CHAPTER THREE

Understanding Host-Multipathogen Systems: Modeling the Interaction Between Ecology and Epidemiology

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Summary

We present a new mathematical framework for exploring the ecological and immunological interactions between multiple infectious diseases. The mechanism underlying the ecological interaction is the modulation of susceptible numbers for one pathogen as a result of quarantining or mortality following infection with a competitor. Immunological interactions are assumed to result from immunosuppression or cross-immunity to co-circulating pathogens, both during and after infection. This model is briefly examined to explore the consequences of these factors for the coexistence of multiple infectious diseases. We show that strong competition among pathogens reduces the region of coexistence, while substantial immunosuppression acts to facilitate pathogen community persistence. The dynamics of this model in the presence of seasonal changes in contact rates are presented and compared with historical case notification data for measles and whooping cough. We finish by highlighting how such a mathematical framework may be used to systematically investigate the role played by alternative competing mechanisms in shaping the observed dynamics of multipathogen systems.

Background

Infectious diseases have become an increasingly important and high-profile public health issue, in large part as a result of the emergence of new pathogens (Daszak et al. 2000; Dobson and Foufopoulos 2001; Lipsitch et al. 2003), the continued persistence and resurgence of older infectious diseases (Keeling and Gilligan 2000; Orenstein et al. 2004), and concerns over possible deliberate exposure (Halloran et al. 2002). Indeed, the World Health Organization's Global Burden of Disease project estimated that in 2000, more than 10 million deaths worldwide were due to infectious and parasitic diseases. Understanding the precise

mechanisms underlying disease dynamics, spread, and evolution, therefore, has never been of greater importance.

To achieve detailed understanding for a particular pathogen, epidemiologists routinely study aspects of the causative etiological agent (be it a virus, bacterium, fungus, or protozoan) and typically assume no interaction with other pathogens. A good example of such an approach would be the study of measles, which some have argued has become the *C. elegans* of large-scale epidemiological dynamics (Grenfell et al. 2001). Many decades of research, coupled with extensive long-term data, have resulted in a deep understanding of measles epidemiology, with a large body of work to explain its observed epidemics (Bartlett 1957; Bjornstad et al. 2002; Bolker and Grenfell 1996; Ellner et al. 1998; Ferguson et al. 1996; Rohani et al. 1999; Schenzle 1984; Soper 1929) and explore the most effective eradication programs (Earn et al. 1998; Hethcote 1988; Nokes and Swinton 1997).

These popular approaches to epidemiology may, however, represent an oversimplification of disease communities and may be ignoring some key interactions. In a nutshell, the understanding obtained from studying (for example) only the measles virus and its interaction with humans may paint only part of the true picture. In recent years, these single-host, single-pathogen approaches have been extended to incorporate multiple hosts (see chapter 1, this volume; Dobson 2004; Gog et al. 2002; Greenman and Hudson 1999) and multiple pathogens (Ferguson et al. 2003; Gupta et al. 1998). These studies of "community epidemiology" can be broadly categorized according to the scale of interest. At the antigenic and cellular scale, studies have typically explored the immunological interaction between pathogens as a result of coinfection within a host (Garcia-Garcia et al. 2003; Kirschner 1999; May and Nowak 1994). An especially exciting area of recent research in this field is bacterial interference, a process in which competing autochthonous microorganisms block adhesion events and prevent infection by pathogenic bacteria (Reid et al. 2001). This mechanism, which has also been studied in the context of viral infections, is considered by some to have greater public health potential than vaccines because it relies on the competitive exclusion of pathogens and does not require host immune stimulation (Huovinen 2001; Reid et al. 2001; Tano et al. 2002). There are, however, obvious concerns surrounding the prophylactic administration of live organisms. At the ecological level, shared pathogens have been demonstrated to be influential in shaping extinction dynamics by causing apparent competition between species (Holt 1977; Tomkins et al. 2001). The area that has received much attention has been the dynamics of pathogens with well-established antigenic polymorphism, such as influenza, malaria, adenoviruses, poliovirus, cholera, and dengue

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(Earn et al. 2002; Ferguson et al. 2003; Gupta et al. 1998; Koelle et al. 2005; Read and Taylor 2001). In such systems, it is empirically documented that different strains fluctuate out of phase with each other. This observation is summed up by Bang (1975): "If a significant proportion of a population is not immune to a given agent, the presence of that agent as an epidemic will tend to suppress the appearance of other agents of a similar nature with which interference may occur." He went on to propose that epidemiological interference may account for spatial asynchrony in outbreaks of adenoviruses (1, 2, and 5) and the temporal asynchrony in poliomyelitis (3, 2, and 1) epidemics observed in West Bengal. More recent work in this area has highlighted the significance of cross-immunity between strains that may shape the coexistence, dynamics, and evolution of strains (Dietz 1979; Elveback et al. 1968; Gog and Grenfell 2002; Kamo and Sasaki 2002; Koelle et al. 2005; White et al. 1998).

Until recently, however, the possibility that epidemics of unrelated pathogens might interact has been ignored, despite the suggestion of its likelihood in historical epidemiological literature. For example, in his classic 1894 book, *A History of Epidemics in Britain*, the learned medical historian Charles Creighton commented that "again, the great measles epidemic of 1808 in Glasgow was indeed followed by many deaths from whooping-cough in 1809. Whatever correspondence or relation there may be between measles and whooping-cough, (and it has been remarked by many in the ordinary way of experience), it eludes the method of statistics." Creighton clearly envisaged a strong interaction between these infectious diseases, though he was unclear on the underlying mechanism and had no mathematical framework for its exploration.

One obvious candidate mechanism would be immunity-mediated interaction. Consider the words of James S. Laing, the resident physician of Aberdeen City Hospital, who in 1902 stated, "Most writers assert that there is an intimate association between epidemics of measles and epidemics of whooping-cough, and that an epidemic of the former disease strongly predisposes to the subsequent development of the latter." This reflects the widely recognized fact that after infection with measles, the immune system is suppressed for a period of time, during which an individual may be more susceptible to colonization by other (particularly bacterial) pathogens. It is interesting to note, however, that after studying the average time between successive measles and whooping cough epidemics in case notification data for Aberdeen (figure 3.1), Laing and Hay (1902) concluded, "It would thus appear as if whooping-cough rather paved the way for measles than measles for whooping cough"!

In 1998, Rohani and colleagues proposed an additional *ecological* mechanism that may also contribute to interaction—specifically, interference—among unrelated acute infectious diseases. This possible in-

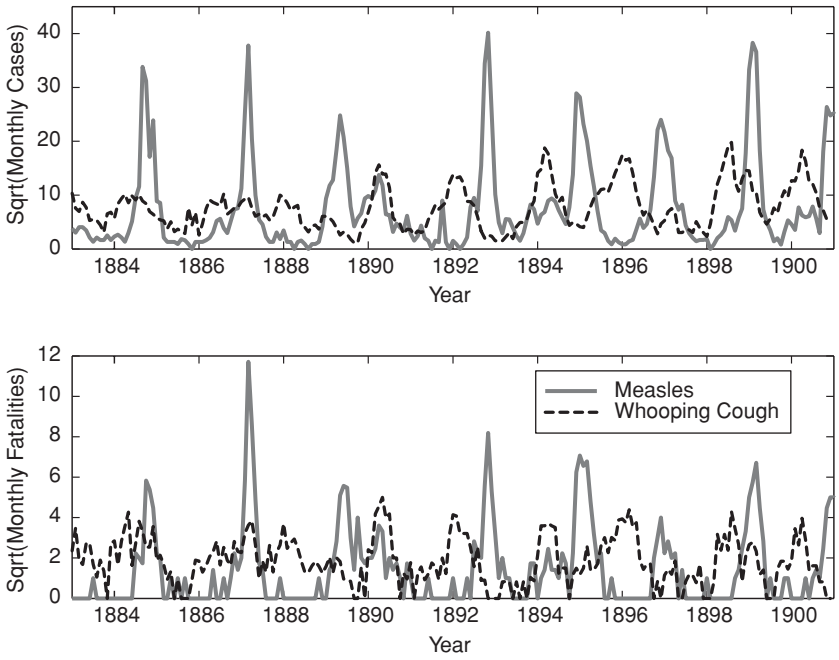

Figure 3.1. Long-term patterns in measles (black lines) and whooping cough (gray lines) epidemics in Aberdeen from 1883 to 1901 (data from Laing and Hay 1902). Panel a shows monthly case notifications, while monthly case fatalities are shown in b. The time series for both infections exhibit a strong biennial component, with a striking phase difference between measles and whooping cough outbreaks.

terference was proposed to arise from the temporary or permanent removal of potential hosts from the susceptible population for one pathogen following an acute infection by one of its direct competitors. The primary mechanism for this removal is the convalescence period, during which individuals are in quarantine and hence unavailable to contract "competing" pathogens. As documented by Emerson (1937), following measles infection, children in the major U.S. cities in the 1920s and 1930s were quarantined for an average of almost ten days, while isolation after an episode of whooping cough lasted nearly four weeks. Modern infection management practices similarly result in the quarantining of infected children for one week after measles infection and two weeks for whooping cough (Nelson et al. 2001). In addition to the possible dynamical consequences of enforced convalescence, in conditions under which infected individuals may suffer death as a result of infection, removal from the susceptible pool can

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become permanent, and the interaction between pathogens is predicted to become stronger. Dynamically, this is very similar to the effects of cross-immunity in strain polymorphic systems, whereby individuals previously infected with one strain may have partial protection against infection by other competing strains (Kamo and Sasaki 2002). The significant prediction of the model of Rohani et al. (1998) was that the epidemics of competing infections would be temporally segregated, with major outbreaks out of phase with each other (as alluded to by Creighton [1894]).

Empirical support for interference effects is provided by case fatality data for measles and whooping cough for fifteen European cities in the pre- and post-World War I years (Rohani et al. 2003). In this era, infected individuals were likely to be as a result of complications following infection, typically secondary viral and bacterial lung infections (pneumonia). In sixteen cities, the population demographic characteristics (notably the per capita birth rates) were conducive to biennial outbreaks. The epidemics of measles and whooping cough were statistically significantly out of phase with each other in fifteen of these sixteen cities (Rohani et al. 2003)—that is to say, epidemic years for these infections did not coincide. This work suggests, therefore, that when disease prevalence is very high and is associated with significant mortality, as remains the case in many developing nations, it may be impossible to fully understand epidemic patterns by studying pathogens in isolation.

Although the patterns revealed in these historical data are consistent with model prediction of disease interference, there remains a need for systematic study of the different possible routes of interaction between different infectious diseases (or strains of the same disease) and their dynamical consequences. In this chapter, we aim to further develop theory on the interaction between infectious diseases. We present a novel general model for examining systems with multiple pathogens. For illustration purposes, our model analyses are focused on measles and whooping cough, but the proposed framework is flexible and may be applied to strain polymorphic as well as to other unrelated diseases. The key ingredient of the formalism we develop is the simultaneous inclusion of immunologically determined components (immunosuppression and cross-immunity) and ecological factors (quarantine and infection-induced mortality).

The Two-Disease Model

Much of the influential epidemiological theory has been based on the SEIR (susceptible, exposed, infected, recovered) paradigm (Anderson and May 1991; Dietz 1976; Keeling and Rohani 2007). In this frame-

work, individuals are categorized according to infection status: the infection-naïve are thought of as susceptible, upon infection they become exposed, and once latency is over they are infected and proceed to transmit the pathogen. After successfully overcoming the infection, individuals are considered recovered and immune for life. This picture does not take into account the possible influence that infection by one pathogen may exert on the community of pathogens competing for the same hosts. A case in point is childhood infections: children may contract a number of infectious diseaes, such as measles, pertussis, mumps, chickenpox, or rubella. Because any child infected with, for example, measles is unavailable to contract any other infectious disease for a period of time (perhaps up to two weeks), we may wonder what effect an outbreak of measles would have on the dynamics of the other candidate infections.

An important step in developing an understanding of the dynamical interaction between multiple infections has been to develop a novel, conceptually simple, mathematical framework that incorporates two pathogens. This work follows in the footsteps of a distinguished and significant body of work dealing with multipathogen interactions, focusing on infections such as influenza, malaria, or dengue, in which genetic diversity is well established (Andreasen et al. 1997; Dietz 1979; Earn et al. 2002; Ferguson et al. 2003; Gilbert et al. 1998; Gog and Grenfell 2002; Gomes et al. 2002; Gupta et al. 1998; Kamo and Sasaki 2002; Taylor et al. 1997). In developing the model, we envisage a simplified natural history of infection for each disease:

- All newborns are fully susceptible to both infections.
- Upon infection, a susceptible individual enters the exposed (infected but not yet infectious) class and has a probability of contracting the "competing" disease simultaneously (represented by the cross-immunity parameter ϕ_i, where $i = 1, 2$).
- After the latent period, the individual becomes infectious but is not yet symptomatic and still has a defined probability (ϕ_i, $i = 1, 2$) of becoming coinfected with the other disease.
- Typically, when symptoms appear, the disease is diagnosed and the individual is sent home to convalesce for an average period, given by $1/\delta_i$ ($i = 1, 2$). During convalescence, the competing infection may be contracted, with the transmission rate additionally modulated by the parameter ξ_i ($i = 1, 2$), which may represent quarantine or temporary cross-immunity (if less than 1) or temporary immunosuppression (if greater than 1).

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- Depending on the disease, host age, and host condition (typically nutritional status), infection may be fatal owing to complications (such as pneumonia and encephalitis, in the case of measles and pertussis). This is represented by per capita infection-induced mortality probabilities ρ_i ($i = 1, 2$).
- Upon complete recovery, the individual is assumed immune to the infection (disease 1) and reactivates susceptibility to disease 2, if previously not exposed to it. At this stage, we introduce the term χ_i to explore the implications of longlasting immunosuppression ($\chi_i > 1$) or cross-immunity ($\chi_i < 1$) for the transmission rate of disease j following infection with disease i.

The mathematical representation of these assumptions is presented in the appendix to this chapter. The key strength of this framework is its flexibility, allowing us to establish unambiguously the dynamical role played by each of the features of the model. For example, as demonstrated rigorously in the appendix, by removing all immune-mediated interaction between infections (i.e., $\phi_i = \chi_i = \xi_i = 1$, $i = 1, 2$) and ignoring ecological considerations ($\rho_i = 0$, $i = 1, 2$), we can strictly decouple the dynamics of the two infections; the model contains two pathogens with entirely independent transmission dynamics. It is also straightforward to extend the model to incorporate vector transmission in order to better understand the serotype dynamics of dengue, for instance (Wearing and Rohani 2006).

Model Predictions

One intuitively obvious possible consequence of interaction among infections is reduced abundance. Surprisingly, however, detailed equilibrium analyses have demonstrated that disease interference does not manifest itself by significantly altering infection prevalence; changes in model parameters such as the convalescence period translate into negligible changes in the number of infectives of either infection (Huang and Rohani 2005). Perhaps more surprisingly, epidemiological interference exerts little influence on the coexistence likelihood of pathogens. Defining the basic reproductive ratio of each infection as $R_0^j = \beta_j \sigma_j / (\sigma_j + \mu)(\gamma_j + \mu)$ ($j = 1, 2$), it is straightforward to show that coexistence requires $R_0^j > 1$ and

$$R_0^j > \frac{R_0^i}{1 + \alpha_i (R_0^i - 1)}, \tag{1}$$

where a_i is a convenient grouping of parameters and is given by

$$a_i = \frac{1}{\sigma_i + \mu} \left\{ \phi\mu + \frac{\sigma_i}{\gamma_i + \mu} \left(\phi\mu + \frac{\gamma_i}{\delta_i + \mu} (\xi\phi\mu + \chi(1 - \rho_i)\delta_i) \right) \right\}, \tag{2}$$

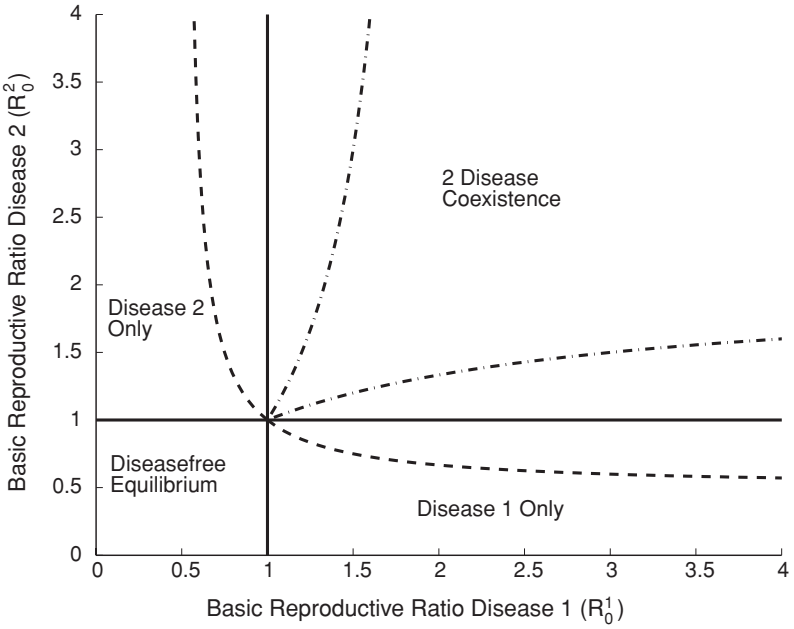

Figure 3.2. The coexistence of two infectious diseases can be affected by immunosuppression and disease interference. In the absence of immunemediated interactions ($\phi_i = \chi_i = 1$, $i = 1, 2$), large levels of disease-induced mortality (50%: dot-dashed line) can cause the region of two-disease coexistence to shrink somewhat. In contrast, strong levels of permanent immunosuppression ($\phi_i = 1$, $\chi_i = 2$, $\rho_i = 0$, $i = 1, 2$) can expand the coexistence domain. Model parameters were $\mu = 0.02$, $\frac{1}{\sigma_1} = \frac{1}{\sigma_2} = 8$ days, $\frac{1}{\gamma_1} = 5$ days, $\frac{1}{\gamma_2} = 14$ days, $\xi = 1$, $\frac{1}{\delta_1} = 7$ days and $\frac{1}{\delta_2} = 14$ days. (From Vasco et al. 2007.)

$i, j = 1, 2, j \neq i$. The diseases are assumed to have symmetrical values of ϕ, χ, and ξ (details provided in Vasco et al. 2007). In figure 3.2, we explore the conditions for disease coexistence in this model. In the absence of pathogen-induced mortality ($\rho_1 = \rho_2 = 0$), the quarantine period alone has little effect on the stable two-disease equilibrium, with the coexistence criterion effectively reducing to $R_0^1, R_0^2 > 1$, since inequality (1) is always satisfied (assuming no immune effects, $\chi = 1$). It is only after we assume a 50% (dash-dotted line) probability of death following infection that the region of endemic two-disease coexistence shrinks slightly. On the other hand, if we ignore ecological factors (such as quarantining and pathogen virulence), immunosuppression resulting from one infection can facilitate the invasion and persistence of the competing disease even if the invading infection has R_0 less than 1 (dashed line).

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To identify the dynamical consequences of disease interaction, Vasco et al. (2007) carried out a systematic comparison of the predicted equilibrium dynamics of the general two-disease model (described in the appendix to this chapter) with the dynamics of each infection in isolation (when $\phi = \chi = \xi = 1$). Similar to the underlying single-disease model, in the absence of seasonality in the transmission rate, the two-infection system demonstrates damped oscillations for much of the parameter space. It is possible to show, however, that when coinfection probability (ϕ) is very small, relatively large levels of permanent immunosuppression (χ) can destabilize the equilibrium (via a Hopf bifurcation), giving rise to large-amplitude cycles. The precise extent of this effect is determined by the assumed quarantine periods and birth rate (Vasco et al. 2007). High birth rates make destabilization less likely, while increased convalescence periods increase the possibility.

While equilibrium studies of system dynamics are illuminating for general multipathogen interactions, an important ingredient for the specific study of childhood infections is seasonal variation in transmission rates due to the school calendar. It is well established that such external forcing can have dramatic effects on measles dynamics (Dietz 1976), with a low amplitude of seasonality generating annual epidemics, while greater levels of forcing can produce biennial and longer-term dynamics (Schwartz and Smith 1983). The dynamics of whooping cough, on the other hand, are rigidly annual, irrespective of changes in the seasonal amplitude (Rohani et al. 2002). When both infections are included in the seasonally forced two-disease model, the epidemics of measles are largely unaffected, while the pattern of whooping cough outbreaks mimics those of measles exactly (Rohani et al. 1998). The explanation for this observation lies in the primary factors that determine an infection's R_0, namely, the transmission rate (β) and the infectious period ($\frac{1}{\gamma}$). Therefore, depending on the precise combination of these traits, infections respond differentially to seasonal variation in contact rates. In general, one of the predictions of the work on two-disease models is that given $R_0^1 = R_0^2$, the bifurcation structure of the model is dictated by the infection with the higher transmission rate—in this case, measles (Huang and Rohani 2005). The most plausible explanation is that at the start of the epidemic calendar (early autumn), when there is a substantial influx of susceptibles in the young school cohort, a higher transmission rate permits an infection to get established first, and its pattern of epidemics sets the template for the competitor.

Here we extend these previous studies by examining the dynamics of the seasonal two-disease model (see the appendix to this chapter) as the coinfection probability (ϕ) and the strength of immunosuppression (χ) are varied. The results of this approach are presented in figure 3.3. The main (central) panel shows how the measles outbreak period changes as ϕ and χ

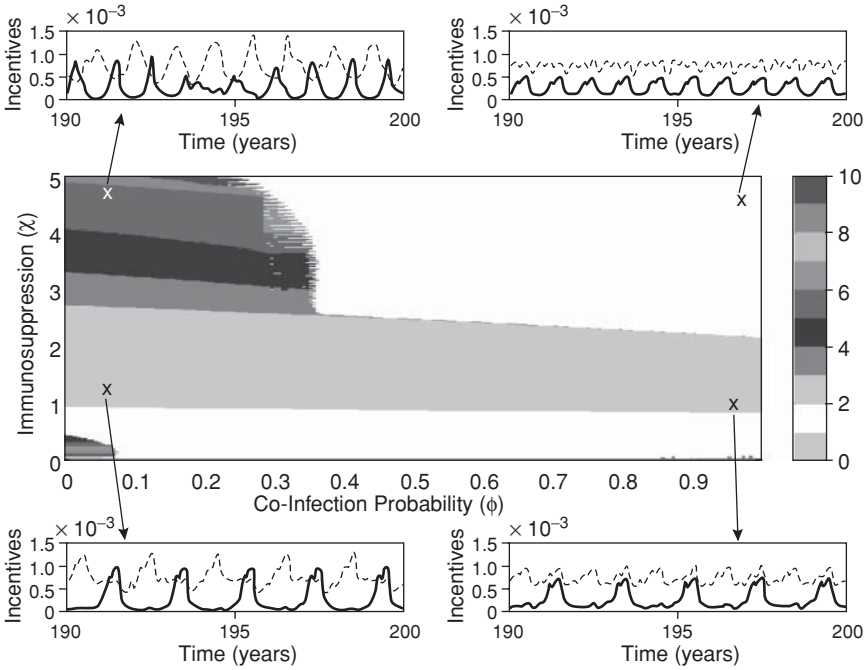

Figure 3.3. The dynamical implications of varying the probability of coinfection ($\phi_1 = \phi_2 = \phi$) and immunosuppression/cross-immunity ($\chi_1 = \chi_2 = \chi$) in a seasonally forced model. The middle panel shows the period of oscillations (in years) observed for disease 1 (measles) as the control parameters are varied. The color coding is explained in the key to the right of the panel. The top and bottom panels represent time series for measles (black lines) and whooping cough (gray lines) in the regions of parameter space marked by crosses. Model parameters **are** $\mu = 0.02$, $b_1 = 0.25$, $\xi = 1$, $\frac{1}{\sigma_1} = \frac{1}{\sigma_2} = 8$ days, $\frac{1}{\gamma_1} = 5$ days, $\frac{1}{\gamma_2} = 14$ days, $\frac{1}{\delta_1} = 7$ days $\frac{1}{\delta_2} = 14$ days, $\bar{b}_1 = 1{,}250$ per year and $\bar{b}_2 = 446$ per year. The dynamics **were obtained** by numerical integration.

are varied. For much of the parameter space (when $\phi > 0.4$), measles epidemics are either annual or biennial. When ϕ is small and coinfection is unlikely, however, changes in immunosuppression levels can give rise to bifurcations, with epidemic patterns that have periods ranging from one to ten years. Of note, χ is clearly the major determinant of dynamics. This figure can be useful in examining the combination of ecological and immunological traits that gives rise to dynamics consistent with data. As shown in figure 3.1, measles and whooping cough epidemics in Aberdeen were both biennial and clearly out of phase with one another. The dynamics summarized in figure 3.3 show, for example, that when infectious

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diseases are strictly independent ($\chi = \phi = 1$), measles epidemics are biennial, whereas whooping cough exhibits annual cycles (bottom right panel), in contrast to empirical findings. As the competitive strength of the interaction is increased (ϕ smaller), whooping cough epidemics also become biennial, but, of importance, their major outbreaks are out of phase with measles epidemics (figure 3.3, bottom left panel), as seen in figure 3.1. In the presence of coinfection ($\phi = 1$), increasing permanent immunosuppression leads to annual outbreaks of both infections (figure 3.3, top right panel). This effect is relatively straightforward to explain, since contracting one infection essentially "primes" individuals for contraction of the other infection, resulting in seasonally driven annual cycles. Strong immunosuppression in conjunction with strong competitive effects generates multiennial quasiperiodic dynamics, with negatively correlated epidemics.

The take-home message from this analysis is that the parameters χ and ϕ both have substantial dynamical consequences, though in subtly different ways. The permanent immunosuppression (or cross-immunity) factor χ strongly affects epidemic periods, while the coinfection parameter ϕ is largely responsible for generating negative correlation between the outbreaks of the two infections (Vasco et al. 2007).

When Would Infections Interfere?

Throughout the model formulation and analyses of data, we have placed heavy emphasis on the study of measles and whooping cough. Children, however, are typically exposed to many more infectious diseases, such as mumps, rubella, or chickenpox. Would we expect *all* of these infections to dynamically interact? By extension, ideally, would any modeling work need to include all of these infections? We believe the answer to this question is likely to be no. Using simple homogeneous models without age structure, it has been demonstrated that dynamical interference effects are most pronounced between infections with a similar basic reproductive ratio (Dietz 1979; Rohani et al. 1998, 2003; Huang and Rohani 2005). A complete understanding of this issue will, however, need age dependence in contact rates to be taken into account. This is because the interference concept relies on "competition" for resources (hosts) between pathogens. For the dynamical effects of this competitive interaction to be noticeable, the pathogens should be infecting largely the same cohort of hosts. Hence, the extent of interference effects is likely to be determined by the relative distributions of age at infection. One way of examining this issue is by studying the mean age at infection, which is dictated by the transmission potential of the disease or its basic repro

ductive ratio, R_0. For *SIR*-type diseases, the mean age at infection (A) is approximately the life expectancy of the host $\left(\frac{1}{\mu}\right)$ divided by R_0 (more precisely, $A \sim \frac{1}{(\mu(R_0-1))}$ (Anderson and May 1991; Keeling and Rohani 2007). Table 3.1 shows that, of the potential childhood infections, measles and whooping cough have very similar mean ages at infection (approximately four to five years; Anderson and May 1982). Hence, these diseases are likely to have been strongly "competing" for children in the same age cohorts, while their interaction with the other childhood infections is likely to have been less intense. This logic suggests that infections such as rubella and chickenpox may also be good potential candidates for the study of interference. We are currently examining this issue using the two-disease model with age-specific transmission (Huang and Rohani 2006).

Conclusions

Understanding the ecology of infectious diseases has become an increasingly important endeavour. Many of the important and high-profile infections, such as influenza, malaria, and dengue, have well-established

Table 3.1
Historical estimates of the mean age at infection for a number of childhood diseases in the twentieth century

Disease	*Time Period*	*Mean Age at Infection (yr)*	R_0
Measles	1944–1979	4.4–5.6	13.7–18.0
	1912–1928	5.3	12.5
Whooping cough	1944–1978	4.1–4.9	14.3–17.1
	1908–1917	4.9	12.2
Chickenpox	1913–1917	6.7	9.0
	1918–1921	7.1	8.5
Mumps	1943	9.9	7.1
	1912–1916	13.9	4.3
Rubella	1972	10.5	6.7
	1979	11.6	6.0
Poliomyelitis	1960	11.2	6.2
	1955	11.9	5.9

Note: Data from Anderson and May (1982).

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antigenic polymorphism. It is generally acknowledged that taking into account immune-mediated interactions among strains is necessary for explaining the ecological and evolutionary dynamics of these infections (Elveback et al. 1968; Ferguson et al. 2003; Gog and Grenfell 2002; Levin et al. 2004). In this chapter, we have reviewed some recent work that has proposed an ecological mechanism for possible interaction among antigenically distinct infections (Rohani et al. 1998, 2003). Specifically, we have put forward a general mathematical and conceptual framework within which issues pertaining to immunological and ecological scale interactions may be explored.

Recent work on the epidemiological dynamics of dengue fever provides an illustration of how this framework may be used in a systematic way to investigate alternative competing hypotheses about the mechanisms responsible for observed patterns of disease. Dengue is a mosquito-borne flavivirus of varying clinical severity that is composed of four antigenically distinct but related serotypes. Long-term surveillance in hyperendemic regions suggests that individual dengue serotypes fluctuate out of phase with each other, while aggregated dengue data exhibit predominantly annual outbreaks together with a less pronounced, two- to four-year cyclic signature (Cummings et al. 2004; Nisalak et al. 2003). Mathematical models of dengue epidemiology have previously been developed to explain these empirical observations. These models can be broadly split into two kinds. The first kind attempts to include as much ecological detail as possible, incorporating a complex array of external environmental factors (Focks et al. 1995); the second is reductionist and focuses on the prevailing immunological hypothesis of antibody-dependent enhancement (ADE), whereby infection with one serotype increases an individual's susceptibility to 20 (or mortality from) infection with another (Ferguson et al. 1999; Kawaguchi et al. 2003). Using the mathematical framework laid out in this chapter and extending it to incorporate a vector population, we were able to take an intermediate route and explore both ecological and immunological mechanisms in a tractable manner (Wearing and Rohani 2006). Our results suggest that ADE may not be as important to explain dengue epidemics as is currently thought. Specifically, in the presence of seasonal variation in the vector population, the key immune-mediated interaction that is necessary to explain the observed dynamics of endemic dengue incidence is the well-documented temporary period of cross-protection. This finding is important for two reasons. First, if ADE is indeed the primary mechanism generating dengue dynamics, then in our model, this gives rise to rapid disease extinction unless the host population size exceeds 10^7. Second, the levels of vaccination required to eradicate serotypes would clearly be different, depending on which factors dominate.

The near-term research agenda for exploring multipathogen interaction will likely involve a number of key issues. Developing a broad understanding of the dynamical consequences of different factors is obviously important. This will ultimately provide some insights into the kinds of patterns that may result from different modes of pathogen interaction. One of the important outstanding issues is *when* disease dynamics influence each other. The use of age-structured, multipathogen models is likely to be informative in generating theory concerning the necessary ingredients for disease interference or facilitation. Exploration of model dynamics will also permit the establishment of rigorous signatures of interaction, with the associated statistical methodologies that may be used to interrogate disease data.

An exciting potential area of application of the generalized model we have proposed in this chapter is the study of a variety of multistrain pathogens whose epidemiological dynamics are intrinsically coupled to evolutionary processes (e.g., dengue, cholera, meningitis, poliovirus, echoviruses). The next step toward a greater understanding of pathogen diversity and dynamics is merging the information contained in both epidemiological and genetic data, an approach recently referred to as phylodynamics (Grenfell et al. 2004). A cogent statistical problem in this area involves the simultaneous estimation of epidemiological and genetic parameters using ecological and genetic time series. Recent advances in population genetics, in particular coalescent theory, enable us to use sequence information sampled from rapidly evolving pathogens over time to infer ecological and genetic parameters (Drummond et al. 2002; Emerson et al. 2001; Vasco et al. 2001). For multistrain pathogens, selective pressures arising from the host immune system can potentially drive the evolutionary outcome and interact with the stochastic forces of mutation, genetic drift, and recombination to determine the final set of sampled sequences and infecteds. The precise form of cross-immunity, enhancement, or immunosuppression will determine how pathogen populations eventually become structured into different antigenic strains and persist or replace each other through time. These considerations imply that incorporating basic evolutionary mechanisms into the two-disease model presented here will have substantial conceptual consequences for our understanding of the population dynamics of epidemics.

Finally, the potential public health implications of disease interference and facilitation remain largely unexamined. Intuitively, one may expect that interference or enhancement between infections may be informative in designing successful vaccination programmes. For instance, if substantial interference between two diseases is well established, then this information can be usefully deployed to derive optimal vaccine pulses.

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According to theory, successful vaccination requires the reduction of susceptible numbers in the population below some critical threshold, N/R_0 (Anderson and May 1991; Kermack and McKendrick 1927; Keeling and Rohani 2007). Therefore, violent epidemics of one disease, together with the associated reduction in susceptible persons following the quarantining of all those infected during the outbreak, can, in theory, be used to time immunization pulses so that eradication may occur with fewer units of vaccine used than predicted by single-disease models (P. Rohani, unpublished data). Additionally, we may also expect interference or enhancement effects to be relevant when contemplating vaccination using multiple vaccines (such as the measles-mumps-rubella and the diphtheria-tetanus-pertussis triple vaccines).

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APPENDIX

In this appendix, we describe the mathematical equations used in the two-disease model. The basic approach is similar to status-based (rather than history-based) models:

$$\frac{dS_0}{dt} = \upsilon N - (\lambda_1 + \lambda_2)\frac{S_0}{N} - \mu S_0 \tag{3}$$

$$\frac{dE_1}{dt} = \lambda_1 \frac{S_0}{N} - \phi_2\lambda_2 \frac{E_1}{N} - (\sigma_1 + \mu)E_1 \tag{4}$$

$$\frac{dI_1}{dt} = \sigma_1 E_1 - \phi_2\lambda_2 \frac{I_1}{N} - (\gamma_1 + \mu)I_1 \tag{5}$$

$$\frac{dE_2}{dt} = \lambda_2 \frac{S_0}{N} - \phi_1\lambda_1 \frac{E_2}{N} - (\sigma_2 + \mu)E_2 \tag{6}$$

$$\frac{dI_2}{dt} = \sigma_2 E_2 - \phi_1\lambda_1 \frac{I_2}{N} - (\gamma_2 + \mu)I_2 \tag{7}$$

$$\frac{dC_1}{dt} = \gamma_1 I_1 - \xi_2\phi_2\lambda_2 \frac{C_1}{N} - (\delta_1 + \mu)C_1 \tag{8}$$

$$\frac{dC_2}{dt} = \gamma_2 I_2 - \xi_1\phi_1\lambda_1 \frac{C_2}{N} - (\delta_2 + \mu)C_2 \tag{9}$$

$$\frac{dS_1}{dt} = (1-\rho_1)\delta_1 C_1 - \chi_2\lambda_2 \frac{S_1}{N} - \mu S_1 \tag{10}$$

$$\frac{dS_2}{dt} = (1-\rho_2)\delta_2 C_2 - \chi_1\lambda_1 \frac{S_2}{N} - \mu S_2 \tag{11}$$

$$\begin{aligned}\frac{dS_{12}}{dt} = {} & (1-\rho_1)(1-\rho_2)\left(\lambda_2 \frac{\phi_2 E_1 + \phi_2 I_1 + \xi_2\phi_2 C_1}{N} + \lambda_1 \frac{\phi_1 E_2 + \phi_1 I_2 + \xi_1\phi_1 C_2}{N}\right) \\ & + (1-\psi_2\rho_2)\chi_2\lambda_2 \frac{S_1}{N} + (1-\psi_1\rho_1)\chi_1\lambda_1 \frac{S_2}{N} - \mu S_{12}\end{aligned} \tag{12}$$

$$\frac{d\varepsilon_1}{dt} = \lambda_1 \frac{S_0}{N} + \phi_1\lambda_1 \frac{E_2}{N} + \phi_1\lambda_1 \frac{I_2}{N} + \xi_1\phi_1\lambda_1 \frac{C_2}{N} + \chi_1\lambda_1 \frac{S_2}{N} - (\sigma_1 + \mu)\varepsilon_1 \tag{13}$$

$$\frac{d\varepsilon_2}{dt} = \lambda_2 \frac{S_0}{N} + \phi_2\lambda_2 \frac{E_1}{N} + \phi_2\lambda_2 \frac{I_1}{N} + \xi_2\phi_2\lambda_2 \frac{C_1}{N} + \chi_2\lambda_2 \frac{S_1}{N} - (\sigma_2 + \mu)\varepsilon_2 \tag{14}$$

$$\frac{d\lambda_1}{dt} = \beta_1\sigma_1\varepsilon_1 - (\gamma_1 + \mu)\lambda_1 \tag{15}$$

$$\frac{d\lambda_2}{dt} = \beta_2\sigma_2\varepsilon_2 - (\gamma_2 + \mu)\lambda_2, \tag{16}$$

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TABLE 3.2
Description of model parameters

Parameter	*Epidemiological Description*	*Typical Range*
ν	Host per capita birth rate	0–1 per year
μ	Host per capita death rate	0–1 per year
β_i	Transmission rate	100–2,000 per year
$1/\sigma_i$	Latent period	1–2 weeks
$1/\gamma_i$	Infectious period	1–3 weeks
$1/\delta_i$	Quarantine period	1–4 weeks
ρ_i	Probability of infection-induced mortality	0–1
ϕ_i	Coinfection probability	0–1
ξ_i	Temporary immunosuppression/ cross-immunity	≥ 0
χ_i	Permanent immunosuppression/ cross-immunity	≥ 0
ψ_i	Differential infection-induced mortality	0–1

Note: Subscripts refer to disease i ($i = 1, 2$).

where all those susceptible to both infections denoted by S_0. The variables E_i, I_i, and C_i ($i = 1, 2$) represent those currently exposed, infectious, or convalescing (respectively) after infection with disease i, with no previous exposure to any infection. The terms S_i ($i = 1, 2$) represent all individuals who are only susceptible to infection j ($j \neq i$) following recovery from i. For bookkeeping purposes, we let ε_i and λ_i/β_i represent individuals latent and infectious with disease i ($i = 1, 2$). Additionally, S_{12} are all those no longer susceptible to either infection and may include those who are still exposed or infectious with one or both diseases (i.e. also in ε_1, ε_2, λ_1 or λ_2). The total population size (N) is the sum of the first ten variables only ($N = S_0 + S_{12} + \sum_{i=1}^{2}(E_i + I_i + C_i + S_i)$). The model's parameters are explained in table 3.2.

It is straightforward to demonstrate that diseases 1 and 2 can be easily decoupled within this framework. Assume there is no disease-induced mortality for either disease ($\rho_1 = \rho_2 = 0$) and no immune-mediated interaction ($\chi_i = \phi_i = 1$, $i = 1, 2$). Then, if we let $Z_i = E_i + I_i + C_i + S_i + S_0$, $i = 1, 2$, our equations can be rewritten as:

$$\frac{dS_0}{dt} = \nu N - (\lambda_1 + \lambda_2)\frac{S_0}{N} - \mu S_0$$

$$\frac{dZ_1}{dt} = \nu N - \lambda_2 \frac{Z_1}{N} - \mu Z_1$$

$$\frac{dZ_2}{dt} = \nu N - \lambda_1 \frac{Z_2}{N} - \mu Z_2$$

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TABLE 3.3
Timings of the major school holidays when *Term* = –1 (during all other times *Term* = +1)

Holiday	*Model Days*	*Calendar Dates*
Christmas	356–6	21 December–6 January
Easter	100–115	10–25 April
Summer	200–251	19 July–8 September
Autumn Half-Term	300–307	27 October–3 November

Note: The autumn half-term break is included as this is the only short holiday that has an identifiable signature in the England and Wales data.

$$\frac{dS_{12}}{dt} = \lambda_2 \frac{Z_1 - S_0}{N} + \lambda_1 \frac{Z_2 - S_0}{N} - \mu S_{12}$$

$$\frac{d\varepsilon_1}{dt} = \lambda_1 \frac{Z_2}{N} - (\sigma_1 + \mu)\varepsilon_1$$

$$\frac{d\varepsilon_2}{dt} = \lambda_2 \frac{Z_1}{N} - (\sigma_2 + \mu)\varepsilon_2$$

$$\frac{d\lambda_1}{dt} = \beta_1\sigma_1\varepsilon_1 - (\gamma_1 + \mu)\lambda_1$$

$$\frac{d\lambda_2}{dt} = \beta_2\sigma_2\varepsilon_2 - (\gamma_2 + \mu)\lambda_2.$$

These equations represent a decoupled system with two dynamically distinct infections (Z_1, ε_2, λ_2) and (Z_2, ε_1, λ_1).

Seasonality

Following the classic work of Schenzle (1984), the transmission rate in this model is assumed to be high during school terms and low at other times. In this manner, the equation describing the transmission rate for disease *i* can be rewritten as follows:

$$\beta_i(t) = \bar{\beta}_i(1 + b_1 Term(t)), \tag{17}$$

where $Term(t)$ is +1 during school term and –1 at other times. The parameter $\bar{\beta}_i$ represents the baseline (or mean) transmission rate. We use the parameter b_1 to represent the amplitude of seasonality. The historical dates of school terms in England and Wales are presented in table 3.3.

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