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Realistic Distributions of Infectious Periods in Epidemic Models: Changing Patterns of Persistence and Dynamics

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Most mathematical models used to study the epidemiology of childhood viral diseases, such as measles, describe the period of infectiousness by an exponential distribution. The effects of including more realistic descriptions of the infectious period within SIR (susceptible/infectious/recovered) models are studied. Less dispersed distributions are seen to have two important epidemiological consequences. First, less stable behaviour is seen within the model: incidence patterns become more complex. Second, disease persistence is diminished: in models with a finite population, the minimum population size needed to allow disease persistence increases. The assumption made concerning the infectious period distribution is of a kind routinely made in the formulation of mathematical models in population biology. Since it has a major effect on the central issues of population persistence and dynamics, the results of this study have broad implications for mathematical modellers of a wide range of biological systems. © 2001 Academic Press

INTRODUCTION

Epidemiological studies have uncovered striking patterns in both the dynamics and persistence of childhood viral diseases such as measles (Bartlett, 1956, 1957, 1960; Black, 1966; London and Yorke, 1973; Olsen and Schaffer, 1990; Bolker and Grenfell, 1993). Before the advent of mass vaccination, recurrent epidemics were seen in large cities in the developed world, usually taking the form of multiannual oscillations, with the numbers of cases falling to low levels between epidemics. Population size is a crucial determinant of disease persistence (Bartlett, 1956, 1957, 1960), as highlighted by Bartlett's notion of the critical community size (CCS)—the smallest population for which persistence occurs without reintroductions from outside. In smaller populations the chain of transmission is likely to be interrupted during interepidemic troughs, leading to frequent disease "fade-outs."

Despite an intensive effort, a mathematical model which predicts satisfactorily both the dynamical and persistence properties exhibited by incidence records remains elusive. Bartlett's stochastic formulation of the basic SIR (susceptible/infectious/recovered) model provides an explanation for persistence properties, but it fails to explain many of the dynamical incidence patterns. The inclusion of seasonality—arising because transmission rates of childhood diseases are much higher during school terms (London and Yorke, 1973; Dietz, 1976, Fine and Clarkson, 1982)—can lead to complex incidence patterns in deterministic models (Olsen and Schaffer, 1990), but with their deeper interepidemic troughs, such models predict an unrealistically large CCS (Bolker and Grenfell, 1993).

With only a few exceptions (Grossman, 1980; Lloyd, 1996; Keeling and Grenfell, 1997, 1998), models for the dynamics and persistence of childhood diseases—in contrast to those for long-lived infections, such as

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HIV—describe the duration of the infectious period by an exponential distribution. This mathematically convenient assumption is equivalent to assuming that the chance of recovery within a given time interval is constant, regardless of the time since infection. Epidemiologically, this is quite unrealistic, as is demonstrated by statistical studies of the transmission dynamics of measles in small communities (Wilson *et al.*, 1939; Hope Simpson, 1952; Bailey, 1954, 1975; Gough, 1977). In reality, the chance of recovery (in a given time interval) is initially small but increases over time, corresponding to the infectious period distribution, hereafter referred to as IPD, being less dispersed (more closely centred around its mean) than an exponential (Bailey, 1954, 1975; Gough, 1977). Stated another way, the exponential distribution overestimates the numbers of individuals whose duration of infection is much shorter or much longer than the mean.

In this paper, we investigate the effects of including more realistic descriptions of the IPD within the standard SIR framework. We first introduce the more general model and then discuss its implications for the key issues of persistence and dynamics. We demonstrate that the inclusion of more realistic IPDs leads to decreased persistence and an increase in dynamical complexity. These effects are then discussed in the light of recent work (Lloyd, 1996; Andersson and Britton, 1997, 2000; Keeling and Grenfell, 1997, 1998), which has begun to address such issues and suggest a possible resolution of the conflicting results obtained by Lloyd and those of Keeling and Grenfell, the latter suggesting that realistic IPDs should decrease, not increase, critical community sizes.

THE MODEL

In order to include a more realistic IPD, the exponential of the basic SIR model (Anderson and May, 1991) is replaced by a gamma distributed IPD (Bailey, 1964; Anderson and Watson, 1980; Lloyd, 1996, 2001a; Andersson and Britton, 1997, 2000). This corresponds to the subdivision of the single infectious class of the SIR model into n stages (Cox and Miller, 1965); newly infected individuals enter the first stage, pass through each successive stage, and recover as they leave the nth stage. It should be pointed out that these stages are a mathematical device used to consider nonexponential IPDs; in general they need not correspond to biological features of the infection (although in some cases it might be possible to give stages a biological interpretation, such as the latent period, early or late stage infection). As the parameter n of the distribution increases, the IPD becomes more closely centred on its mean, with $n \to \infty$ corresponding to all individuals having the exactly same duration of infection. The basic SIR model is recovered when $n = 1$, and for all but the smallest values of n, the IPD is very close to normal.

Making standard assumptions (Anderson and May, 1991; Bolker and Grenfell, 1993; Lloyd, 2001a), and using standard notation (Bolker and Grenfell, 1993; Keeling and Grenfell, 1997; Lloyd, 2001a), the SIR model with a gamma distributed infectious period can be written

$$\begin{aligned} dS/dt &= \mu N - \mu S - \beta SI \\ dI_1/dt &= \beta SI - (n\gamma + \mu)\, I_1 \\ dI_2/dt &= n\gamma I_1 - (n\gamma + \mu)\, I_2 \\ &\vdots \\ dI_n/dt &= n\gamma I_{n-1} - (n\gamma + \mu)\, I_n. \end{aligned} \tag{1}$$

Here, S is the number of susceptible individuals and I is the total number of infective individuals, which equals the sum of the infective individuals, I_j, in each of the n stages. The gamma distribution of infectious periods is determined by its mean and the parameter n. The mean duration of infection (neglecting background mortality) is kept fixed at $1/\gamma$ to enable comparison between models. Per-capita birth and death rates are equal to μ and there is no mortality due to the disease. Thus the population size, N, remains constant, and the number of recovered individuals, R, equals $N - S - I$. The transmission parameter is β, and depends on the probability that an encounter between a susceptible and infective individual results in the transmission of the disease and the rate at which such encounters occur. It is clear that this parameter depends on the structure and size of the population being considered and it can be argued convincingly (see, for instance, de Jong *et al.*, 1995) that it is most natural to take β to be inversely proportional to the population size (see also the discussion in Anderson and May, 1991, pp. 304–306, 313, and 314). In all of our simulations, we scale β with N in this way, but for notational simplicity we only write the N-dependence explicitly when referring to particular parameter values.

A particular strength of SIR-type model formulations is that all of the model parameters can be estimated from available demographic and epidemiological data (Anderson and May, 1991; Bolker and Grenfell, 1993). The birth and death rates are available from demographic data, the average duration of infection and distribution of infectious periods can be estimated from

studies of disease outbreaks in small communities (Wilson *et al.*, 1939; Hope Simpson, 1952; Bailey, 1954, 1975; Gough, 1977), and transmission parameters can be estimated from cross-sectional serological data (Anderson and May, 1991; Bolker and Grenfell, 1993). As these parameters can be estimated independently of the incidence record to which the model's behaviour is being compared, this strengthens the predictive power of the model as it is not being used merely as a curve-fitting device.

DISEASE PERSISTENCE AND THE STOCHASTIC MODEL

One of the most unrealistic features of deterministic epidemic models is the ability of infective numbers to rebound from extremely low levels (such as infective fractions of 10^{-10} in a model exhibiting chaotic incidence patterns (Bolker and Grenfell, 1993)); the fade-out phenomenon cannot occur in deterministic models. Persistence is most naturally studied using a stochastic formulation of the model, in which the movements of individuals between disease classes are modelled by Poisson processes (Cox and Miller, 1965). The rates of the deterministic model are reinterpreted to give the probabilities of individuals moving between classes in a given time interval (Bartlett, 1956), thereby accounting for demographic stochasticity (random effects due to the population consisting of a finite number of individuals). In contrast to the deterministic model, the number of infectives can fall to zero in the stochastic model, after which the disease remains extinct forever, unless infection is reintroduced, for instance, by the immigration of infective individuals from outside the population.

Two straightforward techniques can be used to simulate the stochastic model. The standard Monte Carlo approach (Bartlett, 1956; Renshaw, 1991; Gibson and Bruck, 2000) follows every single transition that occurs in the population. Since the different possible transitions are described by independent Poisson processes, the total rate at which events (of any type) occurs is given by the sum of the rates, T_R, describing the different transitions. It can be shown that the distribution describing the waiting time until the occurrence of the next event (of any type) is exponential with mean equal to the reciprocal of T_R (Cox and Miller, 1965). To perform a single step of the simulation, two random numbers are generated: the first, generated from the appropriate exponential distribution, determines the time until the occurrence of the next event and the second, generated from a uniform distribution on the interval from 0 to T_R, determines which type of event occurs. This simulation technique generates exact realizations of the stochastic process when the model parameters are time-independent. (If, as is the case below in the seasonally forced model, parameters are allowed to vary then the simulation produces approximations to realizations of the model. In our situation, these approximations are extremely good, however, since the seasonal transmission parameter varies negligibly over the average interevent time of the model.)

Since this Monte Carlo technique follows every single-transition that occurs in the population, it is computationally intensive when the population size is large. A computationally more attractive, but approximate, approach employs a fixed time step, h, and makes use of the fact that for a Poisson process of constant rate ϕ the number of events occurring in a time interval of length h is Poisson distributed, with mean ϕh (Cox and Miller, 1965). To utilise this technique, one must assume that transition rates in the model do not change much over times scales of order h. However, since individuals must spend a multiple of h time units in any given class, "coarse-graining" effects can lead to waiting times within this simulation scheme being longer than expected. If an individual is supposed to spend an average of T time units in a given class, a straightforward calculation reveals that the average simulation time spent in that class is $h/[1-\exp(-h/T)]$, which is always greater than T for $h>0$. Assuming $h/T \ll 1$, the expression is approximately equal to $T[1+h/(2T)]$. The simulation time interval is constrained by the natural time scales of the system; h must be short compared to the model's fastest time scale, which in the case of the basic SIR model is the average duration of infection.

Repeated simulation of the stochastic model, each time employing the same parameter values and initial conditions, leads to a collection of non-identical realizations of the model, in marked contrast to similar simulation of the deterministic model. Persistence properties depend on how much these realizations vary from the average behaviour. The higher the variability, the more likely it is that the numbers of infectives fall to low values and that fade-outs occur. From estimates of the variability, the expected time to extinction (fade-out) can be calculated (Nåsell, 1999), from which an expression for the CCS follows (Andersson and Britton, 1997, 2000; Nåsell, 1999).

For a nonlinear model, the equations for the moments of the distribution of states do not form a closed set. The equations for the mean involve the second-order moments, variances, and covariances. The equations for

the second-order moments involve third-order moments, and so on. A moment closure approximation, such as the multivariate normal (MVN) approximation (Whittle, 1957; Isham, 1991; Lloyd, 1996, 2001b), can be used to truncate the set of moment equations at some order, allowing variability to be estimated. An alternative technique, based upon the diffusion equation, in which the stochastic differential equations describing fluctuations are linearized about the endemic equilibrium obtained from the deterministic model, has also been successfully used (van Herwaarden and Grassman, 1995; Andersson and Britton, 1997, 2000; Nåsell, 1999). This approach often gives rise to simpler (often explicit) solutions than those obtained by the MVN approximation. We remark that this second approach gives solutions identical to those obtained using Bartlett's stochastic averaging technique (Bartlett, 1956; Nåsell, 1999).

An illuminating example of the factors which determine persistence is provided by considering the effects of demographic stochasticity on a single species system, assumed to be at equilibrium (Nisbet and Gurney, 1982). Variability is seen to depend on the magnitude of stochastic effects buffetting the system and on the stability of the equilibrium, with more stable systems (i.e., those which return more quickly to equilibrium after a perturbation) exhibiting less variability, and therefore less likely to undergo extinction. This notion that more stable systems are less prone to stochastic fluctuations is well known in ecological theory (May, 1973). It is important to point out, however, that determining variability in more complex models is a much more subtle question, as one must account for the fact that fluctuations in different populations are usually correlated. For more complex models, we would not necessarily expect there to be a simple relationship between equilibrium stability and the importance of demographic stochasticity.

As mentioned above, the stochastic formulation usually allows for the immigration of infective individuals in order to reintroduce infection following fade-out. Whilst the notion of persistence is clear for a closed population, immigration complicates matters somewhat, and many measures of persistence in populations subject to immigration might be quite sensitive to the level of immigration. As a trivial example, allowing a sufficiently high level of immigration would guarantee that an infectious individual would be observed at all times. Furthermore, many measures of persistence may, to a large part, quantify invasion properties of the disease; for instance, the fraction of weeks without cases will depend not only on the chance of fade-out, but also on how long it takes the disease to become reestablished following fade-out. We attempt to minimise the impact of immigration by asking what fraction of simulations exhibit fade-out over a 10-year simulation period: immigration is only allowed during a transient period before this, and if is only included to maximise the chance that the disease is present at the start of the 10-year period.

RESULTS

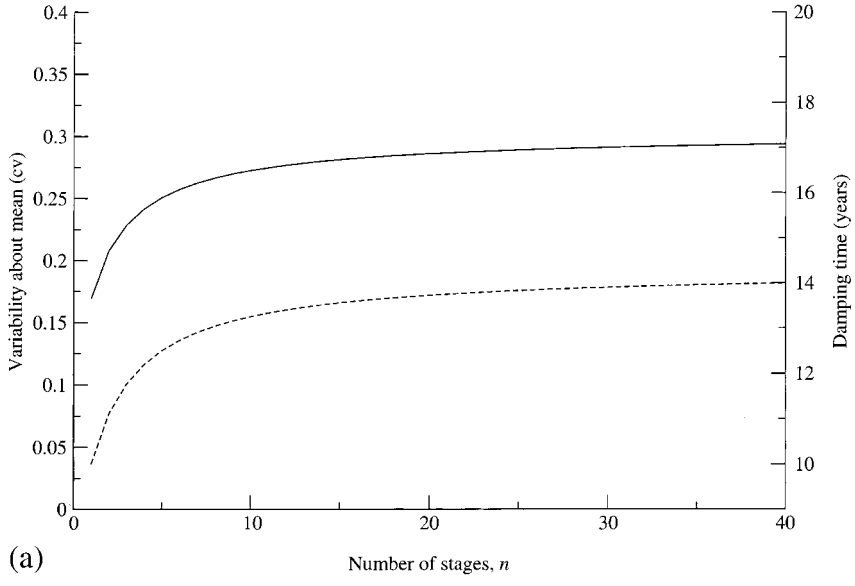
Model without Seasonal Forcing

The dynamics of the deterministic model (Eq. (1)) in the absence of seasonality are simple. Depending on the value of the basic reproductive number (Macdonald, 1952; Anderson and May, 1991), R_0, which, if deaths of infective individuals are neglected, equals $\beta N/\gamma$, the disease either goes extinct (if $R_0 < 1$) or the disease is maintained at an endemic level (if $R_0 > 1$) (Hethcote and Tudor, 1980). In the latter case, the values of S and I at the endemic equilibrium are given by $S^* = N/R_0$ and $I^* = \mu(R_0 - 1)/\beta$, and this equilibrium is approached via damped oscillations whose frequency and rate of damping can be obtained using standard linear stability analysis. Writing the time dependence of the approach to the equilibrium as $\exp(\Lambda t)$, Λ is found to be the dominant root of the following expression (Hethcote and Tudor, 1980; Lloyd, 1996, 2001a)

$$\Lambda + \mu + \beta I^* - \beta S^* [1 - \{1 + (\Lambda + \mu)/(n\gamma)\}^{-n}] = 0. \quad (2)$$

Detailed analyses of this stability expression show that less dispersed IPDs lead to less rapid damping of the endemic equilibrium compared to the SIR model (Grossman, 1980; Lloyd, 1996, 2001a); the more realistic model is less stable than the exponential model (Fig. 1a). This is exactly in accordance with the conventional wisdom in ecological theory; the less dispersed distribution can be thought of as introducing a delay into the system, and delays are known to often (but not always) destabilise population models.

Numerical simulation of the stochastic model shows that less dispersed IPDs lead to larger stochastic fluctuations around the endemic equilibrium (Lloyd, 1996). This increased variability is confirmed by the analytic techniques mentioned above (Andersson and Britton, 1997, 2000), as illustrated in Fig. 1a which shows the coefficient of variation (standard deviation taken over the realizations divided by their mean) for the number of infectives obtained using the MVN approximation. Notice how the variability about the mean increases as



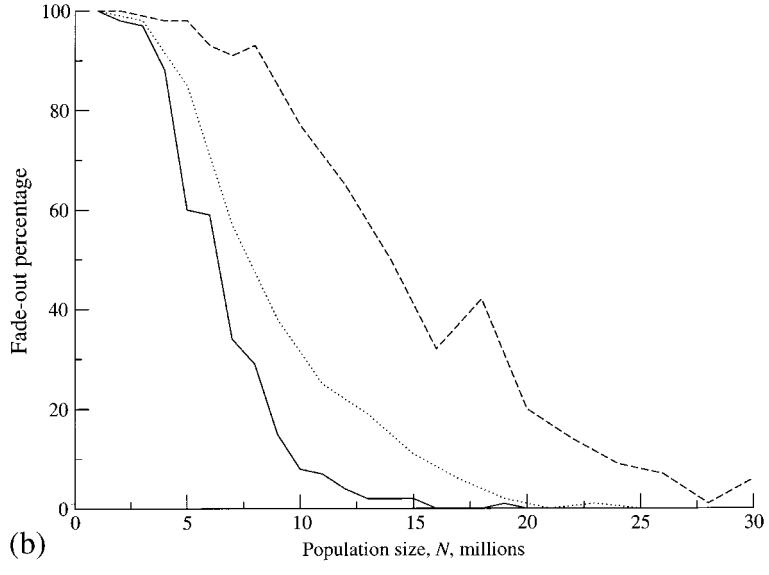


FIG. 1. Increased variability about the equilibrium and decreasing disease persistence with more realistic (less dispersed) distributions of infectious periods in unforced stochastic models. (a) Stability of the endemic equilibrium in the deterministic model, as measured by the damping time (dotted line), as the number of stages, n, varies between 1 and 40. Variability of realizations about the mean of the stochastic model, as measured by the coefficient of variation of the number of infectives (solid line), obtained using the multivariate normal approximation. Model parameters were taken to be: $\beta = 1000/N$ year^{-1} per infective, mean duration of infection $(1/\gamma)$ 3.65 days and $\mu = 0.02$ year^{-1}. R_0 was therefore approximately equal to 10 in these simulations. These parameter values were chosen to be roughly comparable with those generally seen for childhood viral diseases. For the variability estimates, a population size of 100 million individuals was assumed. (b) Disease persistence for the standard (exponential) model, with a single infectious stage (solid line), a 5-stage model (dotted line) and a 50-stage (dashed line) model. All other parameters as in (a). The standard Monte Carlo simulation technique was used to produce 100 realizations for each population size. The fade-out percentage denotes the number of these realizations in which the disease persisted for a period of 10 years after the end of an initial transient period, lasting 30 years, during which immigration of infectives, at a rate of 5 cases per year, was allowed. Error bars for the estimated fade-out percentages are not given, but they could easily be constructed using the standard formula for the exact confidence limits for the estimated probability of success in binomial trials. The absolute level of persistence observed depends both on the measure of persistence employed and on the model parameters used. The very stringent measure of persistence used here leads to apparently lower levels of persistence when compared to many other studies. Similar patterns of persistence are observed when different sets of model parameters are used.

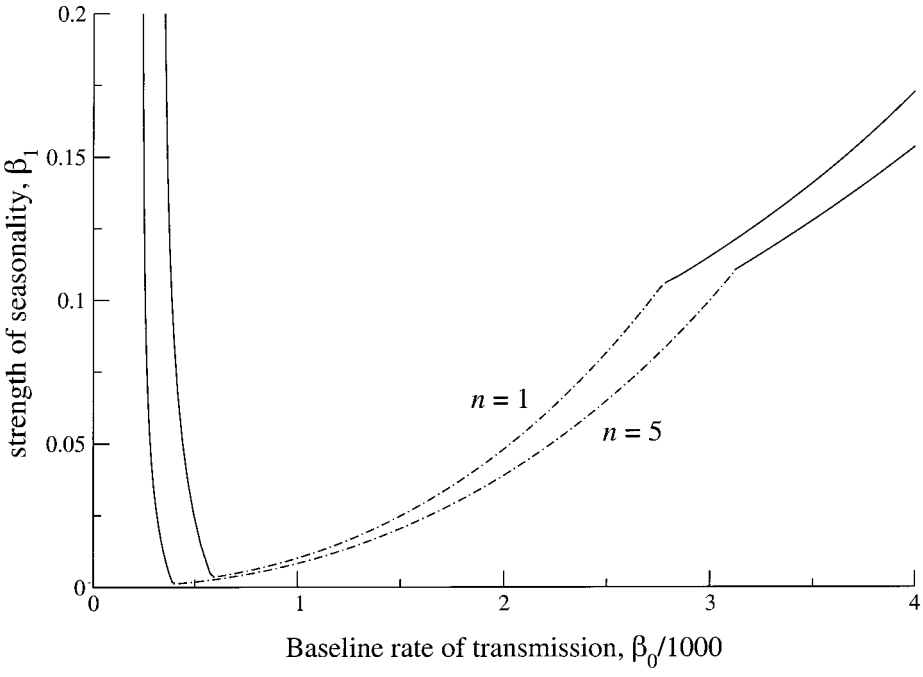


FIG. 2. Lower levels of seasonality are required to achieve biennial oscillations in more realistic models. The curves show the strength of seasonality (β_1) at which period two cycles first appear in the standard model (upper curve) and in a model with 5 stages (lower curve). As discussed in the text, there are two mechanisms by which biennial cycles appear, the line-type denotes which of these is responsible for the their first appearance: the solid curve denotes the period doubling bifurcation and the dot–dashed denotes the tangent bifurcation. All other parameter values are as for Fig. 1.

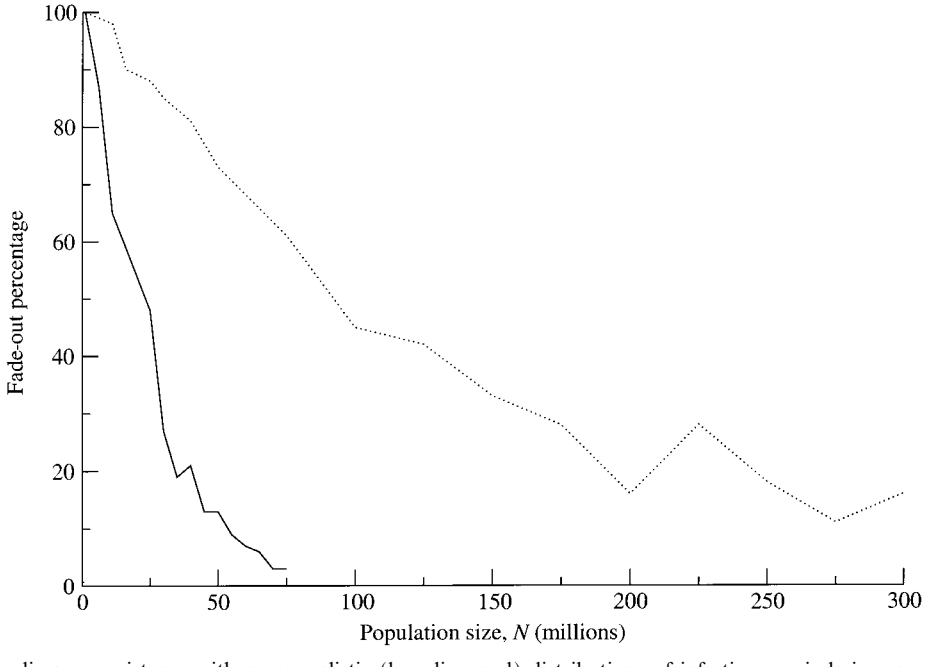


FIG. 3. Decreasing disease persistence with more realistic (less dispersed) distributions of infectious periods in seasonally forced stochastic models. Results are presented for the standard (exponential) model, with a single infectious stage (solid line) and a 5-stage model (dotted line). Models with more stages show even lower levels of persistence (results not shown). The baseline transmission parameter, β_0, was taken to be $350/N$, which is to the left of the minimum point of the $n = 1$ curve on Fig. 2, and the strength of seasonality is taken to be $\beta_1 = 0.03$. Immigration during the transient period was taken to be five cases per year per million individuals in the population. The standard Monte Carlo simulation technique was used to generate 100 realizations of the model at each population size. All other details and parameters were the same as for Fig. 1. Similar results were obtained for different strengths of seasonal forcing and with different baseline transmission parameters (results not shown).

the stability of the endemic equilibrium decreases, as argued above. (The equations underlying these calculations are not given here, but for further details of the multivariate normal approximation in SIR-type models for recurrent epidemics, see Lloyd, 2001b.) As a consequence of this increased variability, the CCS is greater in the more realistic model (Fig. 1b). Inclusion of realistic IPDs leads to an increase in predicted CCS, as supported by the arguments based on ecological theory outlined above.

Model with Seasonal Forcing

Whilst the above discussion mirrors Bartlett's original approach to the question of persistence, it neglects the impact of seasonal forcing, which must be addressed in any serious attempt to predict the CCS. Seasonality is incorporated by allowing the transmission parameter, β, to vary over the course of a year. Many forms have been suggested for this term, ranging from a simple sinusoid (Dietz, 1976) to more complex functions which mimic schools opening and closing with terms and vacations (Schenzle, 1984; Bolker and Grenfell, 1993). We take the simplest possible form, $\beta(t) = \beta_0(1 + \beta_1 \cos 2\pi t)$, which has been widely used in studies of the dynamics of epidemic models. The parameter β_0 is the baseline transmission parameter, and β_1 measures the strength of seasonal variation in transmission.

Seasonality leads to the maintenance of recurrent epidemics in the model. Weak levels of seasonality result in annual oscillations but multi-annual oscillations, such as biennial cycles, are seen with strengthening seasonality. Much attention has been given to the mechanisms by which such cycles arise, such as the period doubling bifurcation (Aron and Schwartz, 1984) and the tangent bifurcation (Schwartz and Smith, 1983; Kuznetsov and Piccardi, 1994).

As in the unforced model, the dynamical effect of the introduction of more realistic IPDs is to destabilize the model (Lloyd, 2001a). Keeping other parameters fixed, lower levels of seasonality are required to achieve biennial oscillations in the more realistic model (Fig. 2.). Notice in particular the steepness of the curves on the left-hand side of this figure, demonstrating how much stronger seasonality may need to be in order to obtain biennial cycles in the standard model compared to more realistic models. For instance, when $\beta_0 = 350/N$, a β_1 value of 0.207 is needed to obtain biennial cycles in the standard model, compared to just 0.011 in the more realistic model with $n = 5$. In a similar way, more complex dynamical behaviours, such as chaos, which are well known to exist for higher levels of seasonality in the basic model (Olsen and Schaffer, 1990), are seen with much weaker forcing in the realistic model (Lloyd, 2001a).

In the seasonally forced stochastic model, realistic distributions are again seen to increase the critical community size (Fig. 3). In this case there is a twofold effect of such distributions: not only is there increased variability about the mean, as seen in the unforced model, but there is also a deepening of the interepidemic troughs, as a consequence of the destabilization of the dynamics. Notice that the differences in persistence between different models are much greater than in the unforced case, bearing witness to this twofold effect.

DISCUSSION

These results are in sharp contrast with those of Keeling and Grenfell (1997, 1998—hereafter referred to as K&G), who observe that the use of more realistic IPDs increases model persistence in simulations of their epidemic model. They support this observation with a general argument and suggest that their result should be fairly general. The results presented here show that the increased persistence is, in fact, not general. The discussion which follows is an attempt to resolve the conflict between these two studies. We shall first argue that the K&G reasoning which led to the claimed generality overlooks an important issue which can lead to decreased persistence in many cases. We then suggest reasons why K&G saw increased persistence in their simulations, highlighting both the more intricate behaviour seen in more complex models and an important difference between the methodologies of their and our studies.

The argument of K&G is based upon the observation, previously made by Malice and Kryscio (1989), that the chance of an individual recovering before passing on the disease is reduced when more realistic IPDs are used. Consequently, the chance that the chain of transmission will be interrupted under these conditions is lower in more realistic models. Whilst this argument correctly addresses the question of disease invasion and initial epidemic behaviour (with the chance of an epidemic occurring, and its initial rate of increase, being higher in models which employ more realistic IPDs (Anderson and Watson, 1980; Malice and Kryscio, 1989; Lloyd, 1996)), it cannot be used to address the general issue of persistence. Even if this mechanism leads to increased persistence through a single interepidemic trough, the use of realistic IPDs increases variability and hence the frequency of episodes in which the number of infectives

falls to low levels—an effect not considered in the analysis of K&G. Our simulations suggest that the effect K&G describe is often not sufficient to overcome the increased chance of fade-out resulting from the destabilization observed with the more realistic model. Of course, the magnitude of the destabilization we describe is dependent on model parameters, leaving open the possibility that parameter regimes might exist in which the K&G effect dominates over the destabilization, and for which the K&G result would hold.

The model of K&G is much more complex than those presented here, as it includes, amongst other biological details, age structure, term-based seasonal forcing and an "exposed" class, corresponding to latently infected individuals who have been infected with the disease but are not yet infectious. Models which include an exposed class are known as SEIR models. Whilst such models are outside the scope of this study, the inclusion of a latent class can have important consequences for disease persistence, so we shall comment briefly on their effects. The inclusion of an exposed class increases the generation time (defined here as the time between initial infection and recovery). This means that the total number of people who are infectious or who will become infectious (i.e., the number of individuals either in the exposed or infectious class) is greater than in the SIR model, and hence leads to an increase in disease persistence. Another effect of the inclusion of an exposed class is that the variability in the generation time is lower in an SEIR model than in an SIR model with the same duration of infectiousness (see Appendix for more details).

Results both from numerical simulations and analytic studies of unforced SEIR models show that their response to changing distributions of exposed and infectious periods is more complex than we observed in the SIR case (Lloyd, 2001a). For diseases with short latent periods, the SEIR model is well approximated by the corresponding SIR model, and so the results described above immediately carry over. For diseases with longer latent periods, the changes in stability and variability about the endemic equilibrium are smaller, probably due to the reduced variability in generation time, and the patterns of these changes are not as clear cut (see also Andersson and Britton, 2000). In agreement with these observations, numerical simulations of the unforced model suggest that we are more likely to obtain the K&G result of increased persistence within an SEIR framework, particularly if the latent period is long compared to the infectious period (see Appendix). The inclusion of seasonality, however, again leads to considerable destabilization of the dynamical behaviour (Lloyd, 2001a), and consequently we still see decreased persistence with the inclusion of realistic distributions in seasonally forced SEIR models (see Appendix).

Whenever two models are compared, we must consider the nature of the comparison being made. For instance, in the case of comparing SIR and SEIR models just discussed, it can be argued that a fairer comparison would be between SIR and SEIR models with the same generation time. A general issue is how parameter values are allowed to differ between the models being compared. In our comparisons, models only differ in the variance of their IPDs. All other epidemiological and demographic parameters remain fixed, corresponding to the notion that they can be independently estimated from available data, as discussed earlier. Since the aim of the K&G study was to model the persistence and dynamics corresponding to a specific incidence record, they chose to tune the parameters so that each model achieved a good fit to the historical incidence record, and consequently the comparison made in K&G is not the same as that made here. Since quite different dynamics can result from changing just the IPD in seasonally forced models (Fig. 2), we would not be surprised to see quite different parameter estimates emerging if different models were fitted to the same data, and so it is quite likely that this plays a part in the observed differences. (Unfortunately, the sets of parameter values are not given in Keeling and Grenfell, 1997, and so it is impossible for us to assess exactly how important this effect was in their simulations.) Apart from the issues raised earlier concerning the increased confidence we can place in models when their parameters are estimated independently of the incidence record to be modelled, we suggest that changing several features of the model at once (infectious period distribution and many model parameters) makes it more difficult to identify the causal mechanisms responsible for the changing patterns of persistence.

Within our SIR framework, we have so far only found one way in which persistence can increase with the inclusion of more realistic IPDs, and this is merely as an artefact of the Poisson variate simulation technique. The use of the stage device to represent the infectious class introduces a much shorter time-scale into the model: the average time spent in each stage is $1/n$ of the average duration of infection. Simulation step lengths appropriate for the basic model may not be appropriate for the more realistic model, because the coarse-graining effect leads to the average simulation time spent in the infectious class being longer than the nominal average duration of infection, reducing the chance of fade-out (Fig. 4). This problem is most acute for the least dispersed IPDs.

The inclusion of realistic IPDs destabilizes SIR-type epidemic models, decreasing persistence and increasing

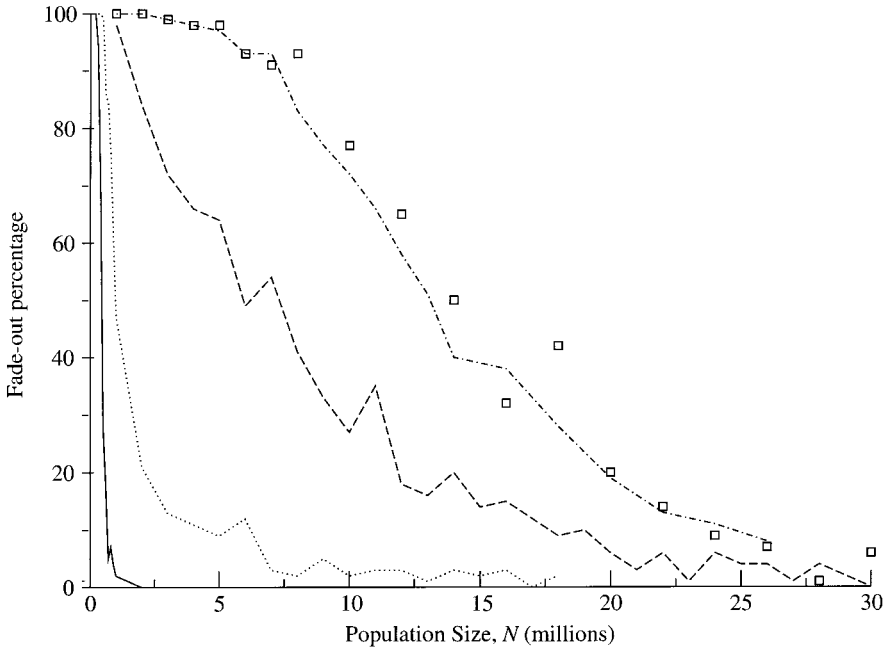


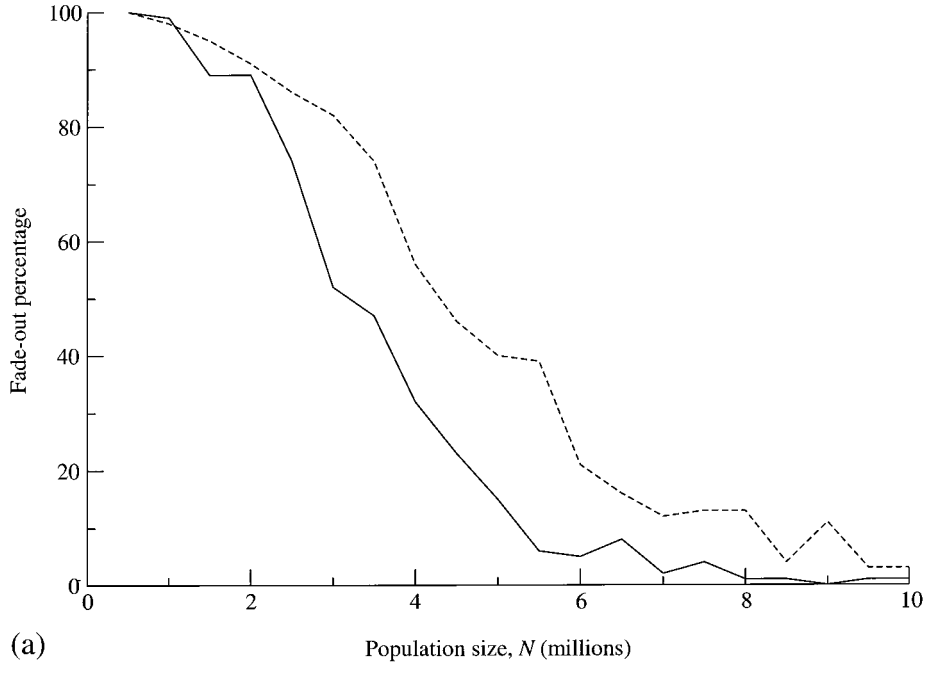
FIG. 4. Apparent changes in persistence with changing step length when using the Poisson variate technique to simulate the 50-stage unforced model presented in Fig. 1. Curves shown used the following step lengths: 0.0365 days (solid curve), 0.01825 days (dotted curve), 0.009125 days (dashed curve), and 0.000365 days (dot–dashed curve). For comparison, the average duration of infection was supposed to be 3.65 days, and the average time spent in each of the 50 stages was therefore supposed to be 0.073 days.

Squares denote the results obtained using the standard Monte Carlo simulation technique. Simulations were also carried out for a step length of 0.00365 days; these results are very close to those obtained for 0.000365 days and the Monte Carlo technique, and are not shown for clarity. All parameters were the same as for Fig. 1. The apparent differences in persistence arise as a result of the coarse-graining effect discussed in the text. Whilst all of the step lengths are short compared to the average duration of infection, 3.65 days, the average time spent in each of the 50 stages is only 0.073 days. Use of the calculation method outlined in the text shows that for the longest step length employed here, the expected simulation time spent in the infectious class is 4.64 days for this model. Consequently, the chance of fade-out is reduced. To illustrate that this problem is most acute for the least dispersed IPDs, use of this step length in the basic model leads to a true average duration of infection of 3.67 days, and of 3.74 days in a model with 5 stages. These calculations are in agreement with simulation results (not shown) which demonstrate that increasing h has a much smaller impact on simulations of the basic model.

the predicted CCS, exactly in agreement with simple arguments based upon ecological theory. Interestingly, it appears that Bartlett realised that the inclusion of a more realistic IPD would increase the CCS predicted by his model. He writes (Bartlett, 1957):

> It is probable that the simplification of a continuous removal rate of invectives tends to favour persistence, partly owing to the increased deterministic damping to an equilibrium level.

As the epidemiological data suggests that infectious periods are poorly described by exponential distributions, the use of an exponential IPD in any particular situation must be justified by demonstrating that its use has little effect on the model being studied. This study suggests that the deployment of more realistic IPDs has a major impact both on the dynamical and persistence properties of SIR-type epidemiological models. Regarding the dynamical properties, the destabilization of the dynamics observed here shows that complex dynamics can be generated using levels of seasonal forcing weaker than previously thought to be required, answering one of the major criticisms directed towards those who advocate the importance of complex dynamics in the incidence of childhood disease (Olsen and Schaffer, 1990; Bolker and Grenfell, 1993). The decreasing levels of persistence pose a greater problem to modellers, however. One of the greatest weaknesses of existing models for childhood diseases is their inability to reproduce realistic patterns of persistence. This study suggests that this may be even more of a problem once realistic IPDs are taken into account. This highlights the need for epidemiologists to gain a better understanding of mechanisms which enhance persistence, such as spatial structure within



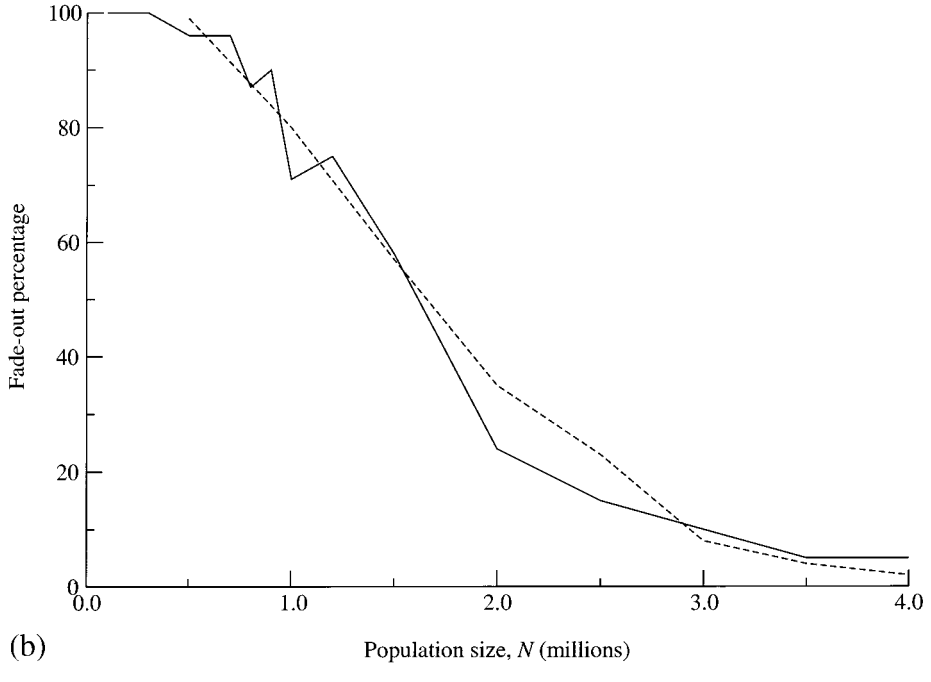


FIG. 5. Changing patterns of persistence in nonseasonal SEIR models. In each case, the solid line represents the behaviour of the standard SEIR model, with exponentially distributed latent and infectious periods, and the dashed line represents that of a more realistic SEIR model with latent and infectious periods described by 5-stage gamma distributions: (a) short-lived latency, $\sigma = 250$ year^{-1}, (b) latent period equal to the infectious period, $\sigma = 100$ year^{-1}, and (c) long-lived latency, $\sigma = 35.842$ year^{-1}. Other parameters: $\beta_0 = 1000/N$ year^{-1} per infective, $\gamma = 100$ year^{-1} and $\mu = 0.02$ year^{-1}. In each case, the Poisson variate simulation technique, with step length 0.00365 days, was used to generate realizations of the model.

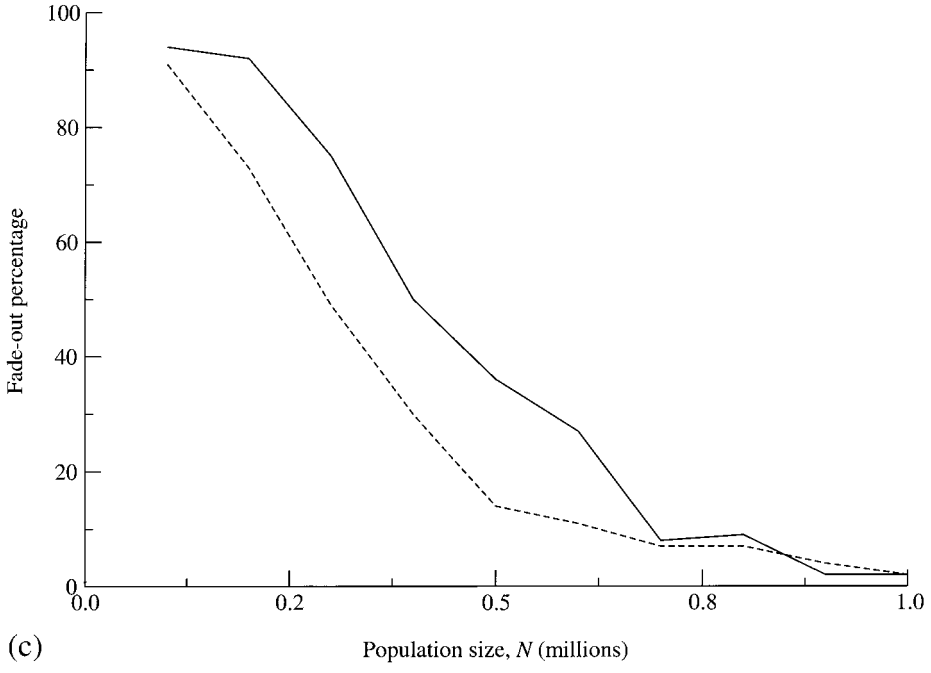


FIG. 5—*Continued*

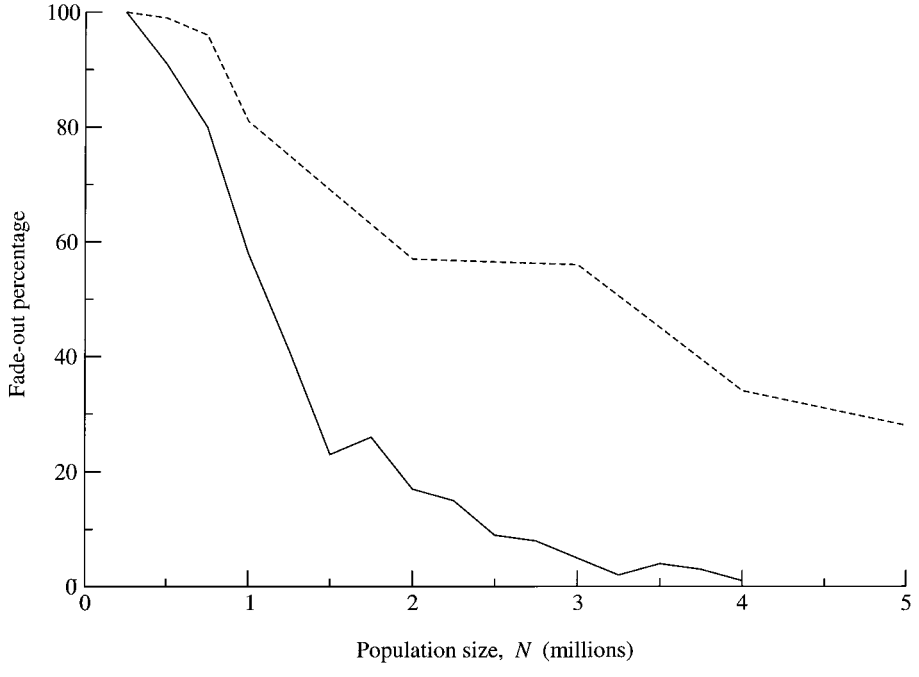


FIG. 6. Changing pattern of persistence in a seasonally forced SEIR model. The solid line represents the behaviour of the standard SEIR model, with exponentially distributed latent and infectious periods, and the dashed line represents that of a more realistic SEIR model with latent and infectious periods described by 5-stage gamma distributions. Model parameters: $\beta_0 = 2000/N$ year^{-1} per infective, $\beta_1 = 0.16$, $\sigma = 35.842$ year^{-1}, $\gamma = 100$ year^{-1} and $\mu = 0.02$ year^{-1}. In each case, the Poisson variate simulation technique, with step length 0.00365 days, was used to generate realizations of the model. Notice that the average latent period is roughly three times the average duration of infectiousness.

epidemics. More generally, the important consequences of an apparently trivial assumption (of the kind routinely made throughout mathematical biology) on the issues of persistence and dynamics, which lie at the centre of most mathematical studies in population biology, should serve as an important lesson for the wider modelling community.

APPENDIX

Persistence Properties of SEIR Models

A latent class of individuals can easily been included with the basic model framework outlined above by allowing newly infected individuals to enter the exposed class, where they remain for an average of $1/\sigma$ time units before moving into the infectious class. In the standard SEIR model, it is assumed that the duration of latency is exponentially distributed and so, if the number of exposed individuals is E, the movement of individuals between the latent and infectious class occurs at rate σE. More general distributions of latent periods can be considered by use of the stage device. See Lloyd (2001a) for further details.

As mentioned above, the generation time in SEIR models is less variable than in SIR models with the same infectious period. As an example, take the simplest SEIR model in which both infectious and latent periods are described by exponential distributions. The generation time is described by the sum of two exponential distributions, which has a variability lower than the single exponential distribution of the corresponding SIR model.

Figure 5 illustrates the changing patterns of persistence seen in the basic SEIR model (which has exponentially distributed latent and infectious periods) and in an SEIR model with 5 stage gamma distributions for both the infectious and latent periods. With short-lived latency (i.e., large values of σ), the persistence patterns are similar to those described for the SIR model, with more realistic distributions of infectious and latent periods leading to decreased persistence (Fig. 5a). For longer latent periods, the differences in persistence are negligible (Fig. 5b), whilst for the longest latent periods, persistence is actually increased in the more realistic model (Fig. 5c).

Even in cases for which the unforced model shows an increase in persistence with the inclusion of realistic distributions of infectious and latent periods, the further destabilization which occurs with the inclusion of a seasonally varying contact rate can lead to decreasing persistence with realistic IPDs. Figure 6 illustrates this phenomenon in a model for which the latent period is roughly three times the length of the infectious period, and for which the corresponding unforced model exhibits the persistence pattern predicted by Keeling and Grenfell (1997, 1998).

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