to 1970). However, the basic assumption underlying our methods is that contact rates vary gradually over time. Such divergence never occurred during model fitting.

Convergence was checked for sensitivity to starting values; estimates did not change when different starting values were used. Sensitivity to the year when the increase started, t_0, was also checked. In addition to $t_0 = 1970$, t_0 was fixed at 1969, 1971 and 1972, but parameter estimates did not change appreciably.

4.4 *Simulation study*

To check the validity of these methods in finite samples we carried out a small simulation study. A simplified model using a 3×3 version of contact matrix B_B (with $\beta_4 = 0$, $\beta_5 = 0$) was fitted to the 1996 survey and the first three age groups of the RCGP data. The estimated values of $S(x, 1996; \beta)$ and $\mu_i(t; \beta)$ were used to generate random data

$$I_{it} \sim \text{Gamma}(\hat{\theta}_i \mu_i(t; \hat{\beta}), \hat{\nu})$$
$$r_a \sim \text{BB}(1 - S(a, 1996; \hat{\beta}), n_a, \hat{\phi})$$

The model was re-fitted to 199 sets of simulated data. To reduce the computational burden, the parameters τ, θ_1, θ_2, ϕ and ν were fixed at their estimated values. The parameter values were all within 8% of the simulated medians, and always fell well within the central 95% of the simulated sampling distribution.

4.5 *Standard Errors and Confidence Intervals*

Computational constraints preclude the use of bootstrapping or profile likelihood methods for obtaining standard errors and confidence intervals. We used the following approximate method; a very similar approach was taken by Aalen et al. (1997). First, we inverted a numerical estimate of the information matrix. We kept τ, the θ_i and any β_i for which $\beta_i < 10^{-4}$ fixed at their estimated values to avoid ill-conditioning. However, the resulting standard errors are too large since they take no account of the fact that the estimation procedure is constrained, particularly to keep the β_i non-negative. In a second stage we attempted to adjust for this. We sampled (3999 samples) parametrically from the (unconstrained) asymptotic multinormal distribution and deleted samples with negative values of non-negative parameters. From this thinned sampling distribution we calculated standard errors for the model parameters and percentile 95% confidence intervals for $\beta_1(t)$, $R_0(t)$ and $v_c(t)$ for $t = 1970$ and $t = 1998$, and for the ratio $\frac{\beta_1(1998)}{\beta_1(1970)}$.

We checked the performance of this approximate method with a simplified model fitted to the 1996 serological survey data using 3-dimensional, non-time-dependent versions of our contact matrices. Standard errors for the model parameters and confidence intervals for R_0 were obtained (a) by non-parametric bootstrapping with constrained estimation (599 samples), (b) by inverting a numerical estimate of the information matrix without allowing for the constrained estimation, and (c) by the two-stage method just described involving parametric bootstrapping. The results are given in table 1. In comparison to standard errors for the non-parametric bootstrap method, the standard errors obtained from both methods (b) and (c) were

larger for the contact rate parameters β_i, and smaller for the beta-binomial shape parameter ϕ. Method (c) produced slightly better results as expected. Furthermore, the confidence intervals for $R_0(t)$ and $v_c(t)$ cannot be calculated using method (b) because of occasional negative parameter values. We conclude that method (c) gives approximate, often conservative but useable standard errors and confidence intervals.

5. Results

Figure 2 shows the fits to the RCGP data and the serological profile $1 - S(x, t; \hat{\beta})$ fitted to the 1996 survey, using each matrix. This shows that models B_A and B_B correctly account for the decline in VZV incidence in 5-14 year olds, resulting from the reduction in number susceptible owing to increased infection rates in under 5's. Models B_C and B_D both over-estimate the incidence for 5-14 year-olds for some period after 1983. Considering the fits to the 1996 serological survey, model B_C under-estimates the proportion seropositive after age 5, owing to a lower value of β_2. Both B_C and B_D show a drop in the proportion seropositive after age 15, these children having experienced low infection rates in childhood.

Table 2 shows the Pearson χ^2 statistics. The four models fitted adequately, but models B_A and B_B achieved the lowest χ^2 values. Applied to the Sheffield serological survey data, matrix B_B provided the best fit, followed by matrix B_A, whereas the fits for matrices B_C and B_D were very poor. Parameter estimates and approximate standard errors for the two best fitting models, B_A and B_B, are given in table 3.

A likelihood ratio test rejected the hypothesis of no time-dependence in the contact rates (i.e. $\beta_1(t)$ constant) for all 4 matrices ($p < 0.0001$).

We also fitted models with $\phi = 0$, corresponding to a binomial error structure for the serological survey data. While the parameter estimates did not change appreciably, allowing for over-dispersion improved the fit of the model.

Estimates of the contact rate for pre-school aged children at or before 1970 $\beta_1(1970)$ and at 1998 $\beta_1(1998)$, the latest year for which we have RCGP data, are given in table 4. Also shown are the fold increases $\frac{\beta_1(1998)}{\beta_1(1970)}$. All analyses show a large increase in the contact rate for the pre-school aged children over the 28 year period.

Estimates of R_0 and v_c before 1970 and in 1998 are given in table 5. The values are highly sensitive to the choice of matrix, as expected (Farrington et al., 2001), and the value of R_0 is greater using matrix B_A than it is using matrix B_B. More surprising perhaps is that the values for each matrix hardly change over time despite the sharp increase in contact rates between pre-school aged children. This is because the leading eigenvalues of the contact matrices are determined largely by the values of β_2 and β_3, which we assumed remain constant over time.

6. Discussion

In this paper we extended methods of analysis valid for stationary endemic infections to situations in which contact rates vary over time. Our methods apply when the contact rates vary slowly on the time scale on which the infection spreads. However, if contact rates were to vary very rapidly, then the local equilibria which lie at the heart of our methods would no longer be valid.

Our method involves iteratively solving a discretized version of the inte-

gral equation describing the local equilibria. This iterative solution must be found at every time point, and for every update of the model parameters. Consequently, our methods are computationally demanding. Our methods for deriving standard errors and confidence intervals are approximate and could clearly be improved.

Our focus throughout has been to relax the assumption that age-specific contact rates are constant. However, augmenting the serological survey data with case reports to this end also throws new light on model selection. Models B_A and B_B appeared to provide a better fit to the data, and better predicted the Sheffield survey data than models B_C and B_D. In particular, our results support the hypothesis that the observed changes in age-specific incidence of VZV is driven by increased contact rates among young children as previously suggested (Ross and Fleming, 2000; Brisson et al., 2001). We were also able to rule out matrix B_C. Such choices cannot generally be made from a single serological survey, owing to the lack of identifiability of the contact matrix from the force of infection. This lack of identifiability is particularly problematic since the basic reproduction number R_0 and critical immunization threshold v_c depend sensitively on the contact structure. Recently, some progress has been made in resolving this unidentifiability by considering several infections transmitted by the same route (Farrington et al., 2001, Kanaan and Farrington, 2004). Modelling changes over time provides a further approach to this difficult problem.

We have only considered changes in contact rates, but non-stationarity can arise for other reasons. For example the age structure of the population may change: our methods could be extended to allow for this. Other non-

stationary effects include epidemics, the presence of which has been shown not to bias results unduly for other childhood infections (Whitaker and Farrington, 2004) and changes in family structure, which requires an entirely different modelling approach (Ball, Mollison and Scalia-Tomba, 1997).

It is also possible to model contact rates using a continuous contact surface (Farrington and Whitaker, 2004), thus avoiding the assumption of constant contact rates within discrete age groups. However incorporating temporal effects into such models would probably require yet stronger parametric assumptions to allow explicitly for age-time interactions.

We conclude that the data are consistent with a substantial increase in contact rates in pre-school children between 1970 and 1998, though the size of the increase depends sensitively on the choice of contact model. Nevertheless, in spite of substantial changes in contact rates in pre-school children, the values of the basic reproduction number R_0 and the critical immunization threshold v_c remained roughly constant over the entire time period. In this sense, neither parameter adequately reflects the changing epidemiology of varicella over time. However, it also follows that changes in contact rates in some age groups are in effect ignorable for the purpose of estimating basic reproduction numbers and critical immunizing thresholds.

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Table 1

Simulations: standard errors and confidence intervals.

Matrix	Parameter	Estimate	SE/ 95% CI by three methods: (a)	(b)	(c)
B_A	β_1	0.298	0.028	0.041	0.039
	β_2	0.265	0.157	0.191	0.154
	β_3	0.099	0.038	0.049	0.041
	ϕ	0.016	0.012	0.009	0.008
	R_0	7.75	(5.04, 13.21)	-	(5.78, 12.84)
B_B/B_D	β_1	0.232	0.011	0.016	0.016
	β_2	0.000*	-	-	-
	β_3	0.093	0.037	0.046	0.043
	ϕ	0.016	0.012	0.008	0.008
	R_0	6.89	(3.21, 13.14)	-	(2.16, 13.54)
B_C	β_1	0.276	0.040	0.051	0.050
	β_2	0.149	0.040	0.049	0.047
	β_3	0.099	0.045	0.055	0.050
	ϕ	0.016	0.012	0.009	0.008
	R_0	7.55	(3.61, 14.99)	-	(3.46, 15.54)

See text for a description of the three methods:
(a) Non-parametric bootstrap
(b) Numerical estimate, unconstrained
(c) Two stage proceedure.
*estimate < 0.0001 therefore fixed at 0.

Table 2

Goodness of fit.

	RCGP and 1996 survey data			Sheffield surveys		
Matrix	χ^2	d.f.	p	χ^2	d.f.	p
B_A	135.1	158	0.906	51.8	33	0.020
B_B	127.4	158	0.965	37.4	33	0.275
B_C	154.4	158	0.567	120.6	33	0.000
B_D	169.2	158	0.256	248.4	33	0.000

Table 3

Parameter estimates (with standard errors where available).

Parameter	Matrix B_A	Matrix B_B
b_1	0.167 (0.027)	0.070 (0.012)
b_2	0.380 (0.066)	0.332 (0.046)
α	0.189 (0.049)	0.328 (0.099)
β_2	0.362 (0.013)	0.285 (0.046)
β_3	0.392 (0.029)	0.020 (0.009)
β_4	0.000	0.005 (0.003)
β_5	0.017 (0.005)	0.006 (0.004)
τ	1995.30	1989.94
θ_1	143.35	133.31
θ_2	65.83	65.88
ν	4.430 (0.521)	4.652 (0.508)
ϕ	0.030 (0.016)	0.026 (0.015)

Table 4

Estimated pre-school contact rates (with 95% confidence interval).

Matrix	$\beta_1(1970)$	$\beta_1(1998)$	$\frac{\beta_1(1998)}{\beta_1(1970)}$
B_A	0.171	0.404	2.372
	(0.131, 0.222)	(0.343, 0.466)	(1.717, 3.236)
B_B	0.070	0.379	5.409
	(0.051, 0.096)	(0.309, 0.428)	(3.425, 7.607)

Table 5

Estimated basic reproduction number and critical immunization threshold (with 95% confidence interval).

Matrix	$R_0(1970)$	$R_0(1998)$	$v_c(1970)$	$v_c(1998)$
B_A	11.79	11.79	0.915	0.915
	(10.05, 13.53)	(10.06, 13.53)	(0.901, 0.926)	(0.901, 0.926)
B_B	3.02	3.14	0.675	0.726
	(2.39, 4.24)	(2.63, 4.28)	(0.591, 0.768)	(0.688, 0.789)

Figure 1. Contact matrices. (Note that b_1 is that given in the equation for β_1).

$$B_A = \begin{pmatrix} \beta_1(t) & \beta_5 & \beta_5 & \beta_5 & \beta_5 \\ \beta_5 & \beta_2 & \beta_5 & \beta_5 & \beta_5 \\ \beta_5 & \beta_5 & \beta_3 & \beta_5 & \beta_5 \\ \beta_5 & \beta_5 & \beta_5 & \beta_4 & \beta_5 \\ \beta_5 & \beta_5 & \beta_5 & \beta_5 & \beta_5 \end{pmatrix}$$

$$B_B = \begin{pmatrix} \beta_1(t) & b_1 & \beta_3 & \beta_4 & \beta_5 \\ b_1 & \beta_2 & \beta_3 & \beta_4 & \beta_5 \\ \beta_3 & \beta_3 & \beta_3 & \beta_4 & \beta_5 \\ \beta_4 & \beta_4 & \beta_4 & \beta_4 & \beta_5 \\ \beta_5 & \beta_5 & \beta_5 & \beta_5 & \beta_5 \end{pmatrix}$$

$$B_C = \begin{pmatrix} \beta_1(t) & \beta_2 & \beta_3 & \beta_4 & \beta_5 \\ \beta_2 & \beta_2 & \beta_3 & \beta_4 & \beta_5 \\ \beta_3 & \beta_3 & \beta_3 & \beta_4 & \beta_5 \\ \beta_4 & \beta_4 & \beta_4 & \beta_4 & \beta_5 \\ \beta_5 & \beta_5 & \beta_5 & \beta_5 & \beta_5 \end{pmatrix}$$

$$B_D = \begin{pmatrix} b_1 & \beta_1(t) & \beta_3 & \beta_4 & \beta_5 \\ \beta_1(t) & \beta_2 & \beta_3 & \beta_4 & \beta_5 \\ \beta_3 & \beta_3 & \beta_3 & \beta_4 & \beta_5 \\ \beta_4 & \beta_4 & \beta_4 & \beta_4 & \beta_5 \\ \beta_5 & \beta_5 & \beta_5 & \beta_5 & \beta_5 \end{pmatrix}$$

Figure 2. Model fit for matrices B_A (top), B_B, B_C and B_D respectively. Left: RCGP consultation rates (per 100,000 person weeks): data (thin lines) and fitted (thick lines). Right: 1996 serological survey: data (points) and model (line).