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16

Population Dynamics of Measles

I. Introduction

Measles is among the best documented of human diseases in terms of epidemiology and population dynamics. This status arises from a combination of three factors. First, the disease represents a major source of mortality and morbidity in human populations, both in the historical record and currently (Anderson and May, 1991). The Arabic physician Rhazes rated measles as at least as important a disease as smallpox (Black, 1984). Measles is still a major killer in developing countries (killing over 1.5 million children a year), despite the existence of an effective vaccine (McLean and Anderson, 1988a,b; see also Chapter 11). The second special feature of measles (which it shares with many other childhood respiratory viral infections) is the relatively simple natural history of transmission of the etiological agent, measles virus (Fine and Clarkson, 1982a; Black, 1984; Nokes and Anderson, 1988a). Essentially, transmission from infectious to susceptible individuals is direct, via respiratory aerosol. Clinical manifestations are relatively distinct and easily diagnosed; infectees undergo short and well-defined incubation and infectious periods. Immunity to re-infection is subsequently effectively lifelong in immunologically competent individuals who survive the primary infection. The third epidemiological factor, which arises from this simple course of infection, is that infection characteristically occurs in self-extinguishing epidemics, since a wave of infection "removes" individuals from the susceptible to the immune class (Hamer, 1906; Soper, 1929; Bartlett, 1957,1960; Black, 1966; Schenzle, 1984; Anderson and May, 1991). Measles epidemics tend to be episodic in small communities (Cliff and Haggett, 1988), but can show remarkably regular oscillations (Brownlee, 1919; Anderson *et al.*, 1984; Cliff and Haggett, 1988), both seasonally and on longer major epidemic time scales, in urban communities that have a sufficiently large rate of recruitment of susceptible children to make the infection endemic (Fig. 1).

In terms of quantitative research on measles epidemiology, the public health importance and dynamic epidemic behavior of measles has spawned two distinct bodies of work: epidemiological modeling and the study of nonlinear dynamics and chaos. We shall consider each one in turn.

A. Epidemiological Modeling

There is a long and distinguished tradition of attempts to understand the dynamics of measles infection, its persistence in commu-

Parasitic and Infectious Diseases

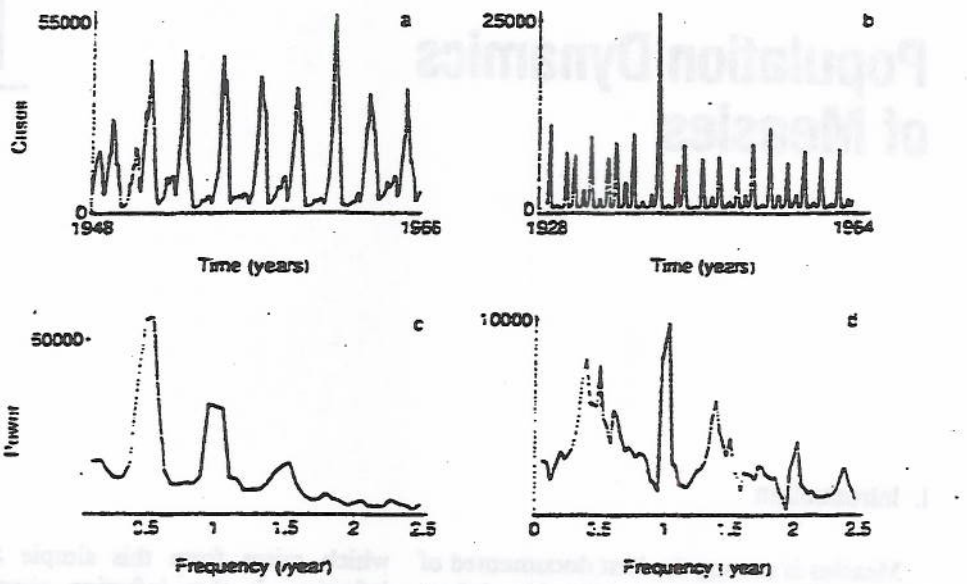

Figure 1 Time series (cases notified) and power spectra for England, Wales, and New York. (a) Weekly case reports for England and Wales, 1948–1968. (b) Monthly case reports for New York City, 1928–1964. (c) Power spectrum for England and Wales data: spectra smoothed with a 3-point running mean (Chatfield, 1975; Priestley, 1982). (d) Power spectrum for New York City, data and method as for c. Spectral analysis of recurring epidemics generates power spectra with peaks that recur at intervals equal to the inverse of the interepidemic period.

nities, and the impact of heterogeneities in transmission with respect to age, season, and spatial organization of the host population (Hamer, 1906; Soper, 1929; Bartlett, 1957,1960; London and Yorke, 1973; Anderson and May, 1985,1991; Dietz and Schenzle, 1985; May, 1986). The advent of an effective vaccine, and its widespread use over the last three decades (Black, 1984), has also generated extensive development of this theory, which addresses the important issue of estimating the critical level of vaccination required to eradicate the infection from a community (Dietz, 1976; Anderson and May, 1982). In parallel with these theoretical developments, the relatively long time series of measles case notifications, which are available for a number of countries, have been analyzed statistically by a number of workers (Brownlee, 1919; Fine and Clarkson, 1982b; Cliff and Haggett, 1988) to assess the relative importance of annual and longer term periodicities in the epidemic pattern (Fig. 1).

B. Nonlinear Dynamics and Chaos

The availability of plausible models and relatively long time series of incidence have also made measles epidemics (which are essentially a manifestation of predator–prey dynamics) of considerable interest to population ecologists (May, 1986). A recent and very stimulating example is the attempt by several groups—notably Schaffer and coworkers (Schaffer, 1985b; Schaffer and Kot, 1985; Kot *et al.*, 1988; Olsen *et al.*, 1988; Olsen and Schaffer, 1990)—to identify fluctuations in measles incidence as manifestations of, for chaotic dynamics. "Chaos" is the general name given to irregular patterns of behavior appearing in systems governed by simple deterministic rules. Chaos

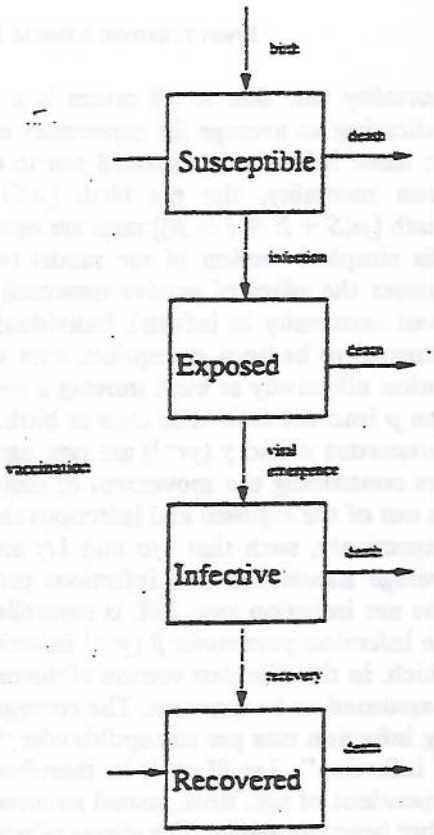

Figure 2 Representation of the compartments and epidemiological transitions in the SEIR (Susceptible/Exposed/Infective/Recovered) model; see text for details.

occurs in models of host–parasite systems as a result of dynamic instability caused by extreme "boom-and-bust" cycles in host and parasite abundance (Schaffer, 1985b; May, 1986). Measles is one of the best candidates for chaotic dynamics in a biological system outside the laboratory. An extensive body of work has identified putative chaotic attractors for measles, based on both observed incidence data (Olsen *et al.*, 1988; Sugihara and May, 1990) and the simplest homogeneous epidemiological model, the SEIR (susceptible/exposed/infectious/recovered) model (Schaffer and Kot, 1985; Rand and Wilson, 1991). However, difficulties do arise with this approach. In addition to the problem that the available measles time series may be simply too short for the statistical methods used to detect chaos (Nychka *et al.*, 1992), the modeling approaches to this problem have tended to ignore more realistic formulations of measles dynamics developed for epidemiological purposes. Currently, this problem is being addressed by analyzing the nonlinear dynamic properties of more realistic epidemiological models (Bolker and Grenfell, 1993).

The following sections review the current status of measles modeling. This subject is vast, so the treatment of most areas necessarily is limited. We begin by discussing the structure and properties of the simple SEIR model, and the effects of biological refinements to improve its epidemiological realism. We then review current work on the nonlinear dynamics of measles, and explore the implications of fusing the epidemiological and nonlinear approaches to measles dynamics. The chapter concludes with a discussion of directions for future work.

II. Basic Model Framework

A. Infection Dynamics

Measles provides one of the most straightforward examples of a directly transmitted microparasitic infection (Anderson and May, 1991; see Chapter 3). The standard pattern of infection for developed countries (Nokes and Anderson, 1988b), which applies effectively to all immunologically competent individuals in the population, is summarized in Fig. 2. After a short period of maternally acquired passive immunity, young children become susceptible to infection. Infective contact with infectious individuals (involving a transfer of virus, predominantly via aerosol) moves individuals into the asymptomatic exposed, or

latent, group for a period of 6–9 days. Then individuals progress to become infective for 6–7 days, showing the characteristic rash of measles for the last few days of this period. Finally, immunocompetent individuals who survive infection (and measles is assumed not to be fatal in the simplest models) are effectively immune to subsequent re-infection, and therefore are recovered and effectively removed from the transmission cycle. The main instrument for disease control is the vaccination of susceptible children with a live attentuated measles strain, developed originally in the 1950s (Black, 1984). In terms of the model, vaccination simply moves individuals directly from the susceptible to the recovered class.

B. Compartmental Structure

The essence of this progression is captured at the population level by the well-known SEIR model, which has a long history of study in mathematical epidemiology (Hamer, 1906; Soper, 1929; Kermack and McKendrick, 1927,1932,1933; Dietz and Schenzle, 1985; May, 1986; Anderson and May, 1991). This model is expressed as a set of three nonlinear ordinary differential equations:

$$\begin{aligned}\frac{dS}{dt} &= \mu N(1-p) - (\mu + \beta I)S \\ \frac{dE}{dt} &= \beta IS - (\mu + \sigma)E \\ \frac{dI}{dt} &= \sigma E - (\mu + \gamma)I.\end{aligned} \tag{1}$$

and makes the following epidemiological assumptions. S, E, I, and R respectively represent the density of susceptible, exposed, infectious, and recovered individuals in a constant total population of size $N = S + E + I + R$ (given this identity, only the three equations for S, E, and I are necessary to specify the system). Average *per capita* mortality rate due to all causes is μ yr^{-1}, indicating an average life expectancy of $1/\mu$ yr; since infection is assumed not to cause extra mortality, the net birth (μN) and death [$\mu(S + E + I + R)$] rates are equal. In this simplest version of the model (which ignores the effect of passive maternally derived immunity in infants), individuals are assumed to be born susceptible, with vaccination effectively at birth moving a proportion p into the recovered class at birth. The parameters σ and γ (yr^{-1}) are rate parameters controlling the movement of individuals out of the exposed and infectious classes, respectively, such that $1/\sigma$ and $1/\gamma$ are the average incubation and infectious periods. The net infection rate, βIS, is controlled by the infection parameter β (yr^{-1} infective^{-1}) which, in this simplest version of the model, is assumed to be constant. The corresponding infection rate per susceptible (the "force of infection": $\lambda = \beta I$ yr^{-1}) is, therefore, independent of age, time, spatial structure, or other heterogeneities. The effects of relaxing this homogeneity assumption have provided a major focus for theoretical studies of measles epidemiology in recent years.

The static and dynamic properties of the SEIR model and its various modifications are summarized lucidly by May (1986). Here, we briefly review the properties of the SEIR model before discussing how epidemiologists have introduced various refinements to improve its explanatory power.

C. Equilibrium Properties of the Model

The equilibrium of the SEIR model (obtained from Eq. 1 when $dS/dt = dE/dt = dI/dt = dR/dt = 0$ at $S = S^*$, $E = E^*$, $I = I^*$, $R = R^*$, E^* and $I^* > 0$) can be used to lay bare many of its essential properties. The crucial quantity is the basic reproduction ratio of infection, R_0—the number of secondary cases caused by the introduction of an infectious individual into a wholly sus-

ceptible population. In terms of Eq. 1, at equilibrium

$$R_0 = \frac{N}{S^*}, \tag{2}$$

where

$$S^* = \frac{(\mu+\sigma)(\mu+\gamma)}{\sigma\beta} \tag{3}$$

is the equilibrium density of susceptibles and N is total population size. R_0 must be greater than 1 for the infection to persist in a community. In terms of patterns of measles incidence before the onset of vaccination, the criterion $R_0 > 1$, along with Eqs. 2 and 3, defines a lower population threshold for persistence of infection:

$$N_T = S^*. \tag{4}$$

An analogous dynamic threshold commonly is observed in practice and shall be shown to be crucial to the population dynamics of measles.

Vaccination of a proportion p at birth reduces the effective value of R_0 to

$$R_0' = (1-p)R_0, \tag{5}$$

so the threshold $R_0' = 1$ leads to the expression

$$p_c = 1 - 1/R_0 = 1 - S^*/N \tag{6}$$

for p_c, the critical vaccination proportion for eradicating the infection. For measles, R_0 is in the range of 12–18, suggesting that p_c is between 92% and 95% (Anderson and May, 1991). The effect on these very approximate calculations of allowing for more biological realism (particularly age-specific heterogeneities in transmission) is discussed subsequently.

D. Dynamic Properties of the Model

For $R_0 > 1$, the SEIR model has a stable positive disease equilibrium that is approached by damped oscillations with approximate period $2\pi[A(1/\sigma + 1/\gamma)]^{1/2}$, where A is the mean age at infection. Typical epidemiological parameters for developed countries before vaccination (when A was 4–5 yrs: May, 1986) generate an "expected" epidemic period of roughly 2 yr, in accord with much of the observed data (Brownlee, 1919; Anderson *et al.*, 1984), although annual and 3-yr periods are seen also (Olsen *et al.*, 1988). The model also indicates an increase in this interval after the onset of vaccination, which again accords roughly with field observations (Anderson *et al.*, 1984). Although these predicted pre- and postvaccination cycle periods are roughly correct for many measles data sets, observed measles time series for large communities show sustained rather than damped oscillations (Fig. 1). Much of measles epidemic theory has been devoted to explaining this recurrent epidemic behavior through refinements of the basic model.

This body of work has aimed at introducing extra biological features into measles models to generate sustained oscillations intermediate between the stability of the continuous-time SEIR model and the unstable neutral cycles of its discrete-time analogs. Since measles is often observed to "fade out" in the troughs between epidemics, the first modification is to allow for the effects of demographic stochasticity (i.e., tracking the fate of individual hosts), replacing the deterministic SEIR model with a discrete stochastic formulation. The seminal work here is by Bartlett (1957, 1960, 1961, 1990), who used a combination of stochastic modeling and data analysis to estimate a lower population threshold for measles persistence of 250 to 500 thousand individuals. This value has also been derived by other workers (Black, 1966; Cliff and Haggett, 1988). However, stochastic effects alone cannot explain the observed pattern of recurrent nonseasonal measles epidemics commonly seen in the cities of developed countries before the vaccination era. The origin of recurrent epidemics has prompted a variety of other modifications to the simple model, most of which are concerned with the inclusion of heterogeneities in transmission.

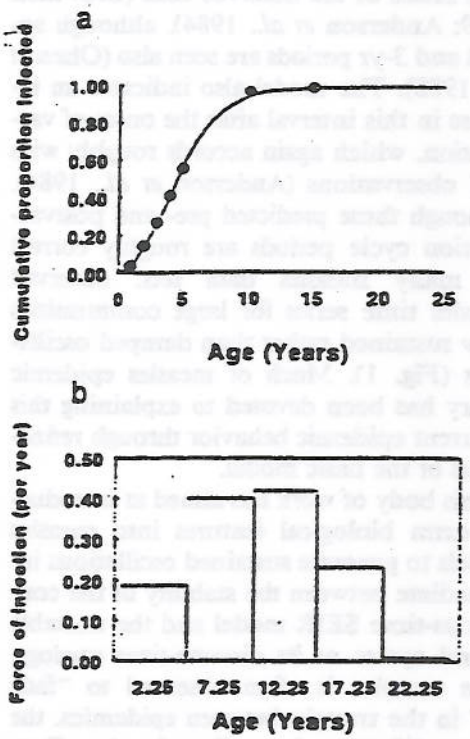

Figure 3 Typical age distribution of measles infections in developed countries before the onset of vaccination. (a) Observed cumulative proportion infected by age in England and Wales. Data from Registrar General's Weekly Reports. (b) Estimated force of infection pattern by age, showing a characteristic peak in school age children. Details of the catalytic model used are given by Grenfell and Anderson (1985). The curve in a shows the fit of this model to the raw data.

III. Modeling Heterogeneities in Measles Transmission

A. Equilibrium Models

1. Age Structure

Since the SEIR model is nonlinear, the simplest way to explore how heterogeneities affect its behavior is by considering the equilibrium properties of the associated models.

Fig. 3a shows a typical cumulative age distribution of infection for measles in developed countries before vaccination (Fine and Clarkson, 1982a; Grenfell and Anderson, 1985). This sigmoid pattern generates estimates of the age-specific force of infection that are emphatically not constant, but rise to a peak in school-age children and subsequently decline in adults (Fig. 3b). The implications of this peak in the force of infection, which reflects higher contact rates between children in school, has been examined by a number of workers (Fine and Clarkson, 1982b; Anderson and May, 1985; Dietz and Schenzle, 1985; Tudor, 1985). The basic theoretical approach is replacing the ordinary differential equations (ODEs) of the SEIR model with partial differential equations (or sets of ODEs), describing the progression of infection through age and time. The equilibrium approach then considers the temporal steady state of the system, leading to a set of ODEs that describes the age distribution of susceptibles, infections, and so on. The general conclusion of this approach is that a peaked force of infection pattern generates a lower estimate of the critical level of vaccination (p_c) than the average infection rate implicitly assumed in the SEIR model (Schenzle, 1984; Anderson and May, 1985), essentially because mass vaccination near birth increases the mean age at infection of unvaccinated individuals, so they are exposed in an older age group with a lower force of infection. This effect is particularly important in other childhood infections, such as rubella and mumps, for which the pattern of morbidity associated with infection peaks in the adult age groups (Anderson *et al.*, 1987; Nokes and Anderson, 1988a).

2. Spatial and Other Heterogeneities

The equilibrium approach has also yielded valuable insights into the impact of spatial heterogeneities and intrinsic (perhaps genetic) differences in infection rate (Bailey, 1975; Anderson and May, 1984; May and Anderson, 1984; Dietz and Schenzle, 1985; May, 1986). The simplest method adds compartments to the basic SEIR model to allow for spatial variations and other differences between groups of individuals.

Probably the most important result to emerge from spatial models of this type is the importance of concentrating limited vaccination efforts on centers of population (May and Anderson, 1984). The dynamic impact of heterogeneities in measles transmission is discussed subsequently.

B. Seasonality and Age Structure in Transmission Dynamics

As shown in the time series analysis of Fig. 1, the most obvious manifestation of heterogeneity in measles transmission dynamics is an annual variation in incidence, generally associated with changes in the contact rate of children, caused by the seasonal pattern of school terms (London and Yorke, 1973; Fine and Clarkson, 1982b). Several workers have modeled the effects of seasonal variations in infection rate (London and Yorke, 1973; Dietz, 1976; Grossman, 1980; Aron and Schwartz, 1984; Schenzle, 1984; Schaffer and Kot, 1985; Aron, 1990). The simplest approach involves replacing the constant infection parameter β of Eq. 1 with a time-varying periodic function, such as

$$\beta(t) = b_0[1 + b_1\cos(2\pi t)], \qquad (7)$$

where b_0 is the average infection rate and b_1 controls the amplitude of variation around it. This formulation has been examined both in the epidemiological literature (London and Yorke, 1973; Dietz, 1976) and in the exploration of nonlinear dynamics in measles incidence (Aron and Schwartz, 1984; Schaffer, 1985a; Schaffer and Kot, 1985; Olsen and Schaffer, 1990; Rand and Wilson, 1991). In terms of the maintenance of recurrent epidemics, seasonal variations in infection rate can interact with the damped epidemics of the SEIR model to produce sustained cycles. An example of this behavior (which can be modeled in terms of resonance for small degrees of seasonal forcing, i.e., for small b_1; Dietz, 1976) is displayed in Fig. 4a. As discussed subsequently, the situation is more complex for large degrees of forcing.

However, an important biological complexity must be addressed first. Specifically, these seasonal variations in transmission are also intimately bound up to the heterogeneities in transmission with age that are illustrated in Fig. 3. In an important paper, Fine and Clarkson (1982a) used measles data for England and Wales to document the sea-

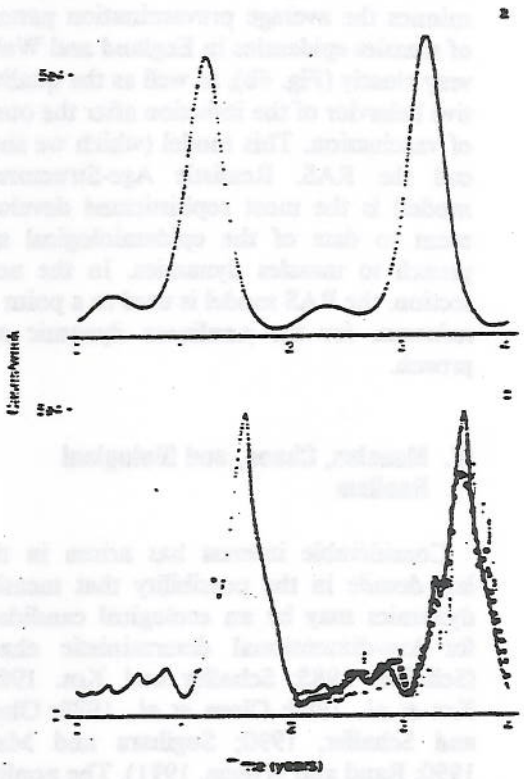

Figure 4 Time series (number of infectives) for two measles models. (a) Sinusoidally forced SEIR model (biennial regime: $c_0 = 1.5 \times 10^{-3}$, $c_1 = 8.5 \times 10^{-4}$). The model is formulated as $\beta = c_0 + c_1[1 + \cos(2\pi t)]$ rather than the more standard form to match the RAS model more closely. (b) RAS model. Contact rates adjusted for best fit (least squares) to England and Wales data. Other parameters are as given by Schenzle (1984). Points represent the mean value of corrected (Fine and Clarkson, 1982a) weekly case reports for England and Wales for a given point in the biennial cycle over the years 1950–1964. Error bars show one standard deviation above and below the mean.

sonal increase in infection rate, particularly of primary school children, associated with the pattern of school terms.

Although introducing age structure alone into the SEIR model does not affect its behavior qualitatively, the combination of age structure and seasonality in transmission has a profound impact. In particular, Schenzle (1984) implemented the qualitative model of Fine and Clarkson in a continuous-time age–cohort formulation that mimics the average prevaccination pattern of measles epidemics in England and Wales very closely (Fig. 4b), as well as the qualitative behavior of the infection after the onset of vaccination. This model (which we shall call the RAS, Realistic Age-Structured, model) is the most sophisticated development to date of the epidemiological approach to measles dynamics. In the next section, the RAS model is used as a point of reference for the nonlinear dynamic approach.

IV. Measles, Chaos, and Biological Realism

Considerable interest has arisen in the last decade in the possibility that measles dynamics may be an ecological candidate for low-dimensional deterministic chaos (Schaffer, 1985; Schaffer and Kot, 1985; Kot *et al.*, 1988; Olsen *et al.*, 1988; Olsen and Schaffer, 1990; Sugihara and May, 1990; Rand and Wilson, 1991). The nonlinear analysis of measles dynamics has been based on both observed incidence time series (Olsen *et al.*, 1988; Sugihara and May, 1990) and data generated from theoretical models (Schaffer, 1985a; Rand and Wilson, 1991; Grenfell, 1992b). Although the main issue in the former case is whether observed time series are sufficiently long to detect the signature of chaos (Nychka *et al.*, 1992), the main theoretical issue is whether the forced SEIR model is sufficiently biologically realistic to represent measles dynamics adequately. This latter issue is addressed in the following sections.

A. Dynamics of the Forced SEIR Model

The dynamical systems literature has spawned a number of approaches for detecting chaos in time series generated from theoretical models. These methods [which are well reviewed by May *et al.* (1992) and Nychka *et al.* (1992)] generally depend on estimating either the dimension of the attractor to which the system's dynamics settle (e.g., zero for a simple equilibrium, 1 for a two-population limit cycle, and fractional for a chaotic attractor), or the tendency for nearby trajectories in phase space (corresponding, for example, to successive minima in the epidemic cycle) to diverge with time in chaotic systems. The characteristic measure of this sensitivity to initial conditions of chaotic systems is the maximum Lyapunov exponent, which is positive if, on average, near trajectories tend to diverge with time and negative if they converge. An important general caveat is that Lyapunov exponents (in addition to all other proposed signatures for chaos) must be interpreted cautiously in the presence of random variability embedded in the nonlinear process.

We illustrate the non-linear properties of the seasonally forced SIR model (a close analog of the SEIR model, but lacking an exposed class) with a series of numerical simulations for a range of values for the amplitude of sinusoidal forcing, controlled by the parameter b_1 in Eq. 7. The results, shown in Fig. 5 as time and I vs S phase space plots, reflect a progression from a simple annual cycle ($b_1 = 0.01$) through a sequence of period doubling as b_1 increases, to irregular chaotic fluctuations at $b_1 = 0.28$, the value proposed by Schaffer and collaborators (Olsen *et al.*, 1988). Although other workers suggest that this degree of seasonal forcing may be unrealistically high (Pool, 1989; Grenfell, 1992b), work on the impact of demographic and environmental noise

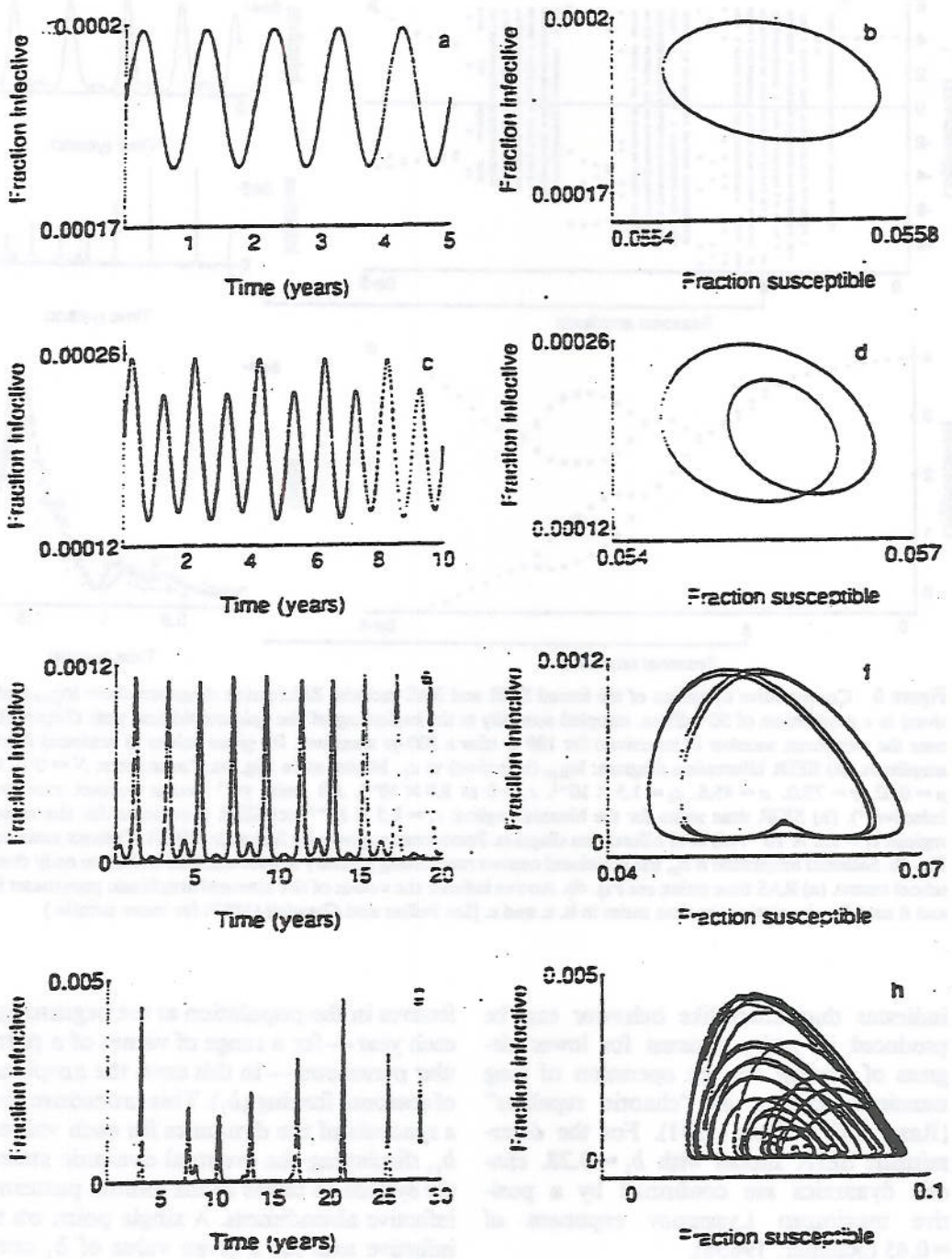

Figure 5 Dynamics of the seasonal SIR model. Time (I vs t) (a,c,e,g) and phase (S vs I) plots (b,d,f,g) for different seasonal amplitudes b_1. Vertical axis shows proportion of population infective; horizontal axis shows time in years. (a,b) Annual cycle ($b_1 = 0.01$); (c,d) biennial cycle ($b_1 = 0.05$); (e,f) 8-yr cycle ($b_1 = 0.267$); (g,h) large amplitude chaos ($b_1 = 0.28$).

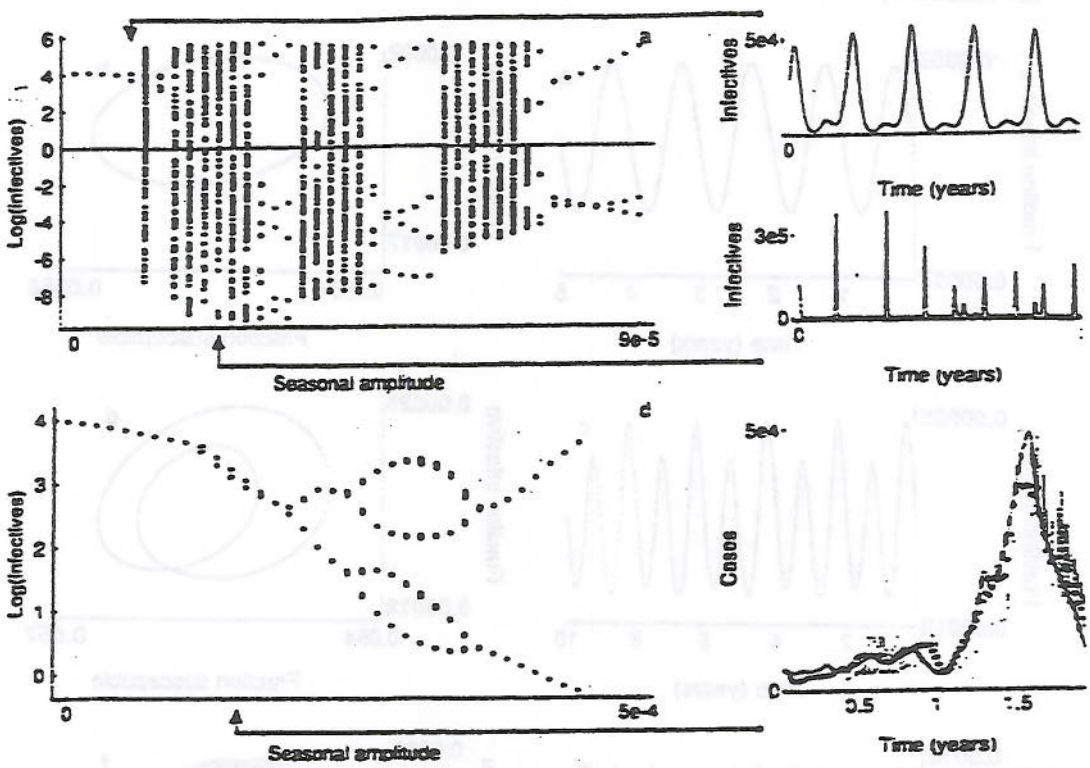

Figure 6 Comparative dynamics of the forced SEIR and RAS models. Bifurcation diagrams show $\log_{10}$ (infectives) in a population of 50 million, sampled annually at the beginning of the epidemiological year (September, near the minimum number of infectives) for 100 yr after a 200-yr transient, for given values of seasonal forcing amplitude. (a) SEIR bifurcation diagram: $\log_{10}$ (infectives) vs c_1. Model as in Fig. 4a. Parameters: $N = 5 \times 10^7$, $\mu = 0.02$, $\gamma = 73.0$, $\sigma = 45.6$, $c_0 = 1.5 \times 10^{-3}$, $c_1 = 0$ to 9.0×10^{-3}. All units yr^{-1} except contact rate (yr^{-1} infective^{-1}). (b) SEIR time series for the biennial regime: $c_1 = 8.5 \times 10^{-6}$. (c) SEIR time series for the chaotic regime: $c_1 = 2.0 \times 10^{-5}$. (d) RAS bifurcation diagram. Parameters as given by Schenzle (1984). Contact rates as in Fig. 4b. Seasonal amplitude is b_2, the additional contact rate among primary school children (effective only during school terms). (e) RAS time series: see Fig. 4b. Arrows indicate the values of the seasonal amplitude parameter in a and d used for simulating the time series in b, c, and e. [See Bolker and Grenfell (1993) for more details.]

indicates that chaos-like behavior can be produced in noisy systems for lower degrees of forcing via the operation of long transients known as "chaotic repellers" (Rand and Wilson, 1991). For the deterministic SEIR model with $b_1 = 0.28$, chaotic dynamics are confirmed by a positive maximum Lyapunov exponent of ≈ 0.45 (Schaffer, 1985a).

Fig. 6a shows a broader view of the dynamics of the model in a standard bifurcation diagram. Bifurcation diagrams are constructed by sampling a system periodically—in this case, recording the number of infectives in the population at the beginning of each year—for a range of values of a particular parameter—in this case, the amplitude of seasonal forcing (b_1). This procedure gives a synopsis of the dynamics for each value of b_1, displaying the eventual dynamic state of the system in terms of the annual pattern of infective abundances. A single point on the infective axis for a given value of b_1 corresponds to a stable equilibrium or an annual cycle at that parameter value; two points correspond to a biennial cycle, and so forth. A large number of points means that the system is continuing to display irregular be-

havior after long transients, a hallmark of chaos. This picture clearly illustrates the transition to chaos with increasing seasonal forcing of the infection rate. However, this irregular deterministic behavior also is characterized by large amplitude fluctuations with very low minima (to $10^{-14} \times$ population size in Fig. 6a). This unrealistically low figure is the basis of a number of criticisms of the SEIR/chaos result (Pool, 1989; Grenfell, 1992b). In particular, the associated degree of "fade-out" of infection appears to be significantly larger than that observed, even in model cities of one million people [i.e., over twice the population threshold empirically derived by Bartlett (1960), and Black (1966)]. Although spatial heterogeneity appears to reduce the degree of fade-out slightly, fade-out remains a significant problem in terms of modeling the nonlinear dynamics of measles with the SEIR model (Grenfell, 1992b). This situation is explored, in terms of the dynamics of the more realistic RAS model, in the next section.

B. Dynamics of the Realistic Age-Structured Model

Fig. 6d presents a bifurcation diagram for the RAS model, corresponding to the SEIR bifurcation diagram of Fig. 6a. The picture that emerges here is dramatically different. Although the RAS model does undergo some period doubling as seasonal forcing increases, no evidence exists of irregular chaotic fluctuations in the density of infectives. The important biological point apparent in Fig. 6d is that the (interepidemic) infective minima for the RAS model are much higher than in the SEIR model (and therefore more biologically realistic). Bolker and Grenfell (1993) showed that this feature, in turn, leads to a lower propensity for chaos, which is associated in this class of models with divergence of model trajectories at low infective densities.

This qualitative difference between SEIR and RAS model dynamics arises from the additional population heterogeneity introduced in the more realistic RAS model. Specifically, the relatively small force of infection in the preschool age group (Fig. 3b) allows this segment of the population to act as a reservoir of infection, preventing the violent swings in infective density that are generated in the highly forced SEIR model (Bolker and Grenfell, 1993).

Overall, this result clearly illustrates a general implication for ecological dynamics: introducing extra biological complexity into models sometimes can simplify their behavior, particularly if the introduction of heterogeneity reduces the propensity for extreme dynamics (Grenfell, 1992a). Adding more realism in terms of demographic noise leaves the model essentially intact although, as discussed by Bolker and Grenfell (1993), additional biologically interesting dynamic complexities emerge as human population size decreases. Specifically, whereas stochastic models for large populations (for example, 50 million) exhibit regular biennial epidemics, these models can break down into more complex behaviors with mixtures of 1-, 2-, and 3-yr cycles in populations of 1 million individuals. This tendency raises the issue of spatial dynamics which, as discussed subsequently, appears to be the major direction for future work in this area.

V. Conclusion and Directions for Future Work

This chapter provides a brief summary of theoretical approaches to the epidemiology and population dynamics of measles. Given the huge breadth of this subject, omissions have been inevitable. For example, the very different epidemiological patterns for measles in developing countries (the most important area in an applied sense) has been modeled successfully (McLean and Anderson, 1988a,b), although any implications of seasonal patterns of infection in these systems have not yet been explored. This chapter has concentrated on the situation in de-

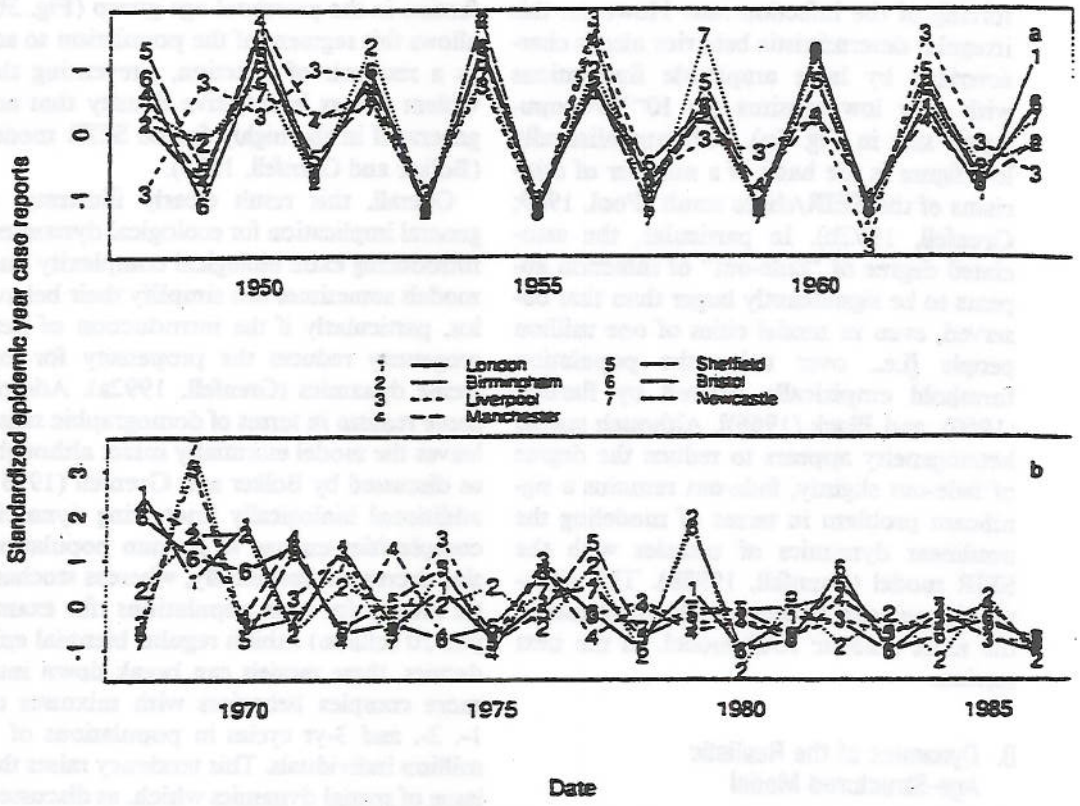

Figure 7 Standardized total measles incidence in epidemiological years (1 Oct–30 Sept) for seven cities in England and Wales. Annual totals for each city were standardized by subtracting the city mean annual incidence, then dividing by the city standard deviation of annual incidence. (a) Prevaccination period. 1948–1966. (b) Vaccination period. 1968–1988.

veloped countries, where the simple SEIR model indicates that relatively strong and predictable seasonality could interact with the propensity for longer term cycles to produce complex chaotic dynamic behavior. An initial evaluation of this result using more realistic epidemiological models indicates that population heterogeneity, in terms of the age distribution of infection, has the potential to simplify this scenario. However, these results interact with the population size (and, therefore, the spatial arrangement) of the host (Bolker and Grenfell, 1993). Spatial dynamics are likely to constitute a major direction for future work in this area.

A. Spatial Heterogeneity and Measles Dynamics

In an interesting discussion of measles dynamics, Olsen *et al.* (1988) underlined the importance of spatial heterogeneity and, in particular, partial spatial coupling between cities in perpetuating the infection. Partial coupling in this context means that susceptible and infective individuals from different places meet often enough to keep disease from fading out entirely in the population, but not so often that the entire population experiences large synchronous epidemics, which also would lead to extinction of the disease. This nonlinear perspective on per-

sistence echoes a large and sophisticated body of work on the spatial geography of measles epidemics (Murray and Cliff, 1975; Cliff and Ord, 1978; Cliff and Haggett, 1988). Although the degree of coupling does not appear to be able to explain completely the persistence of measles in seasonally forced systems, without an appeal to the age effects noted earlier (Grenfell, 1992b), the question of spatial heterogeneity is clearly very important. In particular, more theoretical work is needed to examine the impact of seasonality and age structure on the balance between measles fade-out and coupling in spatial grids with relatively small individual population sizes, corresponding to the spatial arrangement of hosts within and between cities. These questions also can be explored in terms of the available empirical data. For example, Fig. 7 shows observed annual measles notifications for seven cities in England and Wales, before and after the onset of vaccination in 1968. In the prevaccination era (Fig. 7a), epidemics in the cities were relatively in phase, although significant heterogeneities are apparent (Bartlett, 1957), particularly with respect to the Liverpool notifications (which show much higher epidemic minima). The theoretical task is establishing whether England and Wales were coupled sufficiently to be an epidemiological unit before vaccination and the origins (possibly arising from local differences in demography) of systematic departures from the overall pattern. After the onset of vaccination (Fig. 7b), the epidemics in cities were much more irregular in timing, and apparently less in phase with each other. Again, the basis of this irregularity (whether associated with spatial dynamics *per se* or, for example, with regional variations in vaccine uptake) is at the heart of the problem of measles spread and persistence. This issue is also of considerable applied importance since vaccine uptake continues to rise to different extents in different areas.

Overall, recent developments suggest that measles dynamics will continue to present a fascinating challenge for epidemiologists, ecologists, and applied mathematicians. The whole question of the interaction between spatial dynamics and the possibility of chaotic dynamics on some populations scales is likely to be particularly fruitful.

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