The Interplay between Determinism and Stochasticity in Childhood Diseases

Pejman Rohani,[1,2,*] Matthew J. Keeling,[2,3] and Bryan T. Grenfell[2]

1. Institute of Ecology, University of Georgia, Athens, Georgia 30602-2202;
2. Department of Zoology, University of Cambridge, Downing Street, Cambridge CB2 3EJ, United Kingdom;
3. Department of Biological Sciences and Mathematics Institute, University of Warwick, Coventry CV4 7AL, United Kingdom

Submitted August 14, 2000; Accepted November 6, 2001

ABSTRACT: An important issue in the history of ecology has been the study of the relative importance of deterministic forces and processes noise in shaping the dynamics of ecological populations. We address this question by exploring the temporal dynamics of two childhood infections, measles and whooping cough, in England and Wales. We demonstrate that epidemics of whooping cough are strongly influenced by stochasticity; fully deterministic approaches cannot achieve even a qualitative fit to the observed data. In contrast, measles dynamics are extremely well explained by a deterministic model. These differences are shown to be caused by their contrasting responses to dynamical noise due to different infectious periods.

Keywords: population dynamics, epidemiological models, seasonality, stochasticity.

A debate at the heart of ecology has concerned the extent to which observed ecological dynamics are shaped by deterministic processes as opposed to stochasticity (e.g., Andrewartha and Birch 1954; Nicholson 1957). Throughout much of the last century, however, the emphasis in theoretical studies seemed to be firmly on deterministic approaches to ecology. These resulted in many important conceptual breakthroughs (e.g., Pearl and Read 1920; Lotka 1925; Kermack and McKendrick 1927; Nicholson and Bailey 1935; May 1974; Anderson and May 1978; Hassell 1978) and established the basic framework for modeling typical ecological interactions, while highlighting their characteristic dynamics. Such deterministic models are still widely used in present-day ecology and have proved invaluable in providing us with a qualitative understanding of population dynamics.

In recent years, there has been a growing trend toward confronting model predictions with data from studies of ecological systems in the laboratory and in the field. Many of these studies have uncovered a subtle interaction between stochasticity (be it environmental or demographic) and the deterministic nonlinearities inherent in most ecological interactions (Zimmer 1999). These range from studies showing stochastically excited oscillations in the dynamics of Dungeness crab populations (Higgins et al. 1997) to stable manifolds in dynamics of laboratory flour beetle populations (Cushing et al. 1998) and from establishing the role of environmental stochasticity on sheep populations (Grenfell et al. 1998; Coulson et al. 2001) to understanding multiple coexisting attractors in marine microorganism ecosystems (McCauley et al. 1999). These studies represent a growing list of ecological systems that cannot be fully understood by purely deterministic approaches.

In the laboratory flour beetle populations, for example, it has been noted that identical experimental replicates exhibit very different transient dynamics (see also Sait et al. 2000). As Cushing et al. (1998) explained, this was caused by the interaction between demographic noise and the stable manifold of a saddle node. Another example of how stochasticity can affect population dynamics was provided by Grenfell et al. (1998), who showed that fluctuations in Soay sheep populations have two key components. If sheep numbers are low, then density-independent growth is observed, while at intermediate/high numbers, population size may either increase or decrease, depending on environmental conditions and the sex and age structure of the population (Grenfell et al. 1998; Coulson et al. 2001). It is clear that in models of such systems, a stochastic element is essential if the key features of the dynamics are to be successfully captured.

An ideal "field" system for clarifying the interaction between noise and determinism would furnish time series data, reflecting dynamics at a range of spatial scales, levels

* Corresponding author; e-mail: rohani@uga.edu.

Am. Nat. 2002. Vol. 159, pp. 469–481.

of exposure to stochasticity, and parameter regimes. Furthermore, these dynamics would be captured successfully by mechanistic models, which can be tuned to analyze the relative impact of environmental and demographic noise and nonlinear deterministic forces.

A strong candidate for this paradigm is provided by the great microparasitic diseases of childhood, notably measles and whooping cough. The seminal synthesis of deterministic and stochastic approaches to these systems (and more specifically to measles epidemics) is by Bartlett (1957), who demonstrated a strong interaction between demographic stochasticity, environmental variability (seasonality), and delayed density dependence. More recent theoretical studies by Schwartz and Smith (1983) and Rand and Wilson (1991) have also shown how epidemics may be subtly affected by noise. Here, we build on these foundations to examine these interactions in greater detail, with the additional benefit of a different "experimental treatment," as represented by the introduction of nationwide vaccination regimes (Anderson and May 1991).

In this article, we examine models for childhood diseases in developed countries, analyzing the large-amplitude oscillations by studying their behavior near the deterministic dynamical attractor. In a dynamical context, deterministic forces pull trajectories toward an attractor, whereas stochasticity tends to cause trajectories to leave the attractor. Establishing the precise balance between the deterministic forces and the susceptibility of the system to stochastic influences remains a key challenge. We are primarily interested in exploring the importance of dynamical noise for the large-scale prevaccination epidemics of measles and whooping cough in England and Wales. We explain in more detail the results reported recently by Rohani et al. (1999; 2000*a*), who argued that large-scale whooping cough epidemics are extremely sensitive to noise, while measles outbreaks can be effectively explained by simple deterministic models (Earn et al. 2000). We show that while measles and whooping cough are relatively similar, both in broad natural history and reproductive potential, their nonlinear dynamics are subtly different. The deterministic whooping cough attractor (both in the prevaccine and vaccine eras) is shown to be very prone to stochastic effects, causing "transient" dynamics that are qualitatively different from its asymptotic dynamics. The prevaccination measles attractor, however, is very stable, showing pronounced biennial outbreaks, and trajectories pushed off the attractor return to it in a biennial fashion. We explore these phenomena using what we term the "invasion orbit," which highlights the dynamical topology near the deterministic attractor. Note that throughout this article, we refer to the "measles attractor," by which we mean the biennial attractor that is observed in large cities in developed countries in the postwar, prevaccination era. This pattern is clearly seen in the 1950–1968 period in England and Wales and in the postwar period in New York City, Baltimore, and Copenhagen (Earn et al. 2000).

Data

Due to their recognized importance, weekly case reports for diseases such as measles and whooping cough in different cities of England and Wales have been collected since 1939, while records of deaths due to these infections date back to 1897. Similarly high-resolution data sets can be found for many large cities in Europe and North America. Clearly, by ecological standards, these represent precious means of exploring the dynamics of a natural host-parasite system, and indeed, numerous studies of measles epidemics exist (Hethcote 1983; Schaffer and Kot 1985; Olsen and Schaffer 1990; Sugihara et al. 1990; Anderson and May 1991; Bolker and Grenfell 1993; Engebert and Drepper 1994; Ferguson et al. 1996; Ellner et al. 1998; Grenfell and Harwood 1998; Rohani et al. 1998; Earn et al. 2000). While many of these high-profile studies have looked for signals of dynamical chaos in measles time series (Olsen and Schaffer 1990; Sugihara et al. 1990; Engebert and Drepper 1994), others have focused on the mechanisms generating the observed pattern of outbreaks (Hethcote 1983; Schenzle 1984; Bolker and Grenfell 1993; Earn et al. 2000). The observed patterns in England and Wales range from annual outbreaks in the years immediately following World War II to spatially synchronized biennial outbreaks in the period from 1950 to 1968 as well as to complicated dynamics (with no characteristic signal) in the ensuing vaccine era (fig. 1*A*).

The case reports for whooping cough have received much less attention from ecologists, perhaps partly because whooping cough large-scale dynamics appear somewhat irregular (fig. 1*B*). In contrast to measles epidemics, the prevaccine-era dynamics of whooping cough are less regular and spatially uncorrelated (Fine and Clarkson 1982; Grenfell and Anderson 1989; Hethcote 1998; Rohani et al. 1999). In each city, bouts of annual whooping cough outbreaks are punctuated by periods of 2–2.5-yr epidemics. This pattern is drastically altered in the vaccine era, where spatially synchronized 3.5–4-yr outbreaks are observed (Rohani et al. 1999, 2000*a*, 2000*b*).

The England and Wales data are thought to be relatively accurate for measles, representing around 60% of true cases (Clarkson and Fine 1985; Finkenstadt and Grenfell 2000). The accuracy of reporting is thought to be lower for whooping cough (between 5%–25% of actual cases; Clarkson and Fine 1985; Hethcote 1997). Although notification accuracy will alter the amplitude of fluctuations, it is unlikely to affect the dynamical pattern of epidemics. In fact, it has been previously demonstrated that there is

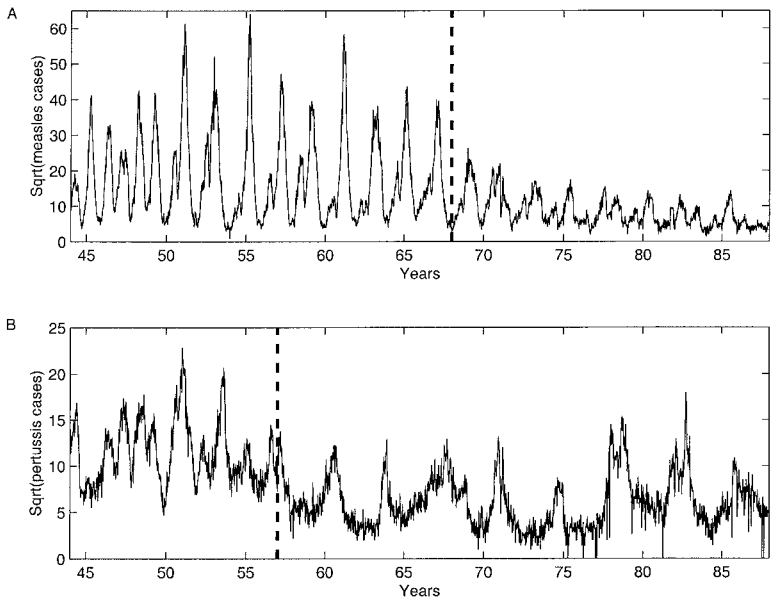

Figure 1: Aggregate measles and whooping cough notifications in England and Wales from 1944 to 1994; data obtained from the Registrar General's Weekly Returns. *A*, Time series for square root of measles cases in England and Wales, with vaccination starting in 1968 (*dotted line*). *B*, Square root of cases of whooping cough in England and Wales, with the onset of national vaccination indicated by the dotted line.

very strong correlation between the case reports we present and isolations of the whooping cough bacterium (*Bordetella pertussis*) by the Public Health Laboratory Service (Miller et al. 1992). There are also independent notifications provided by the Royal College of General Practitioners General Practice Research Unit (Fine and Clarkson 1982) that show a very strong correlation with the case-report data.

SEIR Formalism

Both measles and whooping cough are respiratory infections, with estimated reproductive potentials (R_0) of 16–18 (Anderson and May 1991). Measles is caused by a virus in the morbillivirus family, while (as mentioned above) whooping cough is caused by a bacterium. Both infections are transmitted by aerosol particles and are highly infectious, with approximately 90% of susceptible (close) family contacts acquiring the infection (Behrman and Kliegman 1998). The latent period ($1/\sigma$) for both diseases lasts approximately 8 d, and the effective infectious period ($1/\gamma$) is about 5 d for measles and approximately 14 d for whooping cough (Behrman and Kliegman 1998; Rohani et al. 1999). The infection process is well described by the classic SEIR (susceptible, exposed, infectious, or recovered) formalism in which hosts are categorized according to infection status. Although the immunological response to whooping cough can be more complex than measles, its overall dynamics can be qualitatively well captured by this modeling framework (Rohani et al. 1999, 2000*a*).

The basic system of differential equations describing the SEIR framework for a constant population of size N are given by

$$\frac{dS}{dt} = \mu N - \left[\frac{\beta(t)I}{N} + \mu\right]S, \tag{1}$$

$$\frac{dE}{dt} = \frac{\beta(t)I}{N}S - (\mu + \sigma)E, \tag{2}$$

$$\frac{dI}{dt} = \sigma E - (\mu + \gamma)I, \tag{3}$$

$$\frac{dR}{dt} = \gamma I - \mu R. \tag{4}$$

Here, $1/\sigma$ and $1/\gamma$ are the incubation and infectious periods, respectively, and μ gives the per capita birth and death rates. Since measles and whooping cough are infections that primarily affect children, the model incorporates a time-dependent contact rate ($\beta[t]$) to mimic the aggregation of children in schools. Term-time forcing is implemented by making $\beta(t) = b_0 \times (1 + b_1)$ on school days and $\beta(t) = b_0 \times (1 - b_1)$ otherwise (b_0 is the basic contact rate, and b_1 denotes the amplitude of seasonality). Note that in our simulations, we use a slightly lower amplitude

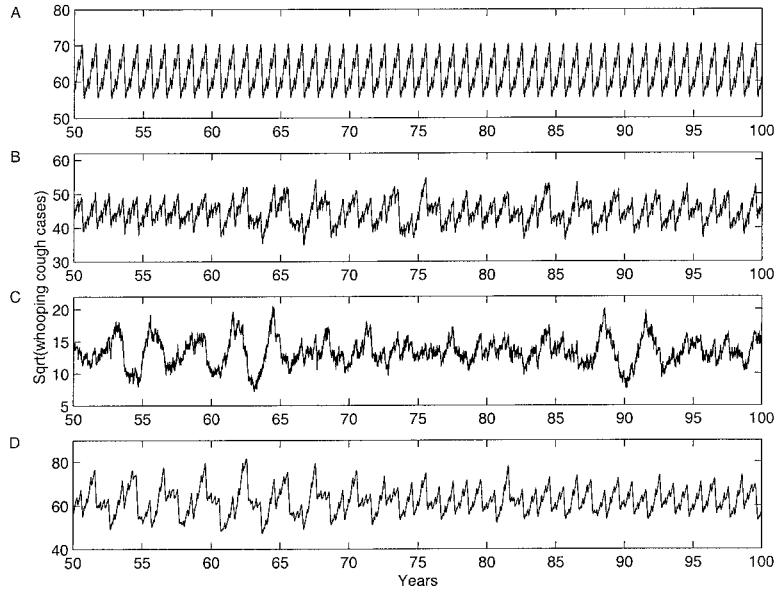

Figure 2: The dynamics of whooping cough as obtained using different implementations of the susceptible, exposed, infectious, or recovered (SEIR) model. *A*, Model is fully deterministic with $N = 5 \times 10^6$, yielding rigidly annual epidemics. *B*, Similar dynamics are observed with the analogous Monte Carlo simulation model with a large population size, $N = 5 \times 10^6$. *C*, Smaller population size, $N = 5 \times 10^5$, gives a mixture of annual epidemics and multiannual outbreaks, as was observed in the England and Wales data. *D*, We mimicked the effects of environmental stochasticity by making the transmission rate a normally distributed random variable, $\beta(t) \sim N(\bar{\beta}, 0.5 \times \bar{\beta})$. This gives qualitatively the same results as the Monte Carlo simulations. The following parameters were used in all simulations: $\mu = 0.02$/yr; $1/\sigma = 8$ d; $1/\gamma = 14$ d; $b_1 = 0.15$; $b_0 = 416$ (giving an R_0 of 17).

of forcing for whooping cough. We do this because our analyses of both age-structured models and time series approaches (similar to those of Finkenstädt and Grenfell 1999) reveal that whooping cough transmission is less seasonably variable than measles transmission, despite the two diseases' identical underlying contact patterns. We stress that although this lower level of seasonality for whooping cough provides a better fit to the observed data, the dynamical differences reported here are not qualitatively dependent on it.

In this article, we also explore the analogous stochastic (Monte Carlo) model, which assumes the same intrinsic processes as the above equations but is event driven (the algorithm for the process is described in detail in the appendix; Bartlett 1957; Grenfell 1992). The Monte Carlo model reveals the role that demographic noise can play in determining dynamics. However, we have also explored models with environmental stochasticity by adding multiplicative noise to the transmission parameter $\beta(t)$. Our results are not qualitatively affected by the choice of stochastic model.

Numerical Experiments

In this section, we investigate the dynamics of measles and whooping cough by means of numerical experiments. As outlined below, we are predominantly interested in exploring the "stability" of the deterministic attractor for these infections. Hence, much of what follows describes the consequences of perturbations and the qualitative behavior of transients.

The classic work of Schenzle (1984) showed how a deterministic, term-time forced age-structured SEIR model successfully captured the dynamics of measles in the prevaccination era. Recently, the work of Earn et al. (2000) suggested that age structure may not be essential for modeling large-scale measles epidemics. The message from their work was important; simple, carefully constructed, and parameterized deterministic SEIR models can reproduce the qualitative dynamics of measles extremely effectively. The same cannot be said for whooping cough, however, where both the deterministic SEIR and age-structured models produce rigidly annual outbreaks (fig. 2*A*; results for age-structured model not shown), in contrast to the observed epidemics. To understand this anomaly, we explored the dynamics of the corresponding Monte Carlo simulation SEIR model. For large population sizes (upward of 5 million), where one may expect the effects of demographic stochasticity to be negligible, the Monte Carlo model predicted largely annual whooping cough outbreaks with some longer period outbreaks (fig. 2*B*).

For smaller population sizes, however, we observe a mixture of annual and multiannual epidemics (fig. 2*C*). The same phenomenon is also observed in the deterministic model when significant environmental stochasticity is included (fig. 2*D*).

A repeat of this analysis for measles reveals no qualitative difference between the dynamics of large and small places or deterministic and stochastic models (fig. 3*A*–3*D*). This clearly points toward important differences between the stability of the measles and whooping cough attractors.

Conventionally, the stability properties of a deterministic attractor are studied by measuring the dominant Lyapunov exponent (Peitgen et al. 1992; Glendinning 1994). Our analysis of local and global Lyapunov exponents, however, failed to explain the observed patterns. In both systems, the dominant global Lyapunov exponent was negative, indicating a stable periodic attractor (with the Lyapunov exponent for whooping cough slightly more negative than that for measles). Essentially, this confirms the asymptotic stability of these attractors; small perturbations eventually die out and trajectories return to the deterministic attractor—it provides no information on the nature of transient dynamics. We also estimated local Lyapunov exponents, which revealed the regions around the measles and whooping cough attractors that are sensitive to perturbations (Keeling et al. 2001). Again, this analysis provided no explanation for the observed differences between the dynamics of the two infections.

Instead, we resort to exploring the underlying mechanisms generating these patterns by perturbing the deterministic system and studying the length and characteristics of transients. In figure 4, we present the results of a series of numerical experiments. In each of the three panels, we plot the time series for the deterministic measles model, with a perturbation at year 50. The perturbation takes the form of moving a fraction of those exposed and infectious into the recovered class, and the magnitude of the perturbations increases in successive panels of figure 4. Clearly, small perturbations have virtually no effect on the dynamics of measles, with the trajectories in figure 4*A* and 4*B* showing no discernible response. When perturbation levels become appreciably high (50% in fig. 4*C*), a slight change in the amplitude of the oscillations can be observed, although the period of these transients remains at 2 yr. We repeated these perturbation experiments at a number of points along the attractor, with no tangible qualitative difference in the observed results. Hence, the biennial measles attractor appears to robust to moderate perturbations, and trajectories that are pushed off the attractor return to it rapidly and are also biennial. In direct contrast, whooping cough dynamics appear to be very sensitive to perturbations. As shown in figure 5, all perturbations (identical in proportion to those applied to measles) result in trajectories moving off the attractor. Furthermore, whooping cough transients are characteristically different from the asymptotic dynamics, showing a clear multiannual component with a period of around 2–2.5 yr.

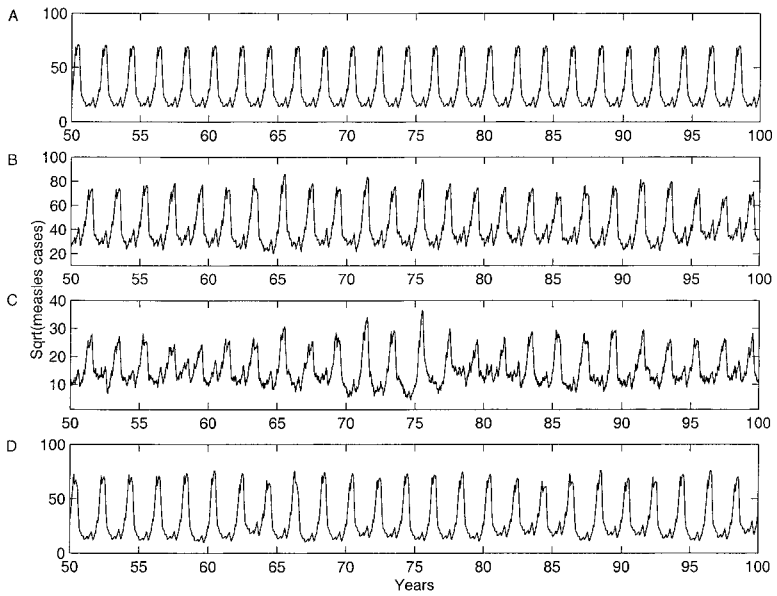

Figure 3: Identical analysis to that presented in figure 2 for measles dynamics. Model parameters: $\mu = 0.02$/yr; $1/\sigma = 8$ d; $1/\gamma = 5$ d; $b_0 = 1{,}250$; $b_1 = 0.25$.

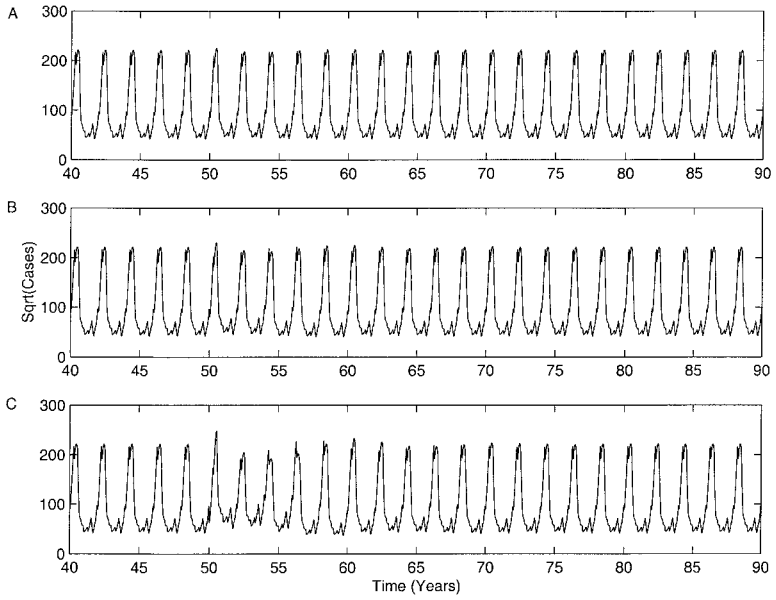

Figure 4: Numerical experiments to demonstrate the robustness of the measles attractor to perturbations. We ran the deterministic model for 50 yr, instantaneously removed a fraction of those in the exposed and infectious classes, and observed the length and characteristics of the ensuing transients. *A*, 10% of infectives were removed, with no tangible effects. *B*, Level of perturbation was increased to 20% with little discernible result. *C*, When 50% of infectives are removed, however, a noticeable change is observed. The transients, however, are biennial and approach the asymptotic attractor rapidly.

It is possible to summarize these findings by plotting the interepidemic period. Simply, at a specifically chosen point on the attractor (explained in detail below), we make a perturbation to the infective population and evaluate the time taken for a single epidemic cycle (illustrated in fig. 6*A*). This is repeated for different perturbation levels. In mathematical terms, we define (S^*, E^*, I^*) to be the fixed point of the unforced system (with β constant and $R_0 = 17$) and $(\hat{S}[t], \hat{E}[t], \hat{I}[t])$ to be a trajectory on the deterministic attractor at time t. Then, we perturb the system at time t_0, where $\hat{S}(t_0) = S^*$ and $\hat{I}(t_0) > I^*$, by applying a displacement, D, to the number of infectious individuals such that

$$S(t_0) = \hat{S}(t_0) = S^*,\ E(t_0) = \hat{E}(t_0),\ I(t_0) = \hat{I}(t_0) + D.$$

We then establish the time taken for a complete revolution in the forced system, which gives the initial interepidemic period $T(D)$ following the perturbation. More rigorously, this "return time" is given by

$$T(D) = \min [t > 0 : S(t + t_0) = S^*, I(t + t_0) > I^*]. \quad (5)$$

The results of this analysis for measles and whooping cough are shown in figure 6*B*, which demonstrates that for small displacements, the interepidemic period is unaffected. For larger perturbations (5×10^{-5} to 5×10^{-3}), however, there is a clear distinction between the two diseases; although both systems eventually return to their respective attractors, measles dynamics maintain the period of 2 yr, whereas whooping cough epidemics show multiannual fluctuations, with a period of 2–3 yr. When the displacements become extremely large, both infections take many years to approach the deterministic attractor and have long interepidemic periods (cf. Schwartz and Smith 1983).

Invasion Orbit

These findings can be understood better by exploring the topology of the system in the neighborhood of the deterministic attractor. We do so by taking annual samples of the numbers of susceptibles and infectives (at a single instant every year). In this manner, the biennial measles attractor is represented by two fixed points, and the annual whooping cough attractor is simply a fixed point in (S, I) space. To uncover the dynamical properties of the system in the neighborhood of the fixed point(s), we define the "invasion orbit." This is achieved by starting simulations at time t_δ with a very low proportion (10^{-30}) of

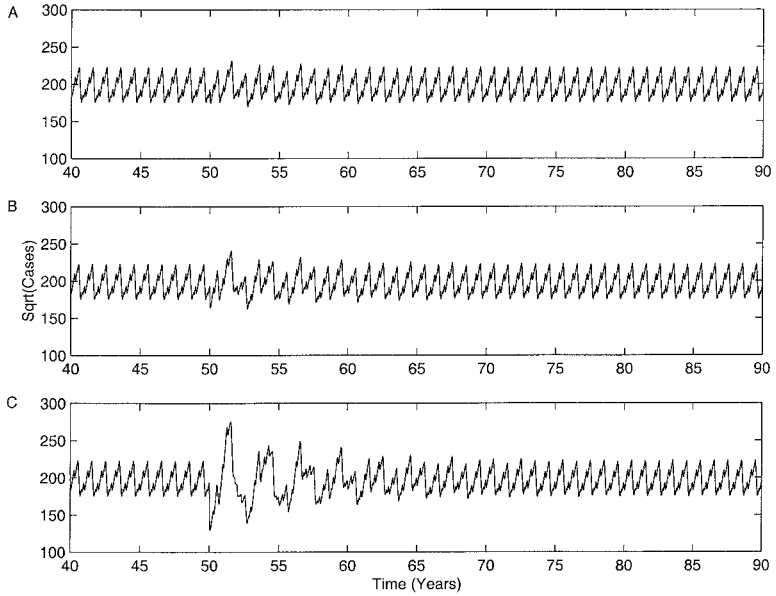

Figure 5: Numerical experiments to demonstrate the susceptibility of the whooping cough attractor to perturbations. As in figure 4, we ran the deterministic model for 50 yr, instantaneously removed a fraction of those in the exposed and infectious classes, and recorded the transient dynamics. For whooping cough, even a 10% perturbation level (*A*) results in a noticeable change. With higher levels of perturbation (20% and 50% in *B* and *C*, respectively), there are clear deviations from the deterministic attractor resulting in relatively long transient dynamics with a multiannual period.

infectives and a population composed almost entirely of susceptibles. For a number of years, we note the numbers of susceptibles and infectives at a single instant every year, after the initial transients have been discarded. The process is repeated a large number of times for increasing values of ($t_\delta \in [0, 1]$) yr; this is akin to imposing changes in initial conditions (cf. Rand and Wilson 1991). Plotting these points in phase space gives the invasion orbit: the route by which the infection invades the system and approaches the deterministic attractor. In technical terms, this gives the unstable manifold of the disease free equilibrium, $(S^*, E^*, I^*, R^*) = (N, 0, 0, 0)$.

The invasion orbits for measles and whooping cough are presented in figure 7. They demonstrate that the measles invasion orbit appears to be strongly biennial, as was suspected. Trajectories that are pushed off the attractor by noise are swept back onto it via the invasion orbit, which exhibits biennial dynamics (fig. 7*A*). The scenario for whooping cough is very different. The invasion orbit is "star" shaped and has a clear multiannual component, giving rise to fluctuations with a 2–3-yr period as trajectories approach the vicinity of the annual attractor (fig. 7*B*).

Does this approach explain disease dynamics in the vaccine era? For measles, a plausible explanation already exists. Earn et al. (2000) proposed that the character of measles epidemics is determined by the supply of susceptibles to the population. In particular, an increase in the proportion vaccinated (or equivalently, a decrease in the population birth rate) results in reduced recruitment of susceptibles, corresponding to a lowering of the effective R_0 (an observation that had previously been made by Dietz [1976] and by May [1986] for unforced systems). Models predict that measles epidemics in the vaccine era are in a region of parameter space dominated by multiple-coexisting attractors with finely intertwined basins of attraction. Hence, the complex spatiotemporal pattern of outbreaks may be the result of an intricate interaction between process noise and multiple attractors. Numerical simulations of a stochastic model appear to confirm these predictions (Rohani et al. 1999).

The epidemics of whooping cough in the vaccine era are, however, less well understood. In particular, it is important to explain why regular, nearly 4-yr epidemics are observed even though the deterministic period is still 1 yr (Hethcote 1998; Rohani et al. 1999, 2000*a*, 2000*b*). We proceed by plotting the initial period ($T[D]$) following a displacement (D), which shows that for a large range of displacements (7×10^{-5} to 2×10^{-3}), the initial period is approximately 4 yr (fig. 8*A*). Again, we believe this period is explained by the invasion orbit which, in the vicinity of the annual fixed point, shows a clear 4-yr structure (fig. 8*B*).

Naturally, we wish to know why two diseases with a

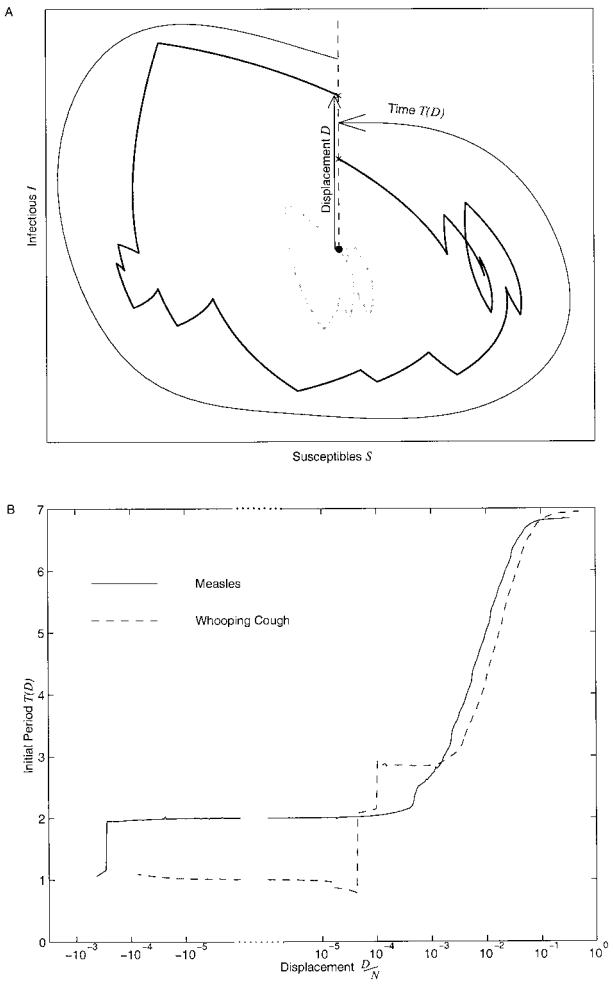

Figure 6: *A*, Illustration of the method used to estimate the initial period ($T[D]$) after a displacement (D) has been applied to the number of infectives. The grey line represents the deterministic attractor, and the black line shows a trajectory following the displacement. *B*, Estimated initial periods for measles (*solid line*) and whooping cough (*dashed line*).

broadly similar natural history, affecting the same population, with roughly the same R_0 can have such different nonlinear properties as observed by their differing responses to stochasticity. The key difference lies in the constituent components of R_0. For the SEIR system, $R_0 \approx \overline{\beta}/\gamma$ (i.e., it is approximately the product of the mean transmission probability, $\overline{\beta}$, and the infectious period, $1/\gamma$). Measles, with an effective infectious period of 5 d, must have a very high mean transmission probability compared to whooping cough, where the infectious period lasts for approximately 14 d.

Differences in the transmission probability and the infectious period are translated into dynamical differences via the interaction with the seasonal changes in contact rates. Given the relatively brief infectious period of measles, the 2-wk school break over Christmas holidays, for example, plays an important dynamical role as the transmission rate remains low over a complete epidemiological generation of the disease (as opposed to the generation length of an individual virus particle). Whooping cough, however, displays much weaker "resonance" with seasonal forcing due to its longer epidemiological generation length and is primarily affected by the relatively long period of low contact rates during the summer months. We believe it is this key difference that explains why the measles attractor is much more robust to perturbations compared to whooping cough.

The reason for the differences in the structure and period of the invasion orbits is, however, not immediately obvious. We speculate that they may be due to the differing natural time scales of the two infections, which dictate the decay of perturbations to the attractor (a lucid account of this is given by May [1986]). By plotting the dynamics annually, the deterministic attractor is contracted to one or two points, and it is simply the behavior of the perturbation that is observed. Locally, at each point on the attractor, the behavior of a small perturbation is governed by the Jacobian at that point. The natural frequency predicted by the Jacobian of the unforced system changes little around the attractor and hence oscillations in the perturbations occur with approximately the period (T) predicted by

$$T = 2\pi\sqrt{AG}. \tag{6}$$

Here, A represents the mean age at infection, $\approx 1/\mu(R_0 - 1)$, and G gives "generation length" of the infection, $G = [1/(\mu + \gamma)] + [1/(\mu + \sigma)]$ (Anderson and May 1991; Hethcote 2000). Using this argument, the natural resonant time scale of measles is 2.05–2.37 yr (given $G = 3.56 \times 10^{-2}$ yr and assuming a mean age at infection of 3–4 yr). For whooping cough, however, again assuming a mean age at infection of 3–4 yr but with $G = 6.02 \times 10^{-2}$ yr, we obtain a natural period of 2.67–3.13 yr. The actual periods observed in the England and Wales data are, however, slightly lower (2–2.5 yr). This is likely to be explained by the waning of immunity in some individuals (Miller et al. 1992; Hethcote 1998), which would reduce the mean age at infection and lower the natural period. In the vaccine era, the mean age at infection for whooping cough is likely to have risen to 5–7 yr, giving a natural period of 3.49–4.14 yr (Rohani et al. 1999). This predicted period is only rigorously true for relatively small perturbations of the kind induced by demographic stochasticity. Deviations that are too small will result in dynamics identical to those of the attractor, while extremely large perturbations cause long-period damped oscillations (fig. 6).

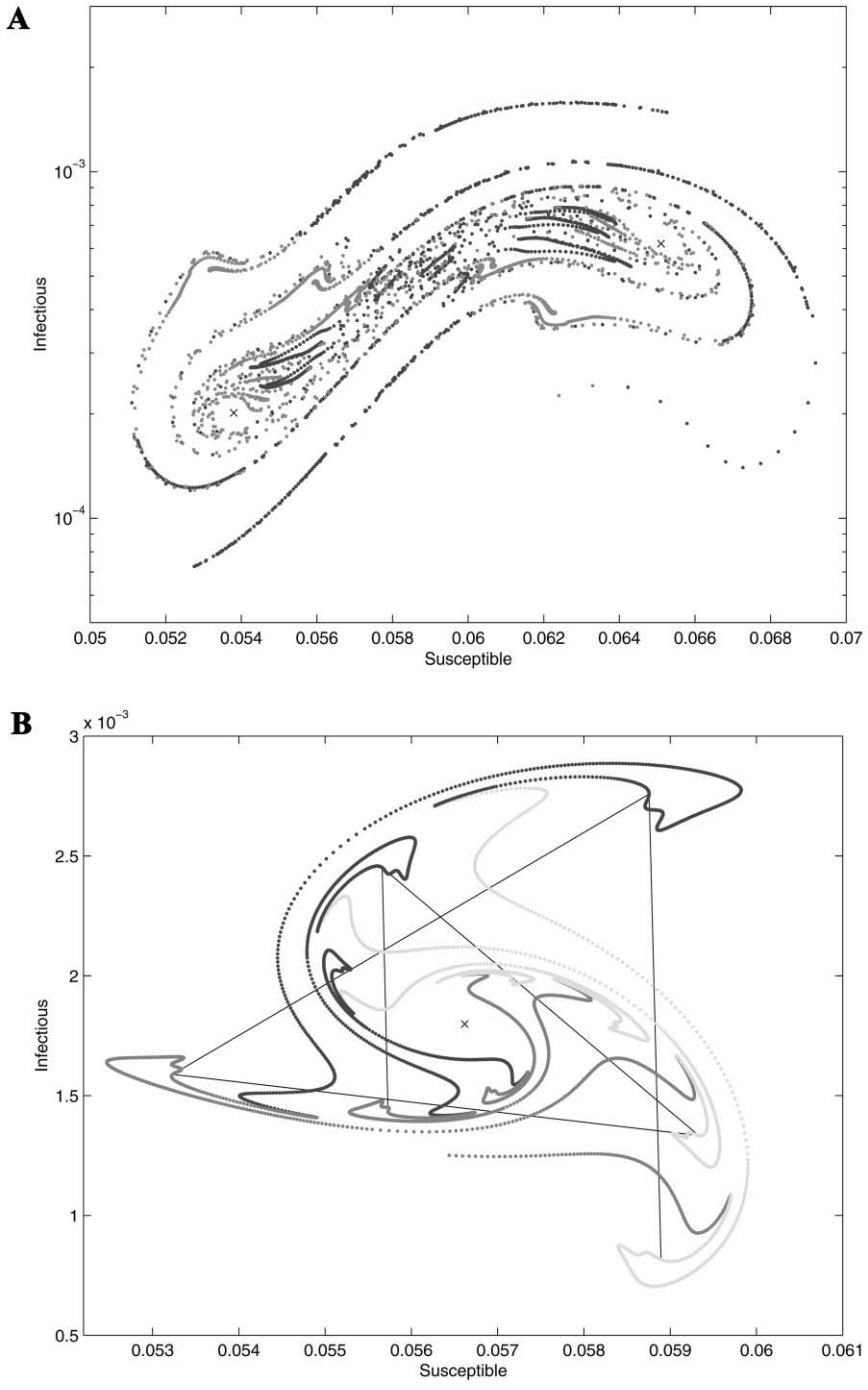

Figure 7: Invasion orbits for (*A*) measles and (*B*) whooping cough. The recipe used to uncover these structures is described in the main text. Model parameters are as stated in figures 2 and 3. *A*, Plotted instantaneous number of infectives and susceptibles for years 20–25. *B*, Plotted instantaneous number of infectives and susceptibles for years 20–30. In both plots, different shadings are used for different years to highlight the relevant multiannual structure of the invasion orbit. The solid line in *B* follows the path of a specific trajectory.

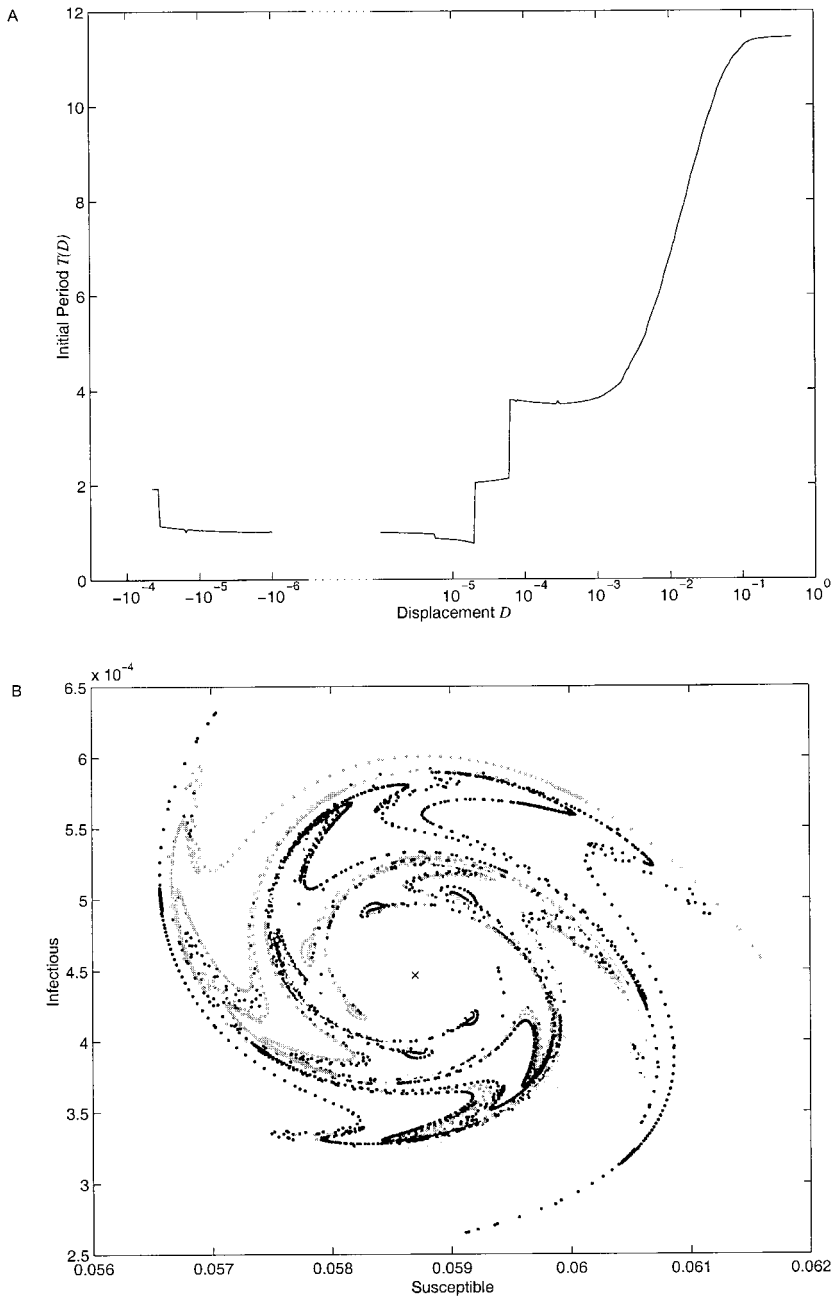

Figure 8: Whooping cough dynamics in the vaccine era. *A*, Initial period following a displacement. *B*, Invasion orbit, clearly highlighting its 4-yr structure. Model parameters are as stated in figure 2 with a vaccination level of 60%. The data points in *B* represent the instantaneous number of infectives and susceptibles for years 60–70.

Discussion

Historically, deterministic approaches to ecological problems have dominated our thinking. With distinguished exceptions, the importance of stochasticity has often been ignored. Two common justifications for this have been that chance events are most important for very small populations (May 1974; Keeling and Grenfell 1999) and that the dynamical effects of stochasticity were thought to be negligible, merely adding some variation to the determin-

istic predictions. It is now becoming increasingly evident that many ecological systems are qualitatively affected by demographic and environmental noise, to such an extent that deterministic models may be incapable of capturing or indeed explaining their dynamics (Bartlett 1957; Higgins et al. 1997; Bjørnstad et al. 1998; Cushing et al. 1998; Grenfell et al. 1998; McCauley et al. 1999; Rohani et al. 1999). A key question in ecology concerns when we do and when we do not need to worry about stochasticity.

In this article, we have explored the consequences of the interaction between stochasticity, nonlinearity, and seasonal forcing, with surprising results. We have shown how two common infectious diseases with striking similarities in natural history and reproductive potential exhibit very different dynamics. This is explained by their differing dynamical responses to stochasticity, the root cause of which lies in differences in their epidemiological time scales. The resulting dynamical consequence of these differences is that the measles attractor in the prevaccine era is highly robust to perturbations and those trajectories pushed off the attractor return to it in a biennial manner. The whooping cough attractor, however, is much more prone to stochastic perturbations, with transient behavior that is qualitatively different from the asymptotic dynamics.

Thus, most features of large-scale measles dynamics can be understood using deterministic models (Schenzle 1984; Anderson and May 1991; Bolker and Grenfell 1993; Earn et al. 2000), although its small-scale behavior is much more prey to stochasticity. In marked contrast, even the large-scale dynamics of whooping cough cannot be understood without allowing for stochasticity (Hethcote 1998; Rohani et al. 1999), even though it is a very similar dynamical process to measles. We have proposed a possible explanation for these findings: differences in the structure of the invasion orbit (the effective geometry of the landscape around the attractor).

This study highlights the advantage of studying such key ecological questions using childhood infections; the biology of these systems is well understood, detailed mechanistic models exist, and extensive data sets at many spatial scales are available. Furthermore, these systems have the added benefit of a great deal of dynamically interesting structure; strong overcompensatory forces and nonlinearity interact subtly with resonance (due to seasonality) and process noise.

We have attempted to untangle the complex dynamics of these infections using classical dynamical-systems approaches. An alternative formalism for exploring these issues has recently been developed by Finkenstädt and Grenfell (2000). They have constructed time series models for measles using "susceptible reconstruction" to formulate a set of discrete-time maps. Although they have looked at these questions in a broader statistical sense, their findings are in strong qualitative agreement with those of this study.

It is interesting to note that this system can be viewed as the epidemiological analogue of the dispersal-colonization trade-off metaphor (define each person as a "patch," disease transmission as "dispersal," and the infectious period as "colonization time"). Within this framework, measles can be thought of as the superior disperser but poorer colonizer while whooping cough successfully colonizes a patch for a longer period of time but is less effective at dispersal (P. Rohani, unpublished manuscript). The persistence consequences of habitat destruction (i.e., vaccination) within this framework are qualitatively different to those presented in studies of simple ecological models (cf. Nee and May 1992; Tilman 1994), highlighting the potential importance of stochasticity and seasonal variation.

One of the clearest messages to emerge from this work is that details sometimes matter. While ecologists have been searching for general patterns to explain ubiquitous phenomena, our study indicates that in nonlinear systems, small differences in biological characteristics can have profound qualitative implications. Given the concentration of effort in explaining the dynamics of measles epidemics, it is tempting to assume that most childhood infections with a roughly similar natural history are likely to behave in a similar manner. As we have shown, this is clearly not the case with whooping cough. Hence, great care is needed when extrapolating on the results of any single study.

Acknowledgments

We thank O. Bjørnstad, B. Blasius, and D. Earn for stimulating discussions on this work. We also thank the three anonymous reviewers whose comments were important in improving this article. M.J.K. and P.R. were supported by a Royal Society University research fellowship. B.T.G. is supported by the Wellcome Trust.

APPENDIX

Stochastic Simulation Algorithm

The Monte Carlo SEIR model assumes the same intrinsic processes as equations (1)–(4) but is event driven (Bartlett 1957). The recipe for the model is as follows. We first estimate a time to the next event (δt) by calculating the sum of the frequencies of all possible events, $\eta = 2 \times \mu N + [\beta(t)IS/N] + \sigma E + \gamma I$, and setting $\delta t = -\log(U_1)/\eta$, where U_1 is a uniform deviate in [0, 1]. Next, we order all possible events as an increasing fraction of η and generate another uniform deviate ($U_2 \in [0, 1]$), to obtain the nature of the next event. For example, if the

uniform deviate is in the interval $[0, \mu N/\eta]$, then the event is a birth $(S \rightarrow S + 1, N \rightarrow N + 1)$, whereas if U_2 lies in $\{\mu N/\eta, [\beta(t)IS/N]/\eta\}$, then the next event is an infection $(S \rightarrow S - 1, E \rightarrow E + 1)$.

Literature Cited

Anderson, R. M., and R. M. May. 1978. Regulation and stability of host-parasite population interactions. I. Regulatory processes. Journal of Animal Ecology 47:219–247.

———. 1991. Infectious diseases of humans. Oxford University Press, Oxford.

Andrewartha, H. G., and L. C. Birch. 1954. The distribution and abundance of animals. University of Chicago Press, Chicago.

Bartlett, M. S. 1957. Measles periodicity and community size. Journal of the Royal Statistical Society 120:48–70.

Behrman, R. E., and R. M. Kliegman. 1998. Nelson essentials of pediatrics. Saunders, Philadelphia.

Bjørnstäd, O. N., M. Begon, N. C. Stenseth, W. Falck, S. M. Sait, and D. J. Thompson. 1998. Population dynamics of the Indian meal moth: demographic stochasticity and delayed regulatory mechanisms. Journal of Animal Ecology 67:110–126.

Bolker, B. M., and B. T. Grenfell. 1993. Chaos and biological complexity in measles dynamics. Proceedings of the Royal Society of London B, Biological Sciences 251: 75–81.

Clarkson, J. A., and P. E. M. Fine. 1985. The efficiency of measles and pertussis notifications in England and Wales. International Journal of Epidemiology 14:153–68.

Coulson, T., E. A. Catchpole, S. D. Albon, B. J. T. Morgan, J. M. Pemberton, T. H. Clutton-Brock, M. J. Crawley, and B. T. Grenfell. 2001. Age, sex, density, winter weather and population crashes in Soay sheep. Science (Washington, D.C.) 292:1528–1531.

Cushing, J. M., B. Dennis, R. A. Desharnais, and R. F. Costantino. 1998. Moving toward an unstable equilibrium: saddle nodes in population systems. Journal of Animal Ecology 67:298–306.

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

Earn, D. J. D., P. Rohani, B. M. Bolker, and B. T. Grenfell. 2000. A simple model for complex dynamical transitions in epidemics. Science (Washington, D.C.) 287:667–670.

Ellner, S. P., B. A. Bailey, G. V. Bobashev, A. R. Gallant, B. T. Grenfell, and D. W. Nychka. 1998. Noise and nonlinearity in measles epidemics: combining mechanistic and statistical approaches to population modeling. American Naturalist 151:425–440.

Engebert, R., and F. R. Drepper. 1994. Chance and chaos in population biology—models of recurrent epidemics and food chain dynamics. Chaos, Solitons, and Fractals 4:1147–1169.

Ferguson, N. M., D. J. Nokes, and R. M. Anderson. 1996. Dynamical complexity in age-structured models of the transmission of measles virus. Mathematical Biosciences 138:101–130.

Fine, P. E. M., and J. A. Clarkson. 1982. The recurrence of whooping cough: possible implications for assessment of vaccine efficacy. Lancet 1:666–669.

Finkenstädt, B. F., and B. T. Grenfell. 2000. Time series modelling of childhood diseases: a dynamical systems approach. Journal of Applied Statistics 49:187–205.

Glendinning, P. 1994. Stability, instability and chaos. Cambridge University Press, Cambridge.

Grenfell, B. T. 1992. Chance and chaos in measles dynamics. Journal of the Royal Statistical Society B 54:383–398.

Grenfell, B. T., and R. M. Anderson. 1989. Pertussis in England and Wales: an investigation of transmission dynamics and control by mass vaccination. Proceedings of the Royal Society of London B, Biological Sciences 236:213–252.

Grenfell, B. T., and J. Harwood. 1997. (Meta)population dynamics of infectious diseases. Trends in Ecology & Evolution 12:395–399.

Grenfell, B. T., K. Wilson, B. F. Finkenstädt, T. N. Coulson, S. Murray, S. D. Albon, J. M. Pemberton, T. H. Clutton-Brock, and M. J. Crawley. 1998. Noise and determinism in synchronised sheep dynamics. Nature 394:674–677.

Hassell, M. P. 1978. The dynamics of arthropod predator-prey systems. Princeton University Press, Princeton, N.J.

Hethcote, H. W. 1983. Measles and rubella in the United States. American Journal of Epidemiology 117:2–13.

———. 1997. An age-structured model for pertussis transmission. Mathematical Biosciences 145:89–136.

———. 1998. Oscillations in an endemic model for pertussis. Canadian Applied Mathematics Quarterly 6:61–88.

———. 2000. The mathematics of infectious diseases. Society for Industrial and Applied Mathematics Review 42:599–653.

Higgins, K., A. Hastings, J. N. Sarvela, and L. W. Botsford. 1997. Stochastic dynamics and deterministic skeletons: population behavior of Dungeness crab. Science (Washington, D.C.) 276:1431–1435.

Keeling, M. J., and B. T. Grenfell. 1999. Stochastic dynamics and a power law for measles variability. Philosophical Transactions of the Royal Society of London B, Biological Sciences 354:769–776.

Keeling, M. J., P. Rohani, and B. T. Grenfell. 2001. Seasonally forced disease dynamics explained by switching between attractors. Physica D 148:317–335.

Kermack, W. O., and A. G. McKendrick. 1927. A contribution to the mathematical theory of epidemics. Pro-

ceedings of the Royal Society of London, Mathematical Sciences 115:700–721.

Lotka, A. J. 1925. Elements of physical biology. Williams & Wilkins, Baltimore.

May, R. M. 1974. Biological populations with non-overlapping generations: stable points, stable cycles and chaos. Science (Washington, D.C.) 186:645–647.

———. 1986. Population biology of microparasitic infections. Pages 405–442 *in* T. G. Hallam and S. A. Levin, eds. Mathematical ecology. Springer, Berlin.

McCauley, E., R. M. Nisbet, W. W. Murdoch, A. M. de Roos, and W. S. C. Gurney. 1999. Large amplitude cycles of daphnia and its algal prey in enriched environments. Nature 402:653–656.

Miller, E., J. E. Vurdien, and J. M. White. 1992. The epidemiology of pertussis in England and Wales. Communicable Diseases Report 2:R152–R155.

Nee, S., and R. M. May. 1992. Dynamics of metapopulations: habitat destruction and competitive coexistence. Journal of Animal Ecology 61:37–40.

Nicholson, A. J. 1957. The self-adjustment of populations to change. Cold Spring Harbor Symposium on Quantitative Biology 22:153–172.

Nicholson, A. J., and V. A. Bailey. 1935. The balance of animal populations. I. Proceedings of the Zoological Society of London 1935:551–598.

Olsen, L. F., and W. M. Schaffer. 1990. Chaos versus noisy periodicity: alternative hypotheses for childhood epidemics. Science (Washington, D.C.) 249:499–504.

Pearl, R., and L. J. Read. 1920. On the rate of growth of the population of the United States since 1790 and its mathematical representation. Proceedings of the National Academy of Sciences of the USA 6:275–288.

Peitgen, H.-O., H. Jürgens, and D. Saupe. 1992. Chaos and fractals. Springer, New York.

Rand, D. A., and H. B. Wilson. 1991. Chaotic stochasticity: a ubiquitous source of unpredictability in epidemics. Proceedings of the Royal Society of London B, Biological Sciences 246:179–184.

Rohani, P., D. J. D. Earn, B. F. Finkenstädt, and B. T. Grenfell. 1998. Population dynamic interference among childhood diseases. Proceedings of the Royal Society of London B, Biological Sciences 265:2033–2041.

Rohani, P., D. J. D. Earn, and B. T. Grenfell. 1999. Opposite patterns of synchrony in sympatric disease metapopulations. Science (Washington, D.C.) 286:968–971.

———. 2000*a*. Impact of immunisation on pertussis transmission in England and Wales. Lancet 355:285–286.

———. 2000*b*. Pertussis transmission in England and Wales. Lancet 355:1553–1554.

Sait, S. M., W.-C. Liu, D. J. Thompson, H. C. J. Godfray, and M. Begon. 2000. Invasion sequence affects predator-prey dynamics in a multi-species interaction. Nature 405:448–450.

Schaffer, W. M., and M. Kot. 1985. Nearly one dimensional dynamics in an epidemic. Journal of Theoretical Biology 112:403–427.

Schenzle, D. 1984. An age-structured model of pre- and post-vaccination measles transmission. IMA Journal of Mathematics Applied in Medicine and Biology 1:169–191.

Schwartz, I. B., and H. L. Smith. 1983. Infinite subharmonic bifurcation in an SEIR epidemic model. Journal of Mathematical Biology 18:233–253.

Sugihara, G., B. T. Grenfell, and R. M. May. 1990. Distinguishing error from chaos in ecological time series. Philosophical Transactions of the Royal Society of London B, Biological Sciences 330:235–251.

Tilman, D. 1994. Competition and biodiversity in spatially structured habitats. Ecology 75:2–16.

Zimmer, C. 1999. Life after chaos. Science (Washington, D.C.) 284:83–86.

Associate Editor: Lewi Stone