THEORETICAL POPULATION BIOLOGY 40, 322–353 (1991)

Disease in Changing Populations: Growth and Disequilibrium

SHRIPAD TULJAPURKAR

Biological Sciences, Stanford University, Stanford, California

AND

A. MEREDITH JOHN

Office of Population Research, Princeton University, Princeton, New Jersey

Received December 29, 1989

This paper examines simple age-structured models of childhood disease epidemiology, focusing on nonstationary populations which characterize LDCs. An age-structured model of childhood disease epidemiology for nonstationary populations is formulated which incorporates explicit scaling assumptions with respect both to time and to population density. The static equilibrium properties and the dynamic local stability of the model are analyzed, as are the effects of random variability due to fluctuations in demographic structure. We determine the consequences of population growth rate for: the critical level of immunization needed to eradicate an endemic disease, the transient epidemic period, the return time which measures the stability of departures from epidemiological equilibrium, and the power spectrum of epidemiological fluctuations and combined demographic–epidemiological fluctuations. Growing populations are found to be significantly different from stationary ones in each of these characteristics. The policy implications of these findings are discussed.

1. INTRODUCTION

The impact of many childhood diseases is especially great in less-developed countries (LDCs). This paper examines simple age-structured models of childhood disease epidemiology, focusing on nonstationary populations which characterize LDCs. There is a considerable amount of literature on age-structured epidemic models (see e.g., Anderson and May, 1983, 1985), most of which deals with stationary host populations. When the size and structure of the human host population are changing over time, however, three key questions arise. First, how does the probability of

transmission of infection change with population size? Second, how do dynamic quantities (such as the period of damped oscillation in the percentage of infected individuals) and static quantities (such as the minimum immunization fraction for eradication of disease) change with population growth rate? Third, how does demographic disequilibrium (produced, for example, by varying fertility rates) affect the temporal pattern of disease prevalence? This paper answers these questions for a class of models which are particularly relevant to the situation in LDCs.

We begin by discussing issues of scale which underly the construction of transmission rates, and formulate a model which incorporates explicit scaling assumptions with respect both to time and to population density. In appropriate limiting cases our model reduces to the constant population model of Dietz (1975) and the more general models of Dietz (1982), and McLean (1986). We then analyze the equilibria and local dynamic stability of our model in the presence of an immunization program, assuming that the human population is at a stable age distribution. This analysis reveals the dependence of critical immunization levels, disease periodicity, and related epidemiological features on population growth rate. Finally we show how demographic disequilibrium (i.e., a nonstable age distribution) and epidemiological disequilibrium jointly damp out over time. This last analysis provides the novel insight that purely demographic variability (in vital rates) can lead to sustained epidemiological cycles. Throughout the paper we address the relationship of our analysis to practical issues of data analysis and policy. We show that population growth can significantly change some rules-of-thumb about immunization program design which have been derived for stationary populations.

The evolution of our model has been influenced by several previous studies. Dietz (1975, 1982) established the form and many basic properties of the class of models from which our model derives. May and Anderson (1985) explored the catalytic model of disease transmission in an exponentially growing population. McLean (1986) discussed the static properties of a related but different catalytic model, and presented some simulations of its dynamics. McLean and Anderson (1988a, b) applied a model with age-specific transmission to data from various LDCs, presenting a variety of parameter estimates and discussing epidemiological lessons from the theory. John (1989a) constructed and analyzed a simulation model which showed that demographic characteristics of the human population can have substantial effect on the transmission of disease. John (1989b) discussed the static properties of a formal model essentially similar to the one we use here, and presented extensive numerical results on the joint dynamics of demographic and epidemiological variables. Greenhalgh (1988) detailed the dynamical stability analysis of catalytic models assuming demographic stationarity.

2. Infection: A Question of Density

Models of disease transmission usually count the numbers X of susceptible individuals and Y of infected and infective individuals. A key ingredient in the models is the transmission rate at which infectives cause infections; the classical catalytic transmission rate of creation of new infections is βXY, where β is a constant, and βY is the force of infection. This catalytic rate of infection is problematic when applied to a growing population, because it scales as the square of the total number. The problem is nicely illustrated by May and Anderson (1985), who study the effect of the catalytic rate in an exponentially growing population. They show formally that since the force of infection must also grow exponentially, susceptibles are eventually swept into the infected pool almost instantly after birth. As May and Anderson point out, this is an extreme situation.

A different approach is to divide Y by total population N to get the infected fraction y, and then write the rate of infection as $\beta(N)\,Xy$. Anderson (1982) uses some indirect evidence to argue that $\beta(N)$ scales as N^c with values of $c \sim 0.05$. However even with this scaling, β will grow exponentially fast if N does. Dietz (1982) suggests a saturating form,

$$\beta(N) = \frac{\beta_0 \beta_\infty N}{\beta_0 N + \beta_\infty},$$

which reaches a finite limit when N grows exponentially to large values. McLean (1986) takes β to be a constant independent of N. These last two formulations do not diverge exponentially when N does, but it is useful to formulate biological criteria to distinguish them.

What are the basic criteria for the definition of a transmission rate? First, the time-scale of analysis is important. It is common practice in biology and applied mathematics to approximate a discrete process by a continuous one which applies to an appropriately scaled time variable. Thus in formulating a model we begin with rates for events that occur over some suitable small time interval, and then construct continuous-time differential equations from these rates. The continuous equations of the model are accurate descriptions only on an appropriately coarse-grained time-scale. They will not describe accurately events that occur within the duration of the basic small time interval (hence the term coarse-grained). In the study of most childhood diseases we do not expect our models to describe accurately what happens within very short time intervals, say times less than a single day. Therefore formulations of rates which lump together events occurring over periods less than the minimum time interval can appropriately be used on a coarse time-scale. Such coarse-grained formulations can include the effects of multiple contacts and inhomogeneous

mixing, resulting in nonlinear transmission rates, as in our model below (for other examples see Liu *et al.*, 1986, 1987). If the model is formulated in terms of infinitesimal intervals whose length strictly goes to zero, a catalytic transmission rate is probably necessary. However, it would then be necessary to change the structure of the model to incorporate the dynamics of multiple events and heterogeneity.

Second, the transmission rate must include both the number of contacts that occur between individuals and the effectiveness of contacts in transferring infection. There is evidence that both rate and effectiveness are functions of the spatial density of the population that is characteristic of the community under study. As noted by Black (1962, pp. 248–249):

> The well-known difference between urban and rural areas in the age when infection ... occurs can be clearly demonstrated ... it may be in these densely populated cities, individual households become less important and tend, in an epidemiological sense, to fuse into one superunit. Thus, the one factor that has been found to correlate with the difference in ... [transmission] rates is the density of susceptibles. This density may be important both at the level of the household and also at the level of the community. It doubtless has its effect through control of the number and range of contacts between susceptibles and of the frequence of opportunity for spread of the disease.

Thus we argue that for a given living unit (e.g., village, city) the transmission rate depends primarily on the local spatial density of people. In addition, for many living units (urban and rural) in both more and less developed countries the spatial density changes on a time-scale much slower than do the disease dynamics of interest, so that we may take these densities to be constant over the time periods of interest in our analysis.

In light of these criteria, we adopt a general model for the force of infection used by John (1989a, b). Over our basic time unit of 1 day, which is the smallest time interval in our description (see Appendix), a susceptible will encounter, on average, m people. Of these, a fraction y are infective, and we define the probability e that contact with an infective results in successful transmission of infection. Then, instead of a catalytic term like βy, the basic force of infection equals the probability that at least one contact produces an infection, which is given by the function

$$g(y) = 1 - [1 - e(D)\, y]^{m(D)}. \tag{1}$$

We expect that $m(D)$ and $e(D)$ will be functions of the population spatial density D of the community of interest; $m(D)$ and $e(D)$ are implicitly dimensionless functions of the basic time unit. In practice we might expect m to be a random variable, because of the variation between individuals in behavior and patterns of contact. Then the probability g in Eq. (1) would

have to be replaced by an average of the nonlinear function on the right-side of (1), taken over the distribution of m. In the appendix we show that this average is well approximated by the function itself, for the typical range of dynamic variables relevant to the diseases we model.

There are two important scaling properties of Eq. (1). The first relates to population spatial density D; as D gets large we expect that $m \propto D^p$ and $e \propto D^{-q}$, with $p > 0$ and $q > 0$. For large m and small e, Eq. (1) is well approximated by the linear catalytic form mey. Using this form in place of the standard catalytic term, we can deduce the behavior of the scaling exponents, p and q, from analyses which relate the coefficient β of the standard catalytic form to community size. Anderson's (1982) analysis suggests a density scaling in which $(p-q)$ is small, of the order of 0.05. Dietz's theoretical saturating catalytic form, written above, leads at high population densities to the scaling $p=1$, $q=1$. It is possible that the scaling exponents are very different in low-density communities, with $p \gg q$, but there is little evidence to guide one's choice.

In this paper Eq. (1) is intended to apply to the urban population of a country on the assumption that the spatial density in all urban areas is not dissimilar. In light of the discussion above, the scaling regime relevant to such a high-density setting is one where $m \propto D$, and $e \propto (1/D)$, so that our canonical case has e proportional to $(1/m)$. We have explored alternative density scalings which may be more relevant in lower density communities, such as villages, and we present illustrative results for the case $e \propto m^{-1/2}$. Our qualitative findings about the consequences of population growth are robust to the choice of spatial scaling, although some of our quantitative results are sensitive to scaling.

The force of infection in Eq. (1) is affected by time-scaling, which happens when the basic minimum time interval of the analysis (in this study, 1 day) is increased or decreased. Our function in Eq. (1) can be scaled to reflect longer intervals by changing m and e, but is not invariant to a shortening of this interval. Given the wide use of the catalytic force of infection, it is worth noting that if we set $m=1$, Eq. (1) reduces to the catalytic form ey. In a general catalytic form, βy, the coefficient β can be larger than 1, whereas e, a probability, is less than 1. However, estimates of β for childhood diseases such as measles are much smaller than 1, so that our model remains analytically sensible even for $m=1$.

3. The Model

We consider a population in which the number of individuals between ages a and $a+da$ is denoted by $N(a, t)\,da$; these individuals can be further

classified as susceptible, $X(a, t)\,da$; infected and infective, $Y(a, t)\,da$; and recovered and immune, $Z(a, t)\,da$. The model is described by two non-independent systems of equations, one describing the dynamics of the host population, and the other describing the dynamics of disease transmission (John, 1989a, b). The dynamics of the host population are described by

$$\begin{aligned} \partial_t N(a, t) + \partial_a N(a, t) &= -\mu(a)\, N(a, t) \\ N(0, t) &= \int_0^\infty f(a)\, N(a, t)\, da \\ \partial_t &= \partial/\partial t,\ \partial_a = \partial/\partial a, \end{aligned} \tag{2}$$

where $\mu(a)$ is the age-specific death rate and $f(a)$ is the age-specific fertility rate.

The second system of equations describes the disease dynamics,

$$\begin{aligned} \partial_t X(a, t) + \partial_a X(a, t) &= -\mu(a)\, X(a, t) - \lambda(a)\, X(a, t) - \theta(a)\, X(a, t) \\ \partial_t Y(a, t) + \partial_a Y(a, t) &= \lambda(a)\, X(a, t) - \mu(a)\, Y(a, t) - \gamma Y(a, t) \\ \partial_t Z(a, t) + \partial_a Z(a, t) &= \theta(a)\, X(a, t) + \gamma Y(a, t) - \mu(a)\, Z(a, t) \\ X(0, t) &= N(0, t) \\ Y(0, t) &= 0 = Z(0, t), \end{aligned} \tag{3}$$

where $\theta(a)$ is the age-specific force of immunization, and γ is the rate at which infected individuals recover. In Eq. (3), the force of infection is given by the function

$$\lambda(t) = g(y(t)) = 1 - [1 - ey(t)]^m, \tag{4}$$

where the proportion of infective individuals is

$$y(t) = \frac{\int_0^\infty Y(a, t)\, da}{\int_0^\infty N(a, t)\, da}. \tag{5}$$

These equations identify states of demographic and epidemiologic equilibrium. Demographic equilibrium is defined as a steady state of exponential growth where

$$N(t) = \int_0^\infty N(a, t)\, da = Q_0 e^{rt} \tag{6}$$

with the host population's growth rate, r, defined according to classical demography (Coale, 1972; Lotka, 1931) and the constant Q_0 determined by the initial population structure at time $t = 0$ (see Appendix). In

demographic equilibrium, the population has a stable age distribution, so that

$$N(a, t) = c(a)\, N(t) \tag{7}$$

with

$$c(a) = \frac{l(a)\, e^{-ra}}{\tau_0}, \tag{8}$$

where

$$l(a) = e^{-\int_0^a \mu(z)\, dz}, \qquad \tau_0 = \int_0^\infty l(a)\, e^{-ra}\, da, \tag{9}$$

and $\int_0^\infty c(a)\, da = 1$. Finally, the per capita birth rate at demographic equilibrium is given by

$$b = \frac{N(0, t)}{N(t)} = \frac{1}{\tau_0}. \tag{10}$$

In this system, epidemiological equilibrium is defined as the state in which the ratios $x(a, t) = X(a, t)/N(a, t)$, $y(a, t) = Y(a, t)/N(a, t)$ and $z(a, t) = Z(a, t)/N(a, t)$ are constant in time. Epidemiological equilibrium implies that the force of infection, $\lambda(t)$, is constant in time. However, the force of infection can be constant only under conditions of demographic equilibrium; thus *demographic equilibrium is a necessary condition for epidemiological equilibrium.*

In the rest of this paper we assume a constant (Type II) mortality schedule,

$$\mu(a) = \mu > 0 \qquad \text{for all } a, \tag{11}$$

and an age-independent immunization rate

$$\theta(a) = \theta \geqslant 0 \qquad \text{for all } a. \tag{12}$$

The mortality function given in Eq. (11) may be replaced with the alternative extreme assumption of no mortality up to an age L of certain death; there is little change in our results so long as L is large ($\geqslant \sim 70$ years). Both these stylized mortality functions ignore the well-documented difference between the high death rate at early ages (less than 5 years) and the somewhat lower death rates of adults. John (1989a) demonstrated that there are significant differences in the age pattern of epidimiologic behavior among populations with different age patterns of vital rates. However, our focus is on aggregate epidemiological measures as a function of host

population demography, so we will ignore realistic age patterns of mortality. On the other hand, our results are sensitive to the assumed age pattern of immunization and will change if, for example, all vaccinations are done at birth. Although many models assume that immunization occurs at a precise target age (such as 9 months or 15 months), we have found that in developing countries, despite a narrow target range of ages at immunization, actual ages at immunization among children are quite widely distributed (John and Tuljapurkar, 1990). This dispersion in achieved age at immunization reflects variation in the supply of immunization services and parental demand. Our assumption (12) is a simple approximation to this dispersed delivery of immunizations characteristic of LDCs.

4. Epidemiology with Demographic Equilibrium

4.1. *Basic Equations*

Given that the population has reached demographic equilibrium described by Eqs. (6)–(10), the dynamics of the model are captured by the behavior of the proportion of susceptibles $x(t) = (\int_0^\infty X(a, t)\, da)/N(t)$, and of infectives, $y(t)$. Using Eq. (11) and Eq. (12), it is shown in the Appendix that $x(t)$ and $y(t)$ follow the simpler differential equations

$$\begin{aligned} d_t x &= b - (r + \mu + \theta + \lambda(t))\, x \\ d_t y &= \lambda(t)\, x - (r + \mu + \gamma)\, y \\ d_t &= d/dt, \end{aligned} \tag{13}$$

where the force of infection, $\lambda(t)$, is defined by Eq. (4). The proportion $z(t)$ of recovered individuals follows from $x(t)$ and $y(t)$, since $x(t) + y(t) + z(t) = 1$. Given solutions to Eq. (13), the age distribution of susceptibles and infectives can be obtained using Eq. (3). Thus the pair of Eqs. (13) describes the dynamics of the epidemiologic system.

The discussion below focuses on the case in which the population-density scaling of the parameters m and e is such that the product me is constant. The numerical results we report are for $m = 10$, and are representative of those for m between 1 and 10. The value of e depends on the density scaling of parameters in the force of infection, Eq. (1). Each figure presented in this paper has an upper panel describing results for the case where $me = 0.95$ is constant, and a lower panel describes corresponding results for the case $m^{1/2}e = 0.95$. Values of the other parameters used in the numerical work are consistent with the observed values typical of measles: μ is chosen to give a life expectancy at birth of 70 years, the recovery rate γ is chosen to give

a mean time to recovery of 14 days. Throughout the numerical analysis, we use the basic time unit of 1 day. Sensitivity analyses, varying these parameter values by amounts within the range of observed values, revealed no significant changes in our conclusions. We consider population growth rates ranging from 0 to 4% per year, which span the range of current (national) population growth rates worldwide. The daily force of immunization, θ, varies as indicated in the text.

4.2. *Disease-Free Equilibrium*

Equilibrium with no disease present, when $y^* = y(t) = 0$ for all t, corresponds to a force of infection $\lambda^* = 0$, and a proportion of total population which is susceptible $x^* = b/(r + \mu + \theta)$. With the simple mortality schedule assumed here (Eq. (11)), $b = \mu + r$, and so $x^* < 1$ in the presence of immunization. The stability of this equilibrium determines whether the introduction of a very small proportion of infectives will initially result in an increase in the prevalence of disease. It is shown in the Appendix that the disease-free equilibrium is stable if the quantity

$$\rho = \frac{b[dg/dy]_{y=0}}{(r+\mu+\theta)(r+\mu+\gamma)} = \frac{meb}{(r+\mu+\theta)(r+\mu+\gamma)} \tag{14}$$

is less than 1 and unstable if $\rho > 1$.

The properties of ρ have considerable epidemiological significance. First, note that ρ is proportional to the product me, and thus scales in the same way as me with population spatial density. Thus, there should be a correlation between the spatial density of living units and the historical record of successful invasions by disease. We would expect invasion by disease to be harder in low-density communities, such as villages in LDCs.

Second, there is a major difference between the effect of population growth rate on ρ in virgin (i.e., no immunization) disease-free communities and in disease-free communities with an ongoing immunization program. When a community has had no immunization ($\theta = 0$), it follows from an expansion of the denominator in Eq. (14) that ρ decreases approximately linearly with host population growth rate, r (for small r, say a few percent per year). On the other hand, when a community has an ongoing vaccination program, Eq. (14) shows that ρ *increases* linearly with r. This surprising difference is derived analytically in the Appendix and illustrated in Fig. 1. Observe that the slope of ρ vs r for the two kinds of communities differs not only in sign but also greatly in magnitude. We thus have the potentially important result that in a disease-free community with some level of ongoing vaccination, invasion becomes easier as the host population growth rate increases. In contrast increased growth rate has very little effect on the ability of infection to invade a virgin community.

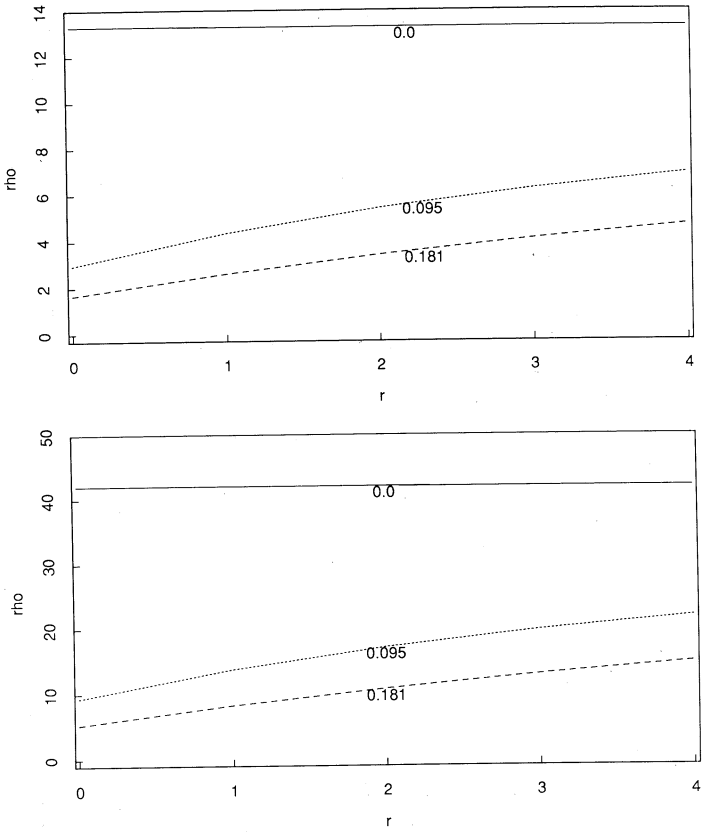

FIG. 1. Values of ρ from text Eq. (14) for increasing population growth rates in percentage per year. The curves are labeled with the annual force of immunization. Top panel: the contact probability parameter scales as the inverse of the contact number parameter. Bottom panel: the contact probability parameter scales as the inverse of the square root of the contact number parameter.

4.3. *Endemic Equilibrium*

The endemic state is one where disease is continuously present with fractions x^* and y^* of susceptibles and infectives, respectively, given by

$$x^* = b/(r+\mu+\theta+\lambda^*)$$
$$y^* = \lambda^* b/(r+\mu+\theta+\lambda^*)(r+\mu+\gamma). \tag{15}$$

These equations are meaningful only if there is a nonzero equilibrium force of infection, λ^*. From the second equation of (15) and the defining

equation (4), it is evident that an endemic equilibrium occurs when there is a nonzero solution to

$$\lambda = g(\lambda b/[r+\mu+\gamma][r+\mu+\theta+\lambda]). \tag{16}$$

Figure 2 shows how the function on the right side of Eq. (16) changes with population growth rate r to yield endemic equilibria for each of several growth rates.

With the force of infection $\lambda(t)$ described by Eq. (4), there is only one nonzero solution of Eq. (16) whenever $\rho > 1$. If $\rho < 1$, the only solution of Eq. (16) is $\lambda^* = 0$. (This property holds more generally for nonincreasing concave functions g; see the Appendix). Thus, if the disease-free equilibrium

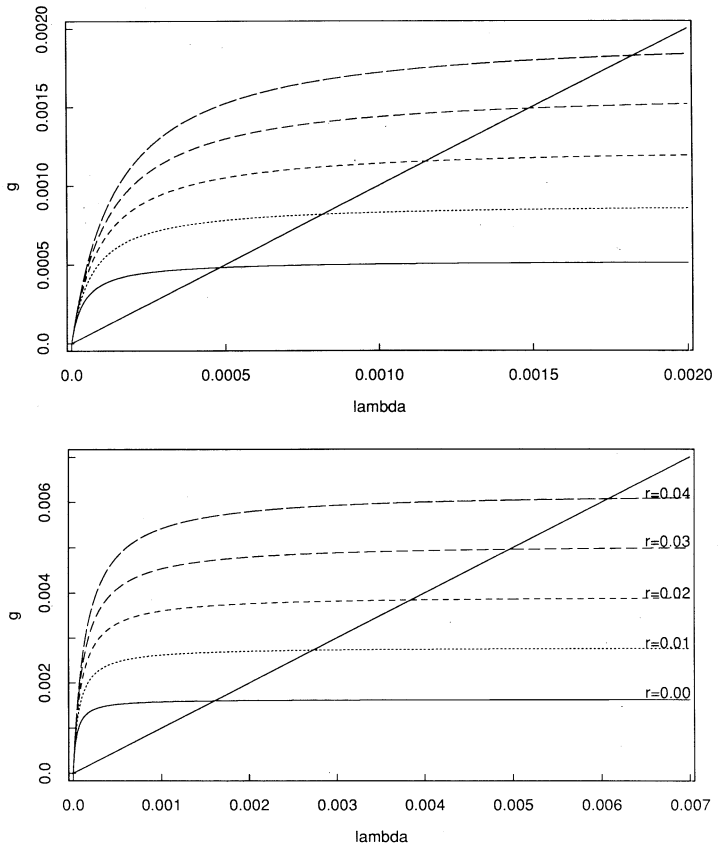

FIG. 2. These plots show how the equilibrium force of infection is determined by the intersection of the diagonal line and the function determining the force of infection. Here the immunization rate $\theta = 0$. The different curves illustrate the effect of population growth rate as labeled in the lower panel. Panels as in Fig. 1.

is unstable, there will be an endemic equilibrium. Conversely, if the disease-free equilibrium is stable, there will be no endemic equilibrium.

4.4. *Features of the Endemic Equilibrium*

Assuming that $\rho > 1$ in Eq. (14), there is an endemic equilibrium for each value of the host population's growth rate, r, and force of immunization, θ. The principal effects of r and θ on the static aspects of endemic equilibrium are enumerated below.

It is clear from Fig. 2 that at a given spatial density (i.e., a given value of the product me), the equilibrium force of infection λ^* increases with growth rate r when there is no immunization. Figure 3 shows the change in equilibrium force of infection, λ^*, with r for three different levels of immunization. Note that λ^* increases approximately linearly with r, with

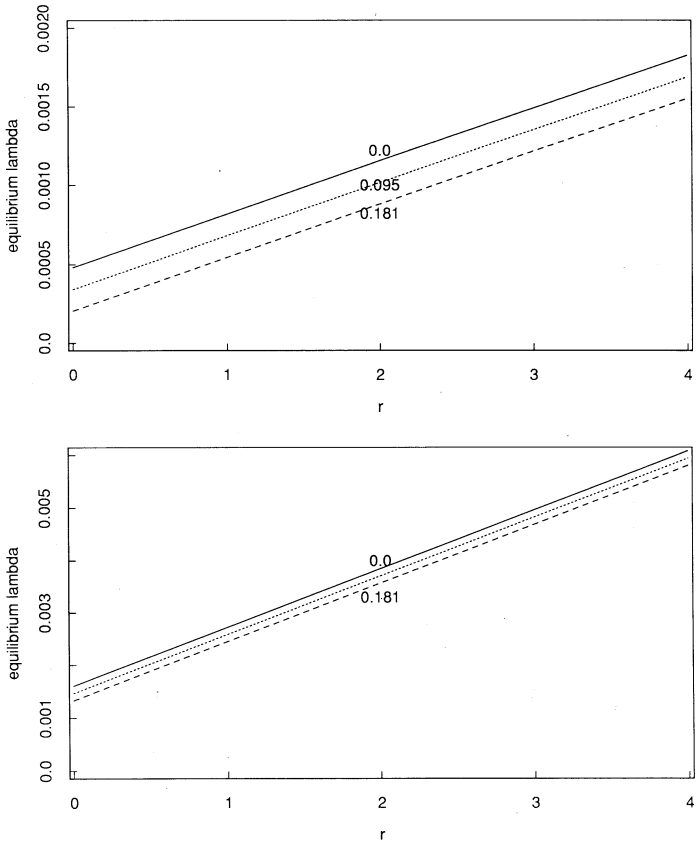

FIG. 3. Equilibrium force of infection in populations which grow at different annual rates. The three curves are labeled by the annual force of immunization in effect. Panels as in Fig. 1.

the three lines having nearly equal slopes. An increase in r from 1 to 2% per year increases the equilibrium force of infection, λ^*, by about 40%. In contrast, the effect of immunization upon λ^* is modest for the values of r presented in Fig. 3: a doubling of the force of immunization θ from 0.095 to 0.181 per year induces a modest change in the force of infection, λ^*. As we discuss below, increases in the force of immunization have similar small effect right up to the critical immunization level at which endemic disease is eliminated.

The equilibrium fraction y^* of infectives changes with both r and θ in a manner very similar to the equilibrium force of infection, λ^*. Figure 4 shows that increasing population growth rate r has a strong positive effect on y^*. Thus one would expect substantial differences in y^* between rapidly growing LDCs and populations with growth rates near zero. As with the

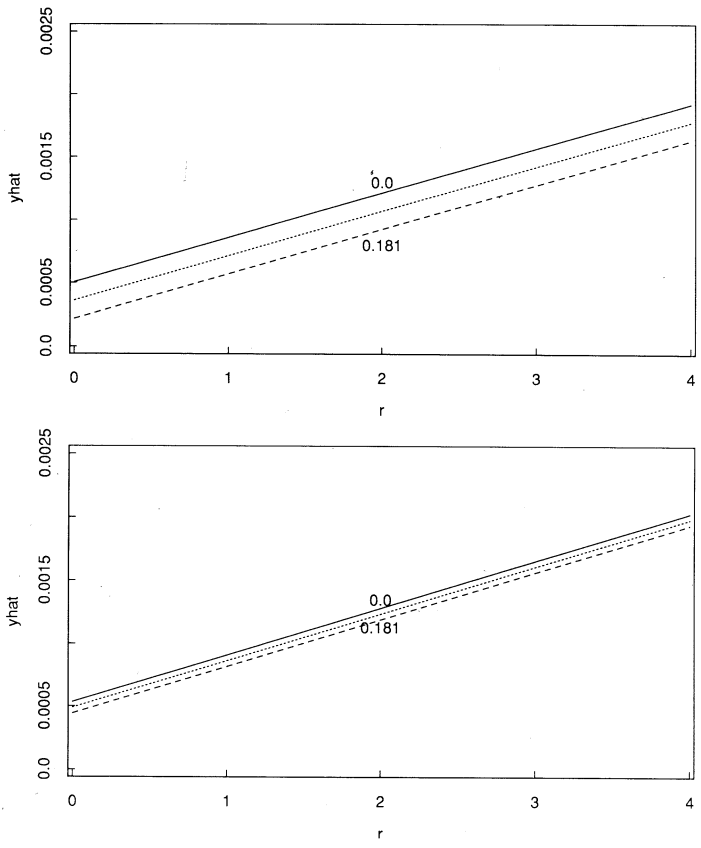

FIG. 4. Equilibrium proportion of infective-infecteds in populations which grow at different annual rates. The curves are labeled by the annual force of immunization in effect. Panels as in Fig. 1.

equilibrium force of infection, increased annual force of immunization θ causes y^* to decrease but at a relatively slow rate.

4.5. *Critical Immunization Rate*

Since an endemic equilibrium only occurs when $\rho > 1$ in Eq. (14), and since ρ decreases with increasing immunization level, there must exist a critical force of immunization, θ_c, above which endemic disease will be eradicated. Setting $\rho = 1$ in Eq. (14) and using the fact that $b = \mu + r$, we find that the critical force of immunization for a population with growth rate r and contact parameters m and e is given by

$$\theta_c = b\left[\frac{me}{r+\mu+\gamma} - 1\right]. \tag{17}$$

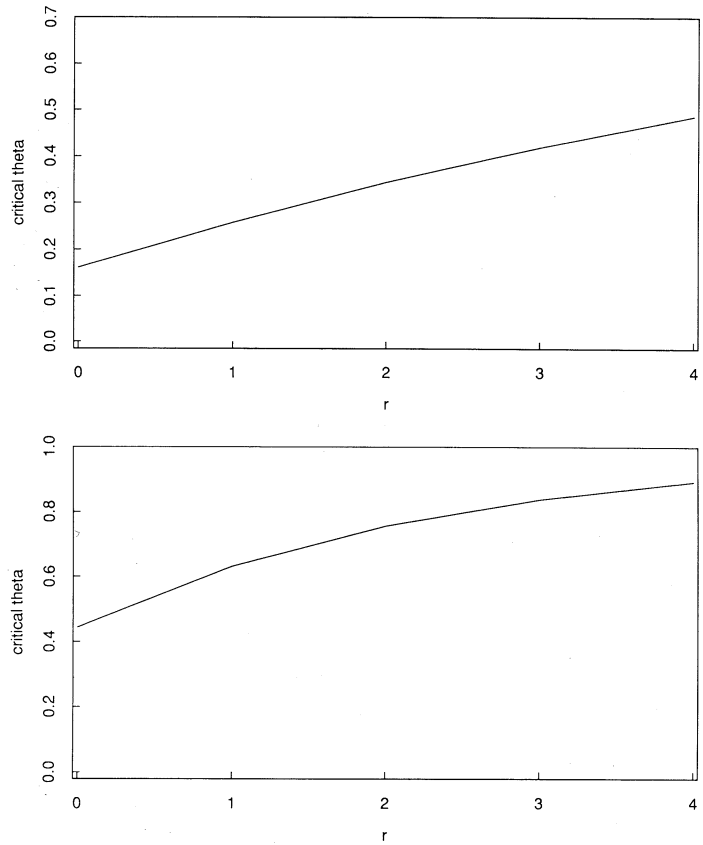

FIG. 5. Critical immunization level, the annual rate of immunization beyond which endemic disease will be eradicated in a population, plotted against the growth rate of the population. Panels as in Fig. 1.

For many childhood infectious diseases, the recovery rate, γ, is numerically much larger than r or μ. In such cases an expansion of the denominator in Eq. (17) shows that the critical immunization force, θ_c, increases approximately linearly with the growth rate, r. Figure 5 demonstrates that for every 1% per year increase in population growth rate, the critical annual force of immunization increases by roughly 10%, and is thus very sensitive to the (purely demographically determined) population growth rate. This finding contrasts sharply with McLean's (1986) conclusion that there is little difference between LDCs and the more-developed countries with respect to the critical level of immunization. The difference between the upper and lower panels of Fig. 5 is the first indication that the alternative density scaling can have sizeable impact. Such differences due to population density scaling may be important in comparing communities when, for example, studying rural vs. urban disease dynamics.

It would be useful to have indicators of some kind which change with immunization level so as to herald the approach to the critical force of immunization. The static (equilibrium) features of our model may not provide any useful indicators: for example, as the annual force of immunization is increased, there is a steady drop in both the equilibrium force of infection, λ^*, and the equilibrium proportion of infectives, y^*. This reduction is essentially linear over most of the range (see Fig. 6 for the equilibrium proportion of infectives), so there is no noticeable change in the marginal effect of increased levels of immunization. On the other hand, the approach to the critical force of immunization is discernable in the dynamic, transient properties of our model, where useful indicators may be found.

4.6. *Local Stability and Transient Dynamics*

In the real world, the demography and epidemiology of a population is constantly subject to perturbations. An analysis of such perturbations begins with a study of the stability of the demographic–epidemiological equilibrium determined by Eqs. (15) and (16). We use the standard method (for an epidemiological example see Greenhalgh, 1988) of examining the dynamics of small deviations from x^* and y^* as determined by Eq. (13). Our analysis (given in the Appendix) shows that the time-dependent behavior of deviations, $v(t) = x(t) - x^*$ and $w(t) = y(t) - y^*$, is exponential. There are two stability exponents, complex numbers ν_1 and ν_2, such that the deviations change as linear combinations of the exponentials $e^{\nu_i t}$. If the real parts of both ν_i are negative, then the deviations $v(t)$ and $w(t)$ die out over time and the equilibrium is locally stable. The general condition for local stability is given in the Appendix. As noted there, in the linear limit of Eq. (4) which occurs for $m \gg 1$ and $e \ll 1$, the equilibrium x^*, y^* is

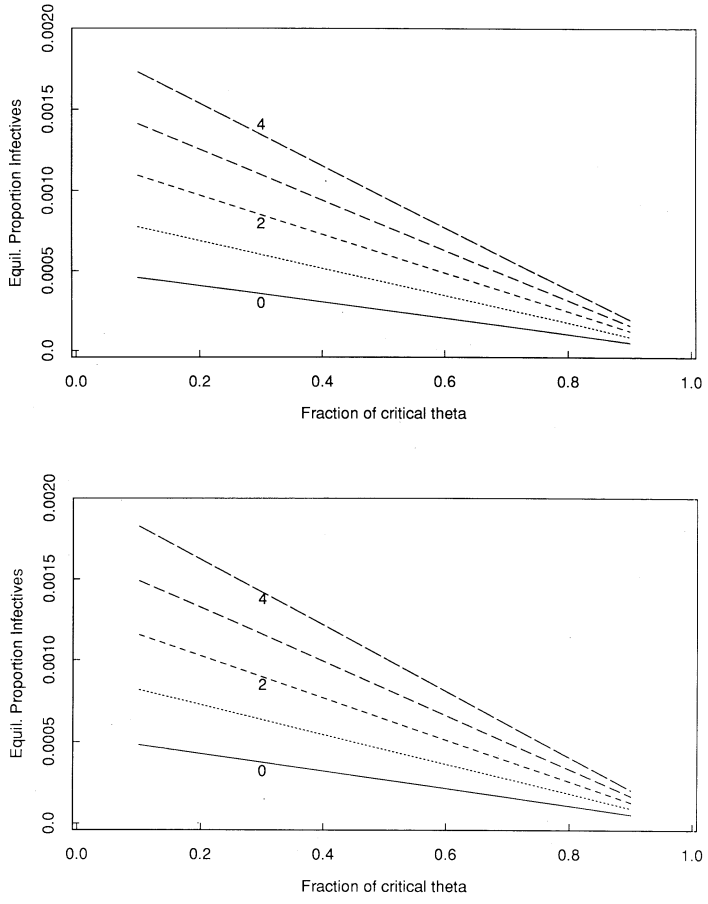

FIG. 6. Decline in the equilibrium proportion of infective-infecteds in a population as annual force of immunization is increased. The horizontal axis shows the force of immunization as a fraction of the critical immunization level. The different curves show the effect of population growth rate. Panels as in Fig. 1.

always stable when it exists (i.e., when $\rho > 1$). In the same limit, the stability exponents are always complex, except possibly when the force of immunization, θ, is extremely close (within a fraction of a percent) to the critical value, θ_c.

We examined numerically the exact behavior of many nonlinear cases, and always found stability with complex-valued exponents. Since this situation appears to be typical for our model, we assume it to be the case in the discussion following.

The significance of stable but complex-valued stability exponents is described by the quantities

$$T_E = \frac{1}{|\Re(v_1)|}, \qquad \Re(v_1) = \text{Real part of } v_1,$$
$$P_E = \frac{2\pi}{|\Im(v_1)|}, \qquad \Im(v_1) = \text{Imaginary part of } v_1. \tag{18}$$

The *return time* T_E is the time interval over which a deviation from equilibrium will decay to about one-third of its initial magnitude. The *period* P_E describes the cyclicity of the perturbed epidemiological process when the population is in demographic equilibrium.

Both the period and the return time of perturbations of the epidemiologic system depend upon the population growth rate, r, and force of immuniza-

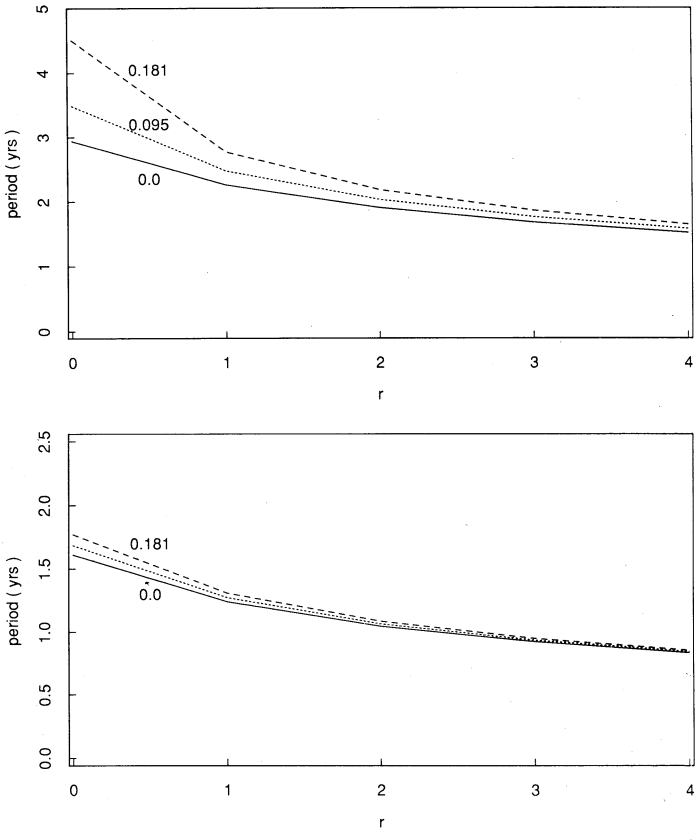

FIG. 7. Period of epidemiological transients in populations for increasing growth rate, for three moderate annual forces of immunization. Panels as in Fig. 1.

tion, θ. For a given force of immunization, the period of epidemiological transients decreases as population growth rate r increases. For a given growth rate r, the period increases as the force of immunization increases; as the force of immunization approaches the critical force θ_c, the period becomes very long. (Indeed, the period can become arbitrarily long if the force of imunization is held at a value infinitesimally close to the critical value, as discussed in the Appendix. This mathematical divergence has no practical importance.) The sensitivity of period to force of immunization is strongly dependent on growth rate r. Figure 7 shows the decrease of period with r for three different values of θ: immunization has a large effect on period only in the stationary ($r = 0$) population. Figure 8 shows period at

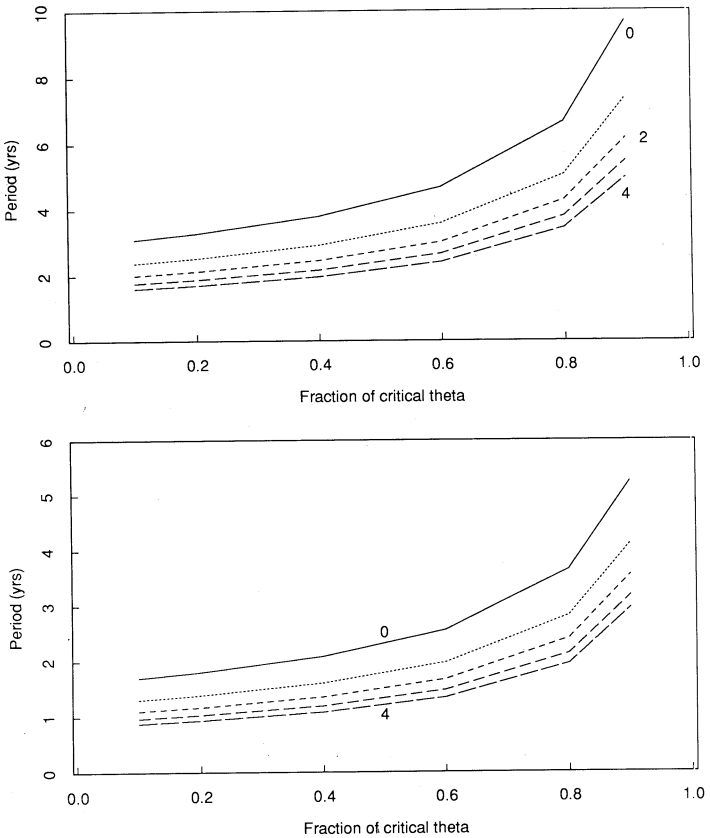

FIG. 8. Period of epidemiological transients in populations as the annual force of immunization increases. The horizontal axis shows the force of immunization as a fraction of the critical immunization level. The different curves show the effect of population growth rate. Panels as in Fig. 1.

immunization levels equal to increasing fractions of the corresponding critical force of immunization for three different growth rates. For each r the periods lengthen greatly as the critical force of immunization is approached; an increase in r of 1% per year significantly reduces the period for any given force of immunization. Figure 8 points to an important difference in models of stationary populations, which predict that transient epidemic period should increase significantly following implementation of an immunization program. In contrast, in rapidly growing populations we find that transient epidemic period increases only slowly with increasing force of immunization. Changes in the period are particularly small in the early stages of an immunization program in a rapidly growing population. However, a substantial increase (e.g., doubling) of the period of epidemic transients indicates the approach of the actual force of immunization, θ, to the critical immunization force, θ_c, even for rapidly growing populations.

The properties of the return time are also remarkably different in rapidly growing and stationary populations. Figure 9 is a plot of return time for the force of immunization expressed as a fraction of the appropriate critical force of immunization. The return time for the stationary population tends to increase with increasing immunization, although the change is very irregular. With increasing growth rate, the return time becomes strikingly insensitive to the force of immunization. This fact has interesting and significant implications for the time-series analysis of epidemiological data, as explained in the next section.

5. Epidemiological and Demographic Disequilibrium

In the real world, the demography and epidemiology of the communities is subject to perturbations, which may be viewed as random variability injected into our formal models. We now use the preceding stability analysis to discuss the temporal behavior of epidemiological variables in the presence of external random variation which is uncorrelated with the internal dynamics of either demography or disease. Such a view of variability is implicit in time-series analyses of epidemiological and demographic data (e.g., Anderson, Grenfell, and May, 1984 for epidemiology; Lee, 1974 for demography). In this section we use our model to describe significant features that should emerge in a time-series analysis of epidemiological data. We focus on one tool of time-series analysis, the power spectrum, and discuss first the properties expected from purely epidemiological transients and then the combined behavior of epidemiological and demographic fluctuation. We ignore here the "demographic" stochasticity (due to finite population size) discussed by Bartlett (1956).

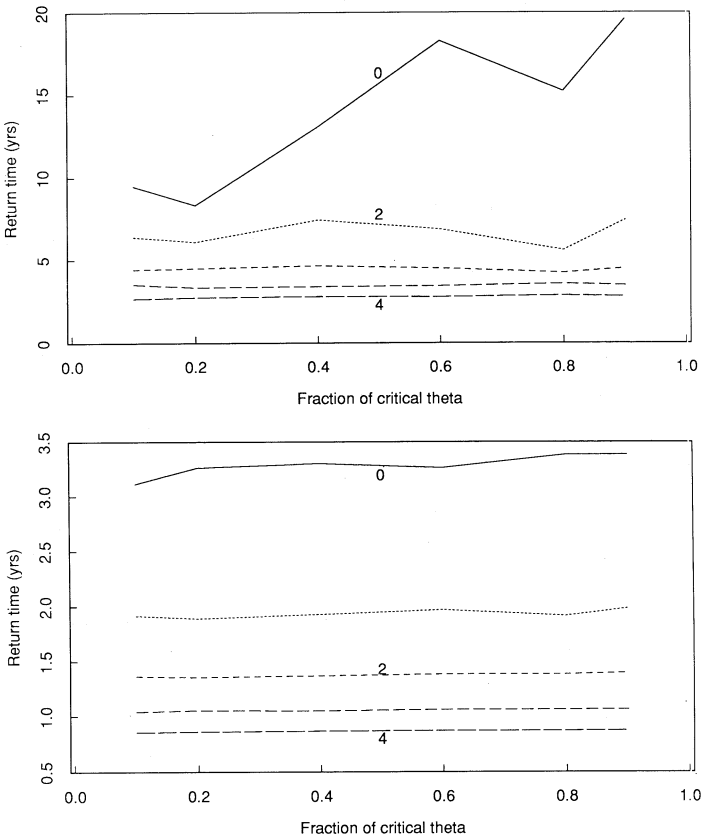

FIG. 9. Return time, describing the stability of epidemiological transients, shown for increasing immunization level. The horizontal axis shows the force of immunization as a fraction of the critical immunization level. The different curves show the effect of population growth rate. Panels as in Fig. 1.

5.1. *Power Spectrum for Epidemiological Disequilibrium*

The behavior of epidemiological transients when demographic equilibrium persists is given by the linearized version of Eq. (13), which appears in the Appendix as Eq. (A3). If we add to the rates of change of these linear deviations some uncorrelated random variation the result is that deviations from epidemiological equilibrium will be generated continually. A time series of a variable such as the proportion of infectives will then fluctuate around its long-time average. We are interested here in the information contained in such fluctuations, and specifically in their power spectrum (see, for example, Box and Jenkins, 1970). Simply put, the power spectrum

describes the contribution of oscillatory behavior at each possible frequency of oscillation to the overall variation in the data. A substantial literature on childhood diseases discusses the existence and significance of periodic oscillations in epidemiological variables (London and Yorke, 1973; Yorke and London, 1973; Fine and Clarkson, 1982a, b, 1986). There is as yet no agreement on the forces that maintain such oscillations. In the next subsection we demonstrate that demographic disequilibrium is one possible force. Here we set the stage by answering the question: if random variation were injected into the epidemiological variables, keeping the demographic structure constant, what would the power spectrum look like?

The power spectrum of the proportion of infectives is defined as follows (other epidemiological variables can be analyzed similarly). Let $w(t)$ be the deviation of the proportion of infectives from its average value at time t, and compute the Fourier transform

$$\hat{w}(\omega) = \int_0^\infty e^{-i\omega t} w(t)\, dt. \tag{19}$$

Then the power spectrum is the function

$$P_w(\omega) = |\hat{w}(\omega)|^2. \tag{20}$$

The usual diagnostic approach in time-series analysis is to compute an estimate of the power spectrum from a finite sample of values of the random variable, and to plot the spectrum against frequency. We describe the features of the theoretical power spectrum generated when the linearized version of our model, Eq. (13), is subject to random perturbation. As shown in the Appendix, our model predicts a power spectrum proportional to the function

$$\frac{1}{(\omega - \omega_E)^2 + (1/T_E)^2}. \tag{21}$$

Here, $\omega_E = 2\pi/(P_E)$, with P_E and T_E as in Eq. (18). As ω increases from 0, this function has a single peak at the frequency $\omega = \omega_E$, and the width of that peak is proportional to $1/T_E$. Thus the power spectrum will have a peak at frequency corresponding to the period in Eq. (18), and the width of the peaks will be inversely proportional to the return time.

It is easy to deduce the implications for the power spectrum of our earlier analysis of period and return time. For stationary populations the power spectrum has its widest and therefore least well-defined peak when there is no or little immunization. As the force of immunization increases, the peak width will narrow and the location of the peak will move to lower

frequency (longer period). For growing populations, the width of the peak in the power spectrum is greater because the return time is lower; on the other hand, the width of the peak will change very little as the force of immunization increases. The location of the peak, which indicates the frequency of epidemic cycles, will move much less and more gradually than in a stationary population as the force of immunization increases.

5.2. *Epidemiological Effects of Demographic Disequilibrium*

Demographers have long recognized that stochastic perturbations affect a population's vital rates, and an extensive theoretical and data-analytic literature deals with the consequences of such perturbations (see e.g., Lee, 1974; Cohen, 1977; Tuljapurkar, 1989). In this paper we show that *purely demographic disequilibrium, whatever its causes, will generate epidemiological disequilibrium.* Our analysis proceeds in the following steps: (i) we state necessary facts about the demography of a population which has been perturbed from its stable age distribution; (ii) we analyze the deterministic dynamics of simultaneous departures from equilibrium in both demographic and epidemiological variables in our model; (iii) we summarize the key features of the epidemiological power spectrum which would be generated by perturbations which affect only the overall demography.

Keyfitz (1968) and Coale (1972) detail the demographic analysis of a population which is not at its stable age distribution. The age structure of the population is given by a sum of exponentials (instead of the single exponential in Eq. (6)),

$$N(a, t) = \sum_{i \geq 0} Q_i c_i(a)\, e^{r_i t}. \tag{22}$$

Here the r_i are roots of Lotka's equation; the only real root $r_0 = r$ is the long-run population growth rate used in Eq. (6). The age-dependent functions in Eq. (22) are

$$c_i(a) = (1/\tau_i)\, l(a)\, e^{-r_i a}, \tag{23}$$

where

$$\tau_i = \int_0^\infty l(a)\, e^{-r_i a}\, da. \tag{24}$$

Births at time t are given by $N(0, t)$ and the birthrate is given by the ratio of births to the total population, with total population

$$N(t) = \sum_{i \geq 0} Q_i e^{r_i t}. \tag{25}$$

We define the differences

$$\kappa_i = r - r_i \tag{26}$$

which describe the speed and periodicity of the demographic approach to a stable age distribution. Here we assume there is demographic disequilibrium at $t=0$, but that it is small so that the ratios

$$|Q_i|/Q_0 \ll 1, \qquad i \geqslant 1. \tag{27}$$

Our epidemiological Eq. (3) can be reduced (see Appendix) to a pair of equations for the variables

$$x(t) = \frac{\int_0^\infty X(a,t)\,da}{Q_0 e^{rt}}, \qquad y(t) = \frac{\int_0^\infty Y(a,t)\,da}{Q_0 e^{rt}}. \tag{28}$$

Note that here x and y are *not* proportions of susceptibles and infectives, although they approach those proportions at long times. The equations for these variables are

$$\begin{aligned} d_t x &= b - (r+\mu+\theta+\lambda(t))\,x + \sum_{i\geqslant 1} (Q_i/Q_0)(e^{-\kappa_i t}/\tau_i), \\ d_t y &= \lambda(t)\,x - (r+\mu+\gamma)\,y. \end{aligned} \tag{29}$$

These equations become identical to the simpler Eq. (13) at long times, when the population gets very close to its stable age distribution. Therefore the equilibria of this time-varying model are the same as those of the simpler model, Eq. (13). In the present set of equations the proportion of susceptibles is given by the time-dependent expression

$$\frac{y(t)}{1+\sum_{i\geqslant 1}(Q_i/Q_0)\,e^{-\kappa_i t}}.$$

It follows that the force of infection, Eq. (4), responds to purely demographic disequilibrium ($Q_i \neq 0$ for $i \neq 0$), thereby generating epidemiological disequilibrium.

Now consider small deviations $v(t)$, $w(t)$ in the variables of (28) away from their equilibrium values x^*, y^*, respectively. The dynamics of these deviations are analyzed by obtaining linearized equations from (29) and solving them. The Appendix gives details of this procedure which yields the final result that the vector

$$\mathbf{u}(t) = \begin{pmatrix} v(t) \\ w(t) \end{pmatrix} \tag{30}$$

has time trajectory given by

$$\mathbf{u}(t) = \sum_{i=1,2} \left(\vartheta_i e^{\nu_i t} + \sum_{l \geqslant 1} \psi_{li} e^{-\kappa_i t} \right) \mathbf{R}_i. \tag{31}$$

The constant vectors $\mathbf{R}_i$ and the coefficients are defined in the Appendix.

The result in Eq. (31) shows that epidemiological variables display a superposition of time dependence: there is the purely epidemiological dynamic which is summarized by the quantities in Eq. (18), and there is the purely demographic relaxation process which is described by Eq. (22). The demographic relaxation process has characteristic return times

$$T_{Di} = \frac{1}{r - \Re(r_i)} \tag{32}$$

and characteristic periods

$$P_{Di} = \frac{2\pi}{|\Im(r_i)|}. \tag{33}$$

The most important demographic transient (Coale, 1972) is known to be a generational cycle with a period of about 20 years.

5.3. *Effect of Demography on the Power Spectrum*

Consider now the consequence of small random perturbations affecting the demographic rates of the population. These would continually generate demographic transients which in turn would produce epidemiological transients. What are the oscillatory properties of such transients? From Eq. (31) it follows that the power spectrum of these oscillations will be dominated by a sum of terms of the form

$$\frac{(\text{constant})}{(\omega - \omega_E)^2 + (1/T_E)^2} + \frac{(\text{constant})'}{(\omega - \omega_{Di})^2 + (1/T_{Di})^2}. \tag{34}$$

The first term is similar to the purely epidemiological term in Eq. (21) and has all the properties discussed earlier. The second term, for values of $i \geqslant 1$, describes the demographic contribution. The dominant demographic contribution is a peak in the power spectrum, located at a frequency corresponding to the generational cycle. In view of the typical epidemiological periodicity of 2–5 years (Figs. 7 and 8), the main demographic peak will be widely separated from the epidemiological peak. Thus a spectral analysis aiming at the high epidemiological frequencies would almost certainly

ignore the much lower frequency demographic contribution. The separation between epidemiological peak and demographic peak would be much greater in populations with high growth rates. Only when the force of immunization in a population is increased and held at close to the critical value θ_c will the epidemic period lengthen to values that might approach the demographic cycle.

6. Conclusions

The rapid growth rates of human populations in many LDCs can be expected to have a significant effect on epidemics and the endemic level of childhood diseases. The major epidemiological conclusions of our analysis of an appropriate class of age-structured epidemic models are listed below.

(1) In a community with some level of ongoing vaccination, invasion by disease becomes easier as the population's growth rate increases. In contrast increased growth rate has very little effect on the ability of infection to invade a virgin community.

(2) The equilibrium proportion of infectives in a community increases when the population's growth rate increases, for any fixed level of immunization.

(3) The critical force of immunization needed to eradicate an endemic disease increases rapidly with population growth rate. For the parameter values we used, the critical force increases by more than 10% for an increase in growth rate of 1% per year.

(4) The rule-of-thumb that transient epidemic period should increase on implementing an immunization program is not generally useful in rapidly growing populations. This rule is particularly inappropriate in the early stages of an immunization program in a fast-growing population. However, a substantial increase (such as a doubling) of the period of epidemic transients does herald the approach of the critical immunization level even for high growth rates.

(5) The return time, which measures the stability of departures from epidemiological equilibrium, changes greatly with population growth rate. With increasing growth rate, the return time becomes insensitive to the level of immunization.

(6) If epidemiological fluctuations are triggered by random perturbations, their power spectrum has features which change substantially with population growth rate. In a stationary population, the power spectrum has its widest and therefore least well-defined peak when there is no or

little immunization. As the force of immunization increases, this peak narrows and the location of the peak will move to lower frequency (longer period). For populations with increasing growth rate, the width of the peak in the power spectrum is greater because the return time is lower; on the other hand, the width of the peak changes very little as the force of immunization increases. The location of the peak moves much less with changing immunization than is the case for a stationary population.

(7) Demographic disequilibrium (i.e., a population away from stable age distribution) results in epidemiological disequilibrium. The dynamics of such combined disequilibrium are a superposition of the purely epidemiological dynamic and the purely demographic relaxation process. As a result continual stochastic perturbations to overall demographic rates can result in sustained epidemiological fluctuations.

(8) A spectral analysis of demographic–epidemiological fluctuations would reveal two widely separated peaks in the power spectrum. A spectral analysis aiming at the long epidemiological frequencies would miss the much shorter frequency demographic contribution. The separation between epidemiological peak and demographic peak would be greater in populations with high growth rates.

Appendix

1. The form of the force of infection (1) and the model (2)–(5) depend on an implicit choice of time scale. This is most clearly demonstrated by starting with a discrete time model in which time is measured in units of length Δ. Our starting point is a discrete-time system of equations; the analog to the first equation of (3) is

$$X(a+\Delta, t+\Delta) = \Pi(a, \Delta)\, X(a, t) - \Theta(a, \Delta)\, X(a, t) - \Lambda(a, \Delta)\, X(a, t),$$

where Π, Θ, Λ are respectively single period values of survival rate, immunization rate and probability of infection. For small Δ, we approximate this discrete equation by the first, continuous, equation in (3), if we make the identifications

$$\mu(a) = \frac{\Pi(a, \Delta)}{\Delta},$$

$$\theta(a) = \frac{\Theta(a, \Delta)}{\Delta},$$

$$\lambda(a) = \frac{\Lambda(a, \Delta)}{\Delta}.$$

For arbitrary Δ, the force of infection function λ must therefore be defined in terms of the time unit. Thus the arguments in John (1989a, b) lead to

$$\lambda(a) = \frac{(1 - [1 - e(D)\, y]^{m(D)})}{\Delta}.$$

The quantities $e(D)$, $m(D)$ are implicitly dimensionless functions of Δ. In the text we assume that the time unit is $\Delta = 1$ day, and thus arrive at (1). There is a suppressed dimension of time^{-1} in the force of infection used throughout the text.

2. Suppose that the number of contacts m is replaced by a random variable M with mean $\mathscr{E}M = m$ and variance σ_m^2. Consider the function

$$G(M) = 1 - (1 - ey)^M.$$

By a standard Taylor expansion we find approximately the difference

$$\mathscr{E}G(M) - G(m) \approx \tfrac{1}{2}\sigma_m^2 [\log(1 - ey)]^2 (1 - ey)^m.$$

For the diseases of interest here it is always the case that $y \ll 1$, with typical values in the range $10^{-2} - 10^{-3}$. By definition $e < 1$, so that $ey \ll 1$ and to high accuracy $\log(1 - ey) \approx -ey$. In addition $0 < G < 1$, and thus

$$\mathscr{E}G(M) - G(m) \approx (ey)^2\, \sigma_m^2.$$

Therefore, unless the variance in M is very large, we may reasonably use the function of the average instead of the averaged function.

3. To derive Eq. (13), use Eqs. (11) and (12) to integrate terms in Eq. (2) with respect to age a. Then substitute

$$x(t) = \frac{1}{Q_0 e^{rt}} \int_0^\infty X(a, t)\, da \tag{A1}$$

and $y(t)$ defined likewise, and use Eqs. (6) and (10).

4. Around any equilibrium x^*, y^* of Eq. (13), insert

$$x(t) = x^* + v(t), \qquad y(t) = y^* + w(t) \tag{A2}$$

and retain only terms linear in v, w to find the local stability equation

$$d_t \mathbf{u} = \mathbf{S}\mathbf{u}, \qquad \mathbf{u} = \begin{pmatrix} v \\ w \end{pmatrix},$$
$$\mathbf{S} = \begin{pmatrix} -(k_1 + \lambda^*) & -x^*\lambda' \\ \lambda^* & -(k_2 - x^*\lambda') \end{pmatrix}. \tag{A3}$$

Here, $k_1 = (\mu + r + \theta)$, $k_2 = (\mu + r + \gamma)$,

$$\lambda' = \left.\frac{d\lambda(y)}{dy}\right|_{y=y^*},$$

and λ^* is the equilibrium force of infection. The eigenvalues v_i, $i = 1, 2$, of **S** are roots of

$$v^2 + Bv + C = 0,$$

where

$$B = \lambda^* + k_1 + k_2 - \lambda' x^*, \qquad C = k_2(\lambda^* + k_1) - \lambda' k_1 x^*. \tag{A4}$$

Stability (when the real parts $\Re(v_i) < 0$) occurs when

$$B > 0 \qquad \text{and} \qquad C > 0. \tag{A5}$$

Complex roots occur when $B^2 > 4C$.

For the disease-free equilibrium, $y^* = 0 = \lambda^*$ and $\lambda' = me$, we find instability ($C < 0$) when

$$\rho = \frac{meb}{k_1 k_2} > 1$$

and stability ($C > 0$, $B > 0$) when $\rho < 1$. Using $k_1 = (\mu + r + \theta)$, $k_2 = (\mu + r + \gamma)$,

$$\rho = \frac{me}{\mu + r + \gamma}$$

when $\theta = 0$. When $\theta \neq 0$, recall that $\gamma \gg (\mu + r)$ to find

$$\rho \simeq \frac{me}{\theta\gamma}(\mu + r) + O[(u + r)^2].$$

Hence ρ decreases slowly with r for $\theta = 0$ and increases with r for $\theta \neq 0$.

5. Demographic and epidemiologic equilibrium. Equation (15) shows that y^* is concave nondecreasing in λ^*. Any nonnegative concave nondecreasing function $g(y^*)$ will therefore be a concave nondecreasing function of λ^*. Thus there will be just one point at which $\lambda^* > 0$ and $\lambda^* = g(y^*(\lambda^*))$, providing that

$$\left(\frac{dg}{d\lambda}\right)_{\lambda=0} = \rho > 1.$$

6. Stability of demographic–epidemiologic equilibrium requires condition (A5). If $m \gg 1$ and $e \ll 1$, then function (1) is effectively linear. For this linear case, algebra shows that if $\rho < 1$, then (A5) is true. For the parameter values used here, with $\gamma \gg r$, μ, θ, it also follows that $B^2 < 4C$ when $\rho \gg 1$. Hence the roots v_1, v_2 of (A4) will in general be complex; real roots can only be expected when $(\rho - 1)$ is of the order of $\mu\theta_c$. This is therefore also the requirement for long-period epidemiological transients.

7. Demographic disequilibrium: Start by integrating (2) with respect to age a and substitute (A1). In the resulting equations use Eqs. (22) and (25) to obtain Eq. (29). Next use Eq. (A2) and expand to linear terms to obtain

$$y(t) \simeq y^* + w(t) - y^* \sum_{i \geqslant 1} (Q_i/Q_0)\, e^{-\kappa_i t}, \tag{A6}$$

$$\lambda(y(t)) \simeq \lambda^* + \lambda' w(t) - y^* \lambda' \sum_{i \geqslant 1} (Q_i/Q_0)\, e^{-\kappa_i t}. \tag{A7}$$

Use Eqs. (A2), (A6), and (A7) in Eq. (29), retaining only terms linear in v, w, and the Q_i $(i \geqslant 1)$ to obtain

$$d_t \mathbf{u} = \mathbf{S}\mathbf{u} + \mathbf{f}(t), \tag{A8}$$

where $\mathbf{u}$, $\mathbf{S}$ are as in (A3) and

$$\mathbf{f}(t) = \sum_{i \geqslant 1} (Q_i/Q_0)\, e^{-\kappa_i t} \begin{pmatrix} \lambda' x^* y^* + [1/\tau_i] \\ -\lambda' x^* y^* \end{pmatrix}. \tag{A9}$$

Writing $\mathbf{R}_i$ for the right eigenvectors of $\mathbf{S}$ corresponding to the eigenvalues v_i, $i = 1, 2$, we can find α_i, $i = 1, 2$, and β_{li}, $l \geqslant 1$, $i = 1, 2$ such that

$$\mathbf{u}(0) = \alpha_1 \mathbf{R}_1 + \alpha_2 \mathbf{R}_2, \tag{A10}$$

$$\begin{pmatrix} \lambda' x^* y^* + [1/\tau_l] \\ -\lambda^* x^* y^* \end{pmatrix} = \beta_{li} \mathbf{R}_1 + \beta_{li} \mathbf{R}_2. \tag{A11}$$

Then standard linear algebraic methods show that the solution of (A8) is

$$\mathbf{u}(t) = \sum_{i=1,2} \left(\vartheta_i e^{v_i t} + \sum_{l \geqslant 1} \psi_{li} e^{-\kappa_i t} \right) \mathbf{R}_i, \tag{A12}$$

with

$$\begin{aligned} \psi_{li} &= \beta_{li}/(v_i + \kappa_l), \\ \vartheta_i &= \alpha_i - \sum_{l \geqslant 1} \psi_{li}. \end{aligned} \tag{A13}$$

6. Power spectra for linear stochastic differential equations are well known. In particular a scalar equation

$$d_t x = \lambda x + \varepsilon(t),$$

where $\varepsilon(t)$ is "white" noise, leads to a spectrum for $x(t)$ of

$$P_x(t) \propto \frac{1}{(\omega - \Im\lambda)^2 + (\Re\lambda)^2}.$$

This is the basis for Eqs. (21) and (34). (See, e.g., Roughgarden (1979) for a biologically oriented discussion of this material). Equation (21) is obtained by adding a noise term to the right side of the differential equation in (A3). Equation (34) is obtained by adding noise to Eq. (A8) and solving the result by Fourier transformation.

ACKNOWLEDGMENTS

We thank M. W. Feldman, Biological Sciences, Stanford University, for use of his computing facilities and for his hospitality, and James Trussell and two diligent referees for comments. This research was supported by NIH Grants HD16640 and HD00639 (Tuljapurkar) and AI29418 (John).

REFERENCES

ANDERSON, R. M. 1982. Transmission dynamics and control of infectious disease agents, *in* "Population Biology of Infectious Diseases" (R. M. Anderson and R. M. May, Eds.), pp. 149–176, Springer-Verlag, Berlin.

ANDERSON, R. M., GRENFELL, B. T., AND MAY, R. M. 1984. Oscillatory fluctuations in the incidence of infectious disease and the impact of vaccination: Time series analysis, *J. Hyg. Camb.* **93**, 587–608.

ANDERSON, R. M., AND MAY, R. M. 1983. Vaccination against rubella and measles: Quantitative investigations of different policies, *J. Hyg. Camb.* **91**, 259–325.

ANDERSON, R. M., AND MAY, R. M. 1985. Age-related changes in the rate of disease transmission: Implications for the design of vaccination programs, *J. Hyg. Camb.* **94**, 365–436.

ANDREASEN, V. 1989. Disease regulation of age structured host populations, *Theor. Pop. Biol.* **36**, 214–239.

BARTLETT, M. S. 1956. Deterministic and stochastic models for recurrent epidemics, *in* "Proceedings, 3rd Berkeley Symposium on Mathematics, Statistics and Probability," Vol. 4, 81–109.

BLACK, F. L. 1962. Measles antibody prevalence in diverse populations, *Am. J. Dis. Child* **103**, 242–249.

BOX, G. E. P., AND JENKINS, G. M. 1970. "Time Series, Forecasting and Control," Holden-Day, San Francisco.

COALE, A. J. 1972. "The Growth and Structure of Human Populations," Princeton Univ. Press, Princeton.

COHEN, J. E. 1977. Ergodicity of age structure in populations with Markovian vital rates. II. General states. *Adv. Appl. Prob.* **9**, 18–37.

DIETZ, K. 1975. Transmission and control of arbovirus diseases, *in* "Epidemiology" (D. Ludwig and K. L. Cooke, Eds.), pp. 104–119.

DIETZ, K. 1976. The incidence of infectious diseases under the influence of seasonal fluctuations, Lecture Notes in Biomathematics, Vol. 11, pp. 1–15.

DIETZ, K. 1982. Overall population patterns in the transmission cycle of infectious disease agents, *in* "Population Biology of Infectious Diseases" (R. M. Anderson and R. M. May, Eds.), pp. 87–102, Springer-Verlag, Berlin.

DIETZ, K., AND SCHENZLE, D. 1985. Mathematical models of infectious disease statistics, *in* "A Celebration of Statistics: The Centenary Volume of the International Statistical Institute" (A. C. Atkinson and S. E. Feinberg, Eds.), pp. 167–204, Springer-Verlag, Berlin.

FINE, P. E. M., AND CLARKSON, J. A. 1982a. Measles in England and Wales. I. An analysis of factors underlying seasonal patterns, *Int. J. Epidemiol.* **11**, 5–14.

FINE, P. E. M., AND CLARKSON, J. A. 1982b. Measles in England and Wales. II. The impact of vaccination programme on the distribution of immunity in the population, *Int. J. Epidemiol.* **11**, 15–25.

FINE, P. E. M., AND CLARKSON, J. A. 1986. Seasonal influences in pertussis, *Int. J. Epidemiol.* **15**, 237–247.

GREENHALGH, D. 1987. Analytical results on the stability of age-structured recurrent epidemic models, *IMA J. Math. Appl. Med. Biol.* **4**, 109–144.

GREENHALGH, D. 1988. Threshold and stability results for an epidemic model with an age-structured meeting rate, *IMA J. Math. Appl. Med. Biol.* **5**, 81–100.

HETHCOTE, H. W. 1976. Qualitative analyses of communicable disease models, *Math. Biosci.* **28**, 335–356.

HETHCOTE, H. W., STECH, H. W., AND VAN DEN DRIESSCHE, P. 1981. Stability analysis for models of disease without immunity, *J. Math. Biol.* **13**, 185–198.

JOHN, A. M. 1989a. Transmission dynamics of childhood infectious diseases: does demography matter? *Pop. Stud.* **44**, 195–215.

JOHN, A. M. 1989b. Endemic disease in fully age-structured host populations, *Theor. Pop. Biol.* **37**, 455–471.

JOHN, A. M., AND TULJAPURKAR, S. D. 1990. "Childhood Infectious Diseases in LDCs: Immunization Program Design and Evaluation Using Demographic–Epidemiologic Models," Population Council Research Division Working Paper No. 21, The Population Council, New York.

KEYFITZ, N. 1968. "Introduction to the Mathematics of Population," Addison-Welsey, Reading, MA.

LEE, R. D. 1974. The formal dynamics of controlled populations and the echo, the boom and the bust, *Demography* **11**, 563–585.

LIU, W., LEVIN, S. A., AND IWASA, Y. 1986. Influence of nonlinear incidence rates upon the behavior of SIRS epidemiological models, *J. Math. Biol.* **23**, 187–204.

LIU, W., HETHCOTE, H. W., AND LEVIN, S. A. 1987. Dynamical behavior of epidemiological models with nonlinear incidence rates, *J. Math. Biol.* **25**, 359–380.

LONDON, W. P., AND YORKE, J. A. 1973. Recurrent outbreaks of measles, chickenpox and mumps. I. Seasonal variation in contact rates, *Am. J. Epidemiol.* **98**, 453–468.

LOTKA, A. J. 1931. The structure of a growing population, *Hum. Biol.* **4**, 459–493.

MAY, R. M., AND ANDERSON, R. M. 1985. Endemic infections in growing populations, *Math. Biosci.* **77**, 141–156.

MCLEAN, A. R. 1986. Dynamics of childhood infections in high birthrate countries, *in* "Immunology and Epidemiology" (G. W. Hoffman and T. Hraba, Eds.), Lecture Notes in Biomathematics, Vol. 65, pp. 171–97. Springer-Verlag, Berlin.

McLean, A. R., and Anderson, R. M. 1988a. Measles in developing countries. I. Epidemiological parameters and patterns, *Epidemiol. Inf.* **100**, 111–133.

McLean, A. R., and Anderson, R. M. 1988b. Measles in developing countries. II. The predicted impact of mass vaccination. *Epidemiol. Inf.* **100**, 419–442.

Roughgarden, J. 1979. "Theory of Population Genetics and Evolutionary Ecology: An Introduction," MacMillan, New York.

Tuljapurkar, S. D. 1989. An uncertain life: Demography in random environments, *Theor. Pop. Biol.* **35**, 227–294.

Yorke, J. A., and London, W. P. 1973. Recurrent outbreaks of measles, chickenpox and mumps. II. Systematic differences in contact rates and stochastic effects, *Am. J. Epidemiol.* **98**, 469–482.