THE ROYAL SOCIETY

# Population dynamic interference among childhood diseases

**Pejman Rohani*, David J. Earn, Bärbel Finkenstädt and Bryan T. Grenfell**

*Department of Zoology, University of Cambridge, Downing Street, Cambridge CB2 3EJ, UK*

Epidemiologists usually study the interaction between a host population and one parasitic infection. However, different parasite species effectively compete, in an ecological sense, for the same finite group of susceptible hosts, so there may be an indirect effect on the population dynamics of one disease due to epidemics of another. In human populations, recovery from any serious infection is normally preceded by a period of convalescense, during which infected individuals stay at home and are effectively shielded from exposure to other infectious diseases. We present a model for the dynamics of two infectious diseases, incorporating a temporary removal of susceptibles. We use this model to explore population-level consequences of a temporary insusceptibility in childhood diseases, the dynamics of which are partly driven by differences in contact rates in and out of school terms. Significant population dynamic interference is predicted and cannot be dismissed in the limited case-study data available for measles and whooping cough in England before the vaccination era.

**Keywords:** measles; whooping cough; population dynamics; epidemiology; interference; vaccination

## 1. INTRODUCTION

Childhood viral and bacterial infections remain an important public health problem and their dynamics also have broader scientific implications. In recent years, analyses of mathematical models (and comparisons with incidence data) have uncovered fundamental mechanisms that control the dynamics and persistence of parasitic infections (Bartlett 1957; London & Yorke 1973; Dietz 1979; Schaffer & Kot 1985; McLean & Anderson 1988; Diekmann & Kretzschmar 1991; Anderson & May 1991; Levin & Durrett 1996; Hethcote 1997; Grenfell & Harwood 1997; Earn *et al.* 1998). Using a theoretical approach, it has been possible to explore the relative benefits of different potential immunization strategies. Is it best, for example, to vaccinate all children at a specific age or to vaccinate children of all ages simultaneously at regular intervals? Should all geographical locations be treated identically or should there be a greater emphasis placed on urban compared to rural areas? Mathematical models have been useful for estimating a critical vaccination level that will eradicate an infection (May & Anderson 1984; Hethcote 1988; Anderson & May 1991; Agur *et al.* 1993; Nokes & Swinton 1997; Stone *et al.* 1998).

Such epidemiological studies usually address the dynamics of one infection at a time. There has been significant and interesting work on mixed infections and cross-immunity—when an individual has been infected by more than one aetiological agent—but these studies have focused on the *immunological* interaction between more than one strain of the same parasite; different strains of malaria and influenza are particularly interesting in this respect (Dietz 1979; Anderson & May 1991; Gupta *et al.* 1994; Taylor *et al.* 1997; Andreasen *et al.* 1997; Gilbert *et al.* 1998).

By contrast, in this paper we investigate non-immunological disease interactions based on ecological considerations that show up only at the population level. The primary mechanism for this disease 'interference' centres on the convalescence period: following an infection, convalescing individuals—who are essentially quarantined at home—are almost completely isolated from the rest of the population. To a good approximation, such individuals are temporarily insusceptible to other infections (Feng & Thieme 1995). Given that different parasites *compete* for hosts, during a major national outbreak of one disease, thousands of susceptibles are effectively unavailable to other parasites for a period of time. This prompts us to ask: what are the potential population-dynamic effects of periods of insusceptibility on host–multi-microparasite systems?

This question is potentially relevant to numerous diseases, but we concentrate here on its consequences for common childhood respiratory infections, such as measles and whooping cough. We present a new model in which susceptibles may be infected by two different diseases, and try to identify signatures of population-level interference between the diseases. Specifically, we are interested in possible changes in the dynamics that may be induced by the presence of another parasite. Is it possible, for example, that the population-level interaction between two diseases can change the frequency of disease outbreaks? Are two diseases likely to be synchronized due to the strength of seasonality in contact rates or will interference prevent large outbreaks from occurring simultaneously in the same year?

*Author for correspondence (pej@zoo.cam.ac.uk).


*Received* 20 July 1998 *Accepted* 23 July 1998

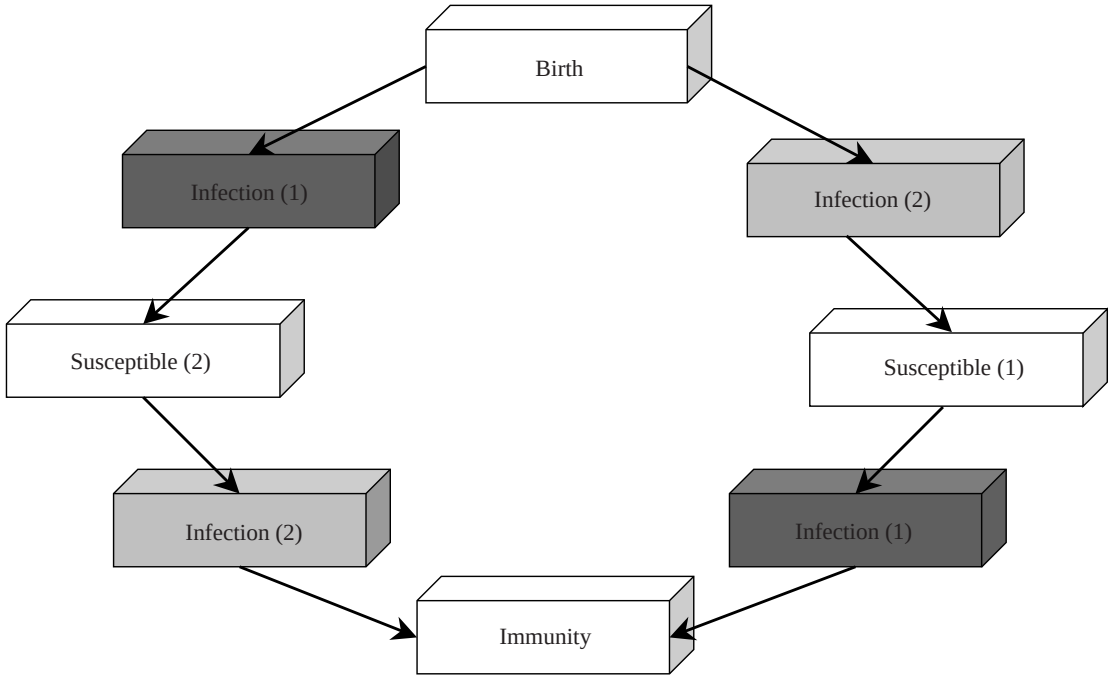


Figure 1. Schematic representation of the main epidemiologic compartments in the two-disease model. For the sake of simplicity, we have omitted the exposed and convalescent classes.

## 2. BIOLOGICAL MOTIVATION FOR THE MODEL

In the classic SEIR model, the host population is divided into four epidemiologic compartments, comprising individuals who are susceptible to a given disease ($S$), exposed but not yet infectious ($E$), infective ($I$) or recovered and immune ($R$) (Anderson & May 1991). We add a fifth compartment containing individuals who are convalescent ($C$). If only one disease is present then our 'SEICR' model will behave identically to the standard 'SEIR' model. If other diseases are present, however, then quarantine of convalescents becomes important. To allow for potential interference among different diseases, we must further subdivide the host population according to infection history relative to each disease. Here, we restrict ourselves to two diseases, which we label '1' and '2'.

In developing our model, we have envisaged a simplified natural history of infection for each disease (figure 1):

(i) a susceptible individual enters the exposed class, and has negligible probability of contracting the second disease simultaneously.
(ii) after the latent period, the individual becomes infectious but is not yet symptomatic and still has negligible probability of contracting the other disease.
(iii) when symptoms appear and the disease is diagnosed the individual is sent home to convalesce.
(iv) after recovering, the individual reactivates susceptibility to the other disease, if previously unexposed to it.

Note that for greater tractability, we have assumed that temporary insusceptibility to a second infection begins as soon as an individual is exposed to the first, whereas the period of isolation does not begin until the individual is quarantined at home. This assumption is not unrealistic. In reality, it is likely that increased non-specific immunological activity following an acute infection will make it difficult for another infection to become established. Clearly, there are some well known examples of opportunistic—usually bacterial—infections that invade those already infected (such as influenza and pneumonia), but these are relatively rare, especially in childhood infections.

Our model has three categories of susceptibles: those who have not contracted either infection and hence are susceptible to both ($S_{1,2}$) and those who have been previously infected by one disease (and have now recovered) but are still susceptible to the other ($S_{i,R}$, $i = 1, 2$). (In our notation, the first index refers to one disease and the second to the status with respect to the other infection.) Thus, the numbers of individuals in these compartments change according to

$$\frac{\mathrm{d}S_{1,2}}{\mathrm{d}t} = \nu\mathcal{N} - \left(\sum_{i=1}^{2}\beta_i(t)I_i/\mathcal{N} + \mu\right)S_{1,2}, \tag{1}$$

$$\frac{\mathrm{d}S_{i,R}}{\mathrm{d}t} = \delta_j C_{j,\mathrm{T}} - (\beta_i(t)I_i/\mathcal{N} + \mu)S_{i,R}. \tag{2}$$

Here $\nu$ and $\mu$ represent the per capita birth and death rates respectively, $\mathcal{N}$ is the total population size, $I_i$ denotes the total number of individuals infected with disease $i$ and $\beta_i(t)$ gives its transmission rate. The equation for $S_{i,R}$ includes the rate, $\delta_j$, at which those previously infected with disease $j$ leave the convalescent class $C_{j,\mathrm{T}}$ (where T signifies temporary insusceptibility to the other disease) and enter the susceptible class for disease $i$. The convalescent period for disease $j$ is $1/\delta_j$. Similarly, there are two categories of infectives for each disease: those who have never contracted the other disease ($I_{i,\mathrm{T}}$, $i = 1, 2$) and

Table 1. *Variables in the two-disease model, with* $i = 1, 2$ *and* $j \neq i$.

| variable | description |
|---|---|
| $S_{1,2}$ | susceptible to both infections |
| $S_{i,R}$ | susceptible to disease i, recovered from $j$ |
| $E_{i,\mathrm{T}}$ | exposed to $i$, temporarily insusceptible to $j$ |
| $E_{i,R}$ | exposed to $i$, recovered from $j$ |
| $I_{i,\mathrm{T}}$ | infectious with $i$, temporarily insusceptible to $j$ |
| $I_{i,R}$ | infectious with $i$, recovered from $j$ |
| $C_{i,\mathrm{T}}$ | convalescing from $i$, temporarily insusceptible to $j$ |

Table 2. *Differential equations in the two-disease model* ($i = 1, 2$ *and* $j \neq i$).

| equation | description |
|---|---|
| $\frac{\mathrm{d}S_{1,2}}{\mathrm{d}t} = \nu\mathcal{N} - \left(\sum_{i=1}^{2}\beta_i(t)I_i/\mathcal{N} + \mu\right)S_{1,2}$ | births, new infections and deaths |
| $\frac{\mathrm{d}S_{i,R}}{\mathrm{d}t} = \delta_j C_{j,\mathrm{T}} - (\beta_i(t)I_i/\mathcal{N} + \mu)S_{i,R}$ | return of convalescents and new infections |
| $\frac{\mathrm{d}E_{i,\mathrm{T}}}{\mathrm{d}t} = \beta_i(t)I_i S_{1,2}/\mathcal{N} - (\mu + \sigma_i)E_{i,\mathrm{T}}$ | new infections, mortality and end of latency |
| $\frac{\mathrm{d}E_{i,R}}{\mathrm{d}t} = \beta_i(t)I_i S_{i,R}/\mathcal{N} - (\mu + \sigma_i)E_{i,R}$ | new infections, mortality and end of latency |
| $\frac{\mathrm{d}I_{i,\mathrm{T}}}{\mathrm{d}t} = \sigma_i E_{i,\mathrm{T}} - (\mu + \gamma_i)I_{i,\mathrm{T}}$ | newly infectious, mortality and diagnosis |
| $\frac{\mathrm{d}I_{i,R}}{\mathrm{d}t} = \sigma_i E_{i,R} - (\mu + \gamma_i)I_{i,R}$ | newly infectious, mortality and diagnosis |
| $\frac{\mathrm{d}C_{i,\mathrm{T}}}{\mathrm{d}t} = \gamma_i I_{i,\mathrm{T}} - (\mu + \delta_i)C_{i,\mathrm{T}}$ | new convalescents, mortality and recovery |

those who are now immune to it because they have acquired it previously ($I_{i,R}$, $i = 1, 2$):

$$\frac{\mathrm{d}I_{i,\mathrm{T}}}{\mathrm{d}t} = \sigma_i E_{i,\mathrm{T}} - (\mu + \gamma_i)I_{i,\mathrm{T}}, \tag{3}$$

$$\frac{\mathrm{d}I_{i,R}}{\mathrm{d}t} = \sigma_i E_{i,R} - (\mu + \gamma_i)I_{i,R}. \tag{4}$$

Here, $1/\sigma_i$ and $1/\gamma_i$ are the latent and infectious periods for disease $i$. (Note that in equations (1) & (2) and elsewhere we have used $I_i \equiv I_{i,\mathrm{T}} + I_{i,R}$.) The key aspect of the new model is, of course, that there are independent equations describing the dynamics of convalescents:

$$\frac{\mathrm{d}C_{i,\mathrm{T}}}{\mathrm{d}t} = \gamma_i I_{i,\mathrm{T}} - (\mu + \delta_i)C_{i,\mathrm{T}}. \tag{5}$$

The full list of variables and parameters together with the set of thirteen differential equations describing the system are presented in tables 1, 2 and 3. A simplified schematic representation of the model is given in figure 1.

Table 3. *Parameters of the two-disease model with* $i = 1,2$.

| parameter | description |
|---|---|
| $\nu$,$\mu$ | *per capita* birth and mortality rates |
| $\beta_i(t)$ | time-varying contact rate for disease $i$ |
| $1/\sigma_i$ | latency period for disease $i$ |
| $1/\gamma_i$ | infectious period for disease $i$ |
| $1/\delta_i$ | convalescence period for disease $i$ |

The structure of our model is similar to that of Dietz (1979), who was concerned with instances when immunological interactions within hosts cause temporary insusceptibility to other strains of the same parasite. Dietz based his model on the simpler SIR framework without exposed and convalescent classes, and deduced dynamical equilibria in the absence of seasonality in contact rates. For childhood diseases, however, the seasonal pattern of contacts among school children is fundamentally important (Bartlett 1957; London & Yorke 1973; Bolker 1993; Grenfell *et al.* 1995; Finkenstädt & Grenfell 1998; Finkenstädt *et al.* 1998) and is included in our analysis. We use a strict 'term-time forcing' function, as introduced by Schenzle (1984): contact rates are high on school days and low on other days.

A different model, concerned with the possible effects of convalescence on the dynamics of a single disease, has been explored previously by Feng & Thieme (1995). They defined the number of 'active' individuals in the population ($A$) as the total population size minus those in the convalescent class ($A = \mathcal{N} - C$) and they scaled the transmission parameter ($\beta$) with $A$ rather than the constant $\mathcal{N}$ (the idea being that only active individuals are homogeneously mixed). This formulation yields a time-varying transmission rate even without explicit forcing and so, with a non-zero convalescent period, epidemic cycles are possible without making $\beta$ explicitly time dependent. We have not adopted this formalism since we see no reason to assume that the removal of a fraction of the population will in fact *increase* the likelihood of susceptibles coming into contact with infecteds.

In the next section, we use our model to explore the dynamics of two childhood infections that have the same basic reproductive ratio ($R_0$) but differ in infectiousness and infectious period: disease 1 has a shorter infectious period than disease 2 ($\gamma_1 > \gamma_2$), but is more infectious ($\beta_1(t) > \beta_2(t)$). In our model, disease 1 is likened to measles and disease 2 is based on whooping cough (pertussis).

## 3. MODEL STRUCTURE AND DYNAMICS

Interference can be identified only by comparison with the dynamics of each infection in isolation, so we first use the deterministic SEIR model and term-time forcing (Schenzle 1984) to summarize the behaviour of each disease when the other is not present, for a range of seasonal forcing amplitudes (London & Yorke 1973; Kuznetsov & Piccardi 1994; Li & Muldowney 1995).

### (a) *Single-disease dynamics*

For sufficiently high seasonal amplitude ($b_1$), disease 1 exhibits biennial outbreaks, with a major outbreak every

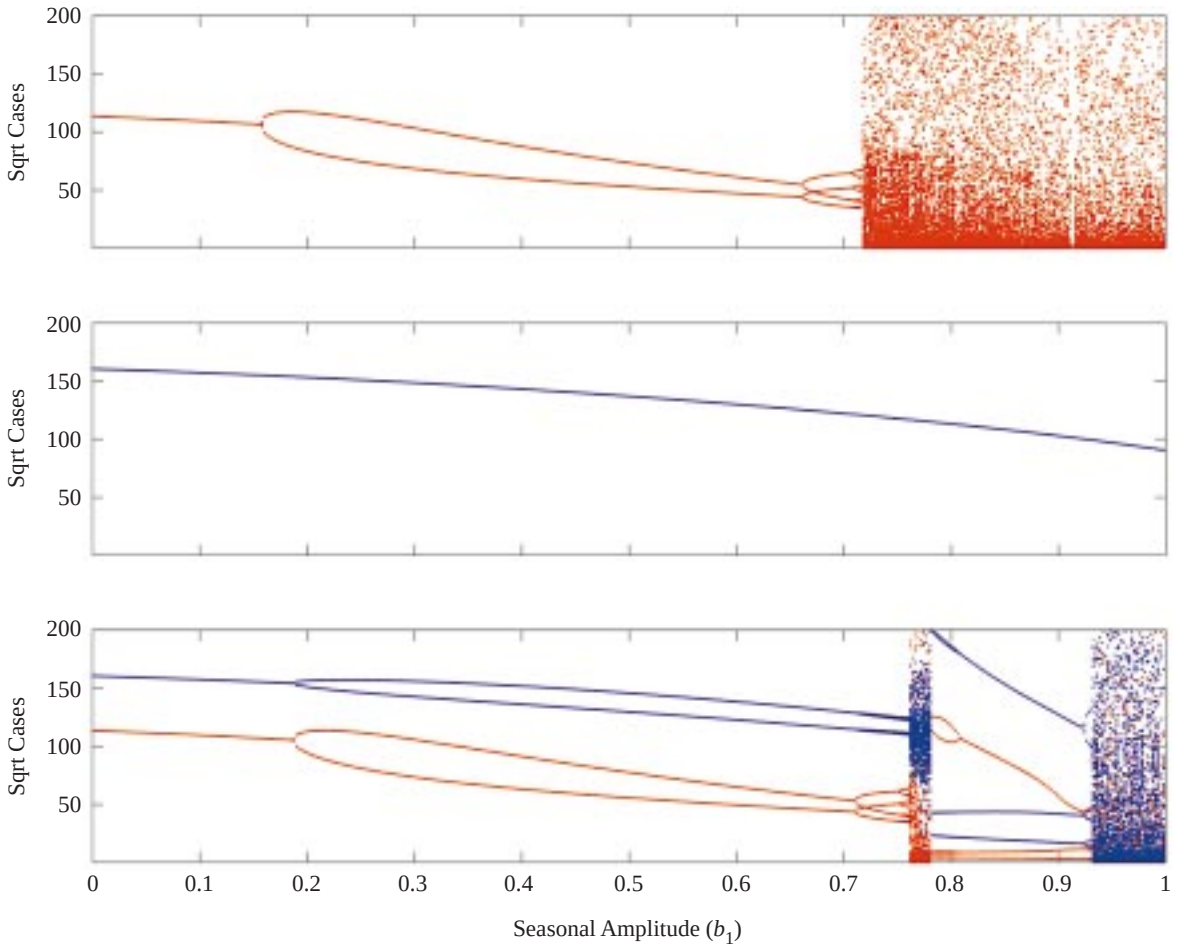


Figure 2. Bifurcation diagrams for the deterministic single-disease *SEIR* model with term-time forcing (*a*) and (*b*) and the deterministic two-disease model (*c*) as a function of seasonal amplitude $b_1$. The term-time forcing is implemented such that the contact rate for disease $i$ on school days is given by $\beta_i(t) = b_{0,i} \times (1 + b_1)$, else $\beta_i(t) = b_{0,i} \times (1 - b_1)$ (where $b_{0,i}$ represents the basic contact rate). (*a*) Disease 1: short infectious period ('measles') with $b_{0,1} = 1250\ \mathrm{yr}^{-1}$, $1/\sigma_1 = 8\,\mathrm{d}$ and $1/\gamma_1 = 5\,\mathrm{d}$. (*b*) Disease 2: long infectious period ('whooping cough') with $b_{0,2} = 625\ \mathrm{yr}^{-1}$, $1/\sigma_2 = 8\,\mathrm{d}$ and $1/\gamma_2 = 10\,\mathrm{d}$. (*c*) Two disease model (measles represented by red dots, whooping cough by dark blue dots) with $1/\delta_1 = 7\,\mathrm{d}$ and $1/\delta_2 = 14\,\mathrm{d}$. In all simulations, $N = 5 \times 10^7$ and $\nu = \mu = 0.02\ \mathrm{yr}^{-1}$. We discarded a 400-year transient before recording the number of infectives on day 1 of the next 100 years. Wrap-around initial conditions were used.

other year. As $b_1$ approaches unity, however, the biennial pattern gives way to chaos (figure 2*a*). In contrast, due to its longer infectious period, the deterministic dynamics of disease 2 are always strictly annual, irrespective of the strength of seasonality (figure 2*b*).

### (b) *Two-disease dynamics*

When the two diseases are combined in our model, it is immediately apparent that they do interfere at the population level (figure 2*c*). The presence of disease 2 'simplifies' the dynamics of disease 1. Compared to the single-disease bifurcation diagram (figure 2*a*), the transition point from annual to biennial outbreaks occurs at slightly higher seasonal amplitude. Interference also reduces the propensity for four-year cycles or more complex dynamics at high levels of seasonality. The interaction has a more striking effect on the dynamics of disease 2, which no longer shows strictly annual cycles. For much of the range of seasonal amplitude, there are major outbreaks only every second year, and when the level of seasonal forcing is extremely high, chaos ensues.

We can gain insight into the effects of disease 1 on disease 2 by reconsidering equation (2) with $i = 1$ and $j = 2$. The rate at which individuals infected with disease 1 return to the susceptible population is dictated by the sum of the incubation, infectious and convalescence periods $(1/\sigma_1 + 1/\gamma_1 + 1/\delta_1)$. If this period is relatively long, there will be many susceptibles temporarily removed from the population, following an outbreak of disease 1. Given that on its own disease 1 exhibits a very strong biennial pattern, this periodic removal of susceptibles effectively introduces another forcing function to disease 2. The net effect of this is to make the dynamics of disease 2 more 'complicated' and similar to disease 1 (hence, rigidly annual dynamics give way to predominantly biennial outbreaks or even chaos).

The effects of disease 2 on disease 1 are a little more subtle. Because of its long infectious period, the dynamics of disease 2 have a very strong annual component, even when they have a period of more than one year. This regular, almost annual, removal of potential susceptibles for disease 1 has the same net effect as lowering the amplitude of the seasonal forcing in contact rates $(b_1)$. As a consequence, the dynamics of the infection with the shorter infectious period are simplified slightly, with a more pronounced annual signature.

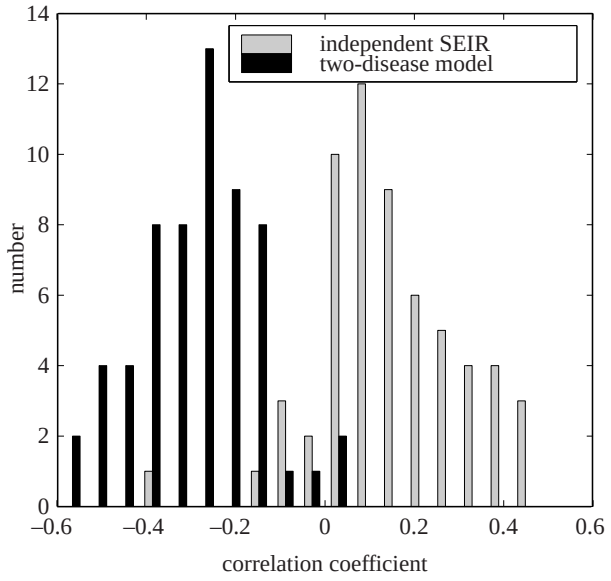


Figure 3. Frequency histograms for the cross-correlation coefficients (CC) of 40-year simulated time-series data for diseases 1 and 2. In (*a*), we plot CCs calculated from 60 realizations of a Monte-Carlo version of the two-disease model. These results show that the temporal dynamics of the two infections are strongly negatively correlated (mean CC $= -0.285$ and s.d. $= 0.134$). Contrast these with (*b*) where we have shown the CCs of data generated using independent Monte-Carlo SEIR models with measles and whooping cough parameters. These show that such strongly negative correlations are very unlikely to arise purely by chance (mean $= 0.149$ and s.d. $= 0.159$). Model parameters are as stated in the caption to figure 2, with $b_1 = 0.1$ and annual immigration rates of 20 per million for disease 1 and 10 per million for disease 2.

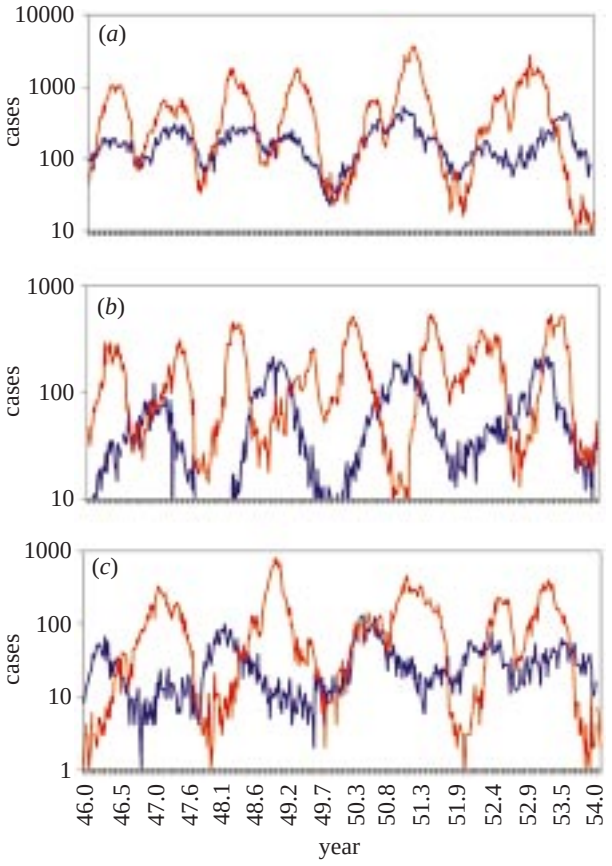


Figure 4. Weekly case-reports for measles (red) and whooping cough (dark blue) in (*a*) London, (*b*) Liverpool and (*c*) Sheffield from 1946–1954 (log scale).

In addition to the general dynamical consequences of disease interaction, the temporal correlation of cases of each disease is of great interest. To explore the correlation between the two infections, we used a stochastic (Monte-Carlo) version of the two-disease model (e.g. Bartlett 1957; Grenfell 1992; Renshaw 1993). Not surprisingly, when the dynamics are annual, the two infections are perfectly in-phase (due to the strong influence of seasonal forcing). Simulation time-series show that given biennial or longer period fluctuations, there is a marked tendency for the diseases to be negatively correlated, with the major outbreaks being out-of-phase. It is interesting to note that during a major outbreak of either infection, the proportion of the susceptible population that is insusceptible is typically less than 5% and yet this has a pronounced effect. In figure 3 we present a frequency histogram for the cross-correlation coefficients of 60 simulations of the stochastic two-disease model and two independent stochastic SEIR models. Clearly, the time-series are significantly more negatively correlated when the two diseases are allowed to interfere. The results for the SEIR model show that although it is possible that chance events may cause outbreaks of two independent diseases to be out-of-phase with each other, this effect is not nearly as pronounced as that resulting from interference.

The key parameters that determine the strength of disease interference are the convalescence rates for each infection ($\delta_1$ and $\delta_2$), although the incubation and infectious periods will also play a role. Results not presented here show that when the convalescence period of either infection is very long ($\delta_1$ or $\delta_2$ are very small), a significant proportion of the potential susceptible population is insusceptible for much of the time. This acts as another source of forcing on the system and can result in a complex pattern of abundance for both infections. However, the primary effect of long convalescence periods is to increase the negative temporal correlation between the diseases.

The most epidemiologically important result to note from this section is that the model confirms that two such infections do indeed have a significant dynamic effect on each other at the population level. We have explored the interaction between two diseases with a large range of parameter values but this did not affect our qualitative results. The effects we have discussed are representative of the generic properties of the two-disease model. To summarize, these are:

(i) the disease with the shorter infectious period shows slightly simpler dynamics
(ii) the disease with the longer infectious period shows more complex dynamics, as dictated by the other infection;
(iii) major outbreaks of the two diseases tend to be negatively correlated, occurring in different years.

What is the likelihood of observing disease interference in practice? To investigate this, we would ideally need

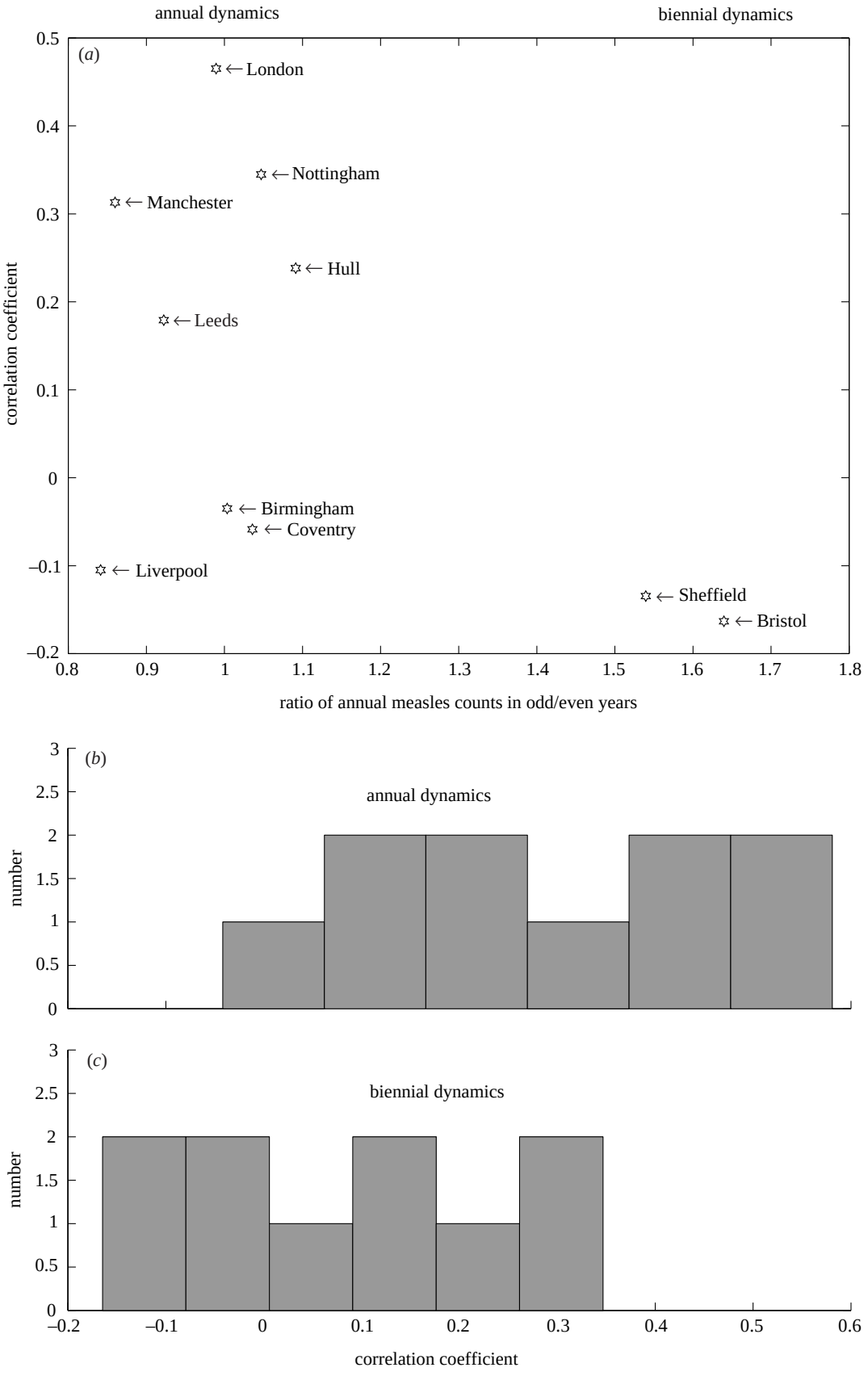


Figure 5. Analysis of data from the top ten cities in England. We used the measles time-series to classify the data as either annual or biennial. In (*a*), we plot the average ratio of annual measles counts (odd/even years) in successive two-year periods versus the estimated cross-correlation coefficient for each city. To explore possible interference effects, we analysed the same data in a different way by plotting the annual measles counts in successive years. The time-series for each city were split into an annual and a biennial section using the distance from the 45° line. In (*b*) and (*c*), we plot the correlation histogram for the annual (mean= 0.297 and s.d. = 0.206) and biennial regimes (mean= 0.089 and s.d. = 0.185), repectively.

long-term pre-vaccination incidence data (longer than twenty years) for a number of childhood infections under constant demographic conditions. These infections must conform to the assumptions of the SEIR model: namely, they should be easily diagnosable, confer life-long immunity following infection and have no vector, animal reservoir or latent transmission. A search of the literature revealed that data of this quality for more than one disease in the same place are not currently available.

## 4. CASE STUDY: MEASLES AND WHOOPING COUGH IN ENGLAND

In the absence of ideal data, we look for interference effects in time-series for measles and whooping cough in England from 1946–1954, which pre-dates mass vaccination for either disease (Grenfell & Anderson 1989). The measles data are thought to be relatively accurate (at least 60% of cases are reported; Clarkson & Fine 1985), whereas the accuracy of reporting is thought to be quite low in the whooping cough data (ranging between 5–25%; Clarkson & Fine 1985; Hethcote 1997).

Measles conforms closely to the SEIR assumptions, but whooping cough is much more complex (discussed below). Both infections have $R_0 \simeq 17$ (Anderson & May 1991) with parameters similar to those we explored in the previous sections.

We have data for the largest 60 cities in England and Wales; to illustrate the wide range of observed dynamics, we have plotted the weekly case reports of measles and whooping cough in London, Liverpool and Sheffield from 1946 to 1954 (figure 4). The pattern of interaction between these two diseases clearly differs from city to city. In London (figure 4*a*), for example, outbreaks of both diseases occur annually in the years immediately following World War II (the so-called 'baby-boom' effect) and naturally the infections are in phase. In later years, both diseases show a biennial pattern; in this regime, there seems to be little consistent correlation between the two infections. Sometimes, during the spring of 1951, for example, the epidemics peak roughly simultaneously while at other times (e.g. 1953), there is no overlap. On the other hand, in Liverpool (figure 4*b*), measles outbreaks always occur annually (associated with high birth rates; Finkenstädt *et al.* 1998) and whooping cough epidemics occur biennially. In these data, there seems to be quite a strong negative correlation between the two infections, which may perhaps be attributable to interference effects. Finally, in Sheffield (figure 4*c*), both measles and whooping cough are biennial for the first 6–7 years, while there is no rigid pattern in later years. What is clear, however, is that their major outbreaks are strikingly out-of-phase with each other, at least during 1946–1951.

We carried out a more systematic analysis of these data by attempting to characterize the periodicity of disease dynamics and comparing this with the estimated correlation cofficient (figure 5). A simple approach is to use the ratio of odd/even year annual measles counts in successive biennia as a guide (figure 5*a*). If the average of this ratio is close to one, then the dynamics may be considered annual. As can be seen in figure 5*a*, the dynamics of measles in Sheffield and Bristol are biennial in the period 1946–1954. The correlation coefficients of measles and whooping cough in this period are negative for these cities. The remaining cities exhibit mostly annual dynamics and as expected from the model predictions, the outbreaks of measles and whooping cough in these cities are either effectively uncorrelated (Birmingham and Coventry) or positively correlated. An exception to this finding is Liverpool, where measles outbreaks are annual and yet the diseases appear to be weakly negatively correlated. This may be better understood by considering the raw time-series (figure 4*b*). The source of the negative correlation between these two infections is clearly caused by the timing of whooping cough outbreaks. While in England and Wales the highest number of cases are usually reported in early spring, in Liverpool, the peak pertussis counts are observed at the turn of the year. The cause of this peculiarity is unclear.

Another potential approach to identify interference effects in the data is to plot annual measles counts in year $t+1$ versus counts in year $t$. The distance of each point from the 45° line gives an indication as to the nature of the dynamics. Using this approach, we characterized sections of the measles time-series in each city as either annual (close to the 45°) or biennial. In figures 5*b*,*c*, we have plotted the frequency histograms for the correlation coefficients of measles and whooping cough weekly data in each city for annual and biennial dynamics, respectively. The differences between these histograms are not statistically significant, but there is a clear shift towards negative correlation cofficients when the dynamics are biennial.

Our analyses of these data do not provide unequivocal evidence for the predictions of our two-disease model, but there appear to be tantalizing glimpses of interference. Unfortunately, a variety of complications plague these short time-series. Birth rates in England and Wales increased significantly after World War II, peaking in 1947 (Finkenstädt *et al.* 1998), which gave rise to outbreaks with a strong annual component in the years 1946–1952 (figure 5*a*). Thus, in large cities (e.g. London), the cases of measles and whooping cough during this period tend to be positively correlated. Another complication may be due, in part, to the fact that sporadic localized whooping cough vaccinations started in the early 1940s (Grenfell & Anderson 1989), hence clouding the data. A further potential contaminant of the data is that (as already mentioned) whooping cough can be difficult to diagnose and case reports are thought to represent only 5–25% of actual cases (most of which do not lead to a lengthy convalescence period). Thus the interference effect may be rather one-sided (somewhat akin to an amensalism): those infected with measles are successfully diagnosed and quarantined (hence adversely affecting pertussis dynamics), but many cases of whooping cough go unnoticed (markedly reducing the interference effects on measles).

It is also possible that this very simple SEICR framework is not sufficient to model the behaviour of whooping cough. Its transmission and the immunological response it elicits are complicated. It is known, for example, that some infectious adults may be asymptomatic and thus act as temporary (and undetected) reservoirs for pertussis (Hodder & Mortimer 1992). The degree of immunity following pertussis infection is also a matter of debate; it

may wane through time (Hodder & Mortimer 1992; Scott *et al.* 1997; Hethcote 1997). If so, then—contrary to our traditional assumptions—whooping cough may not primarily infect children, so term-time forcing of the contact rate may be inappropriate in the absence of age-structure in the model.

## 5. DISCUSSION

We have presented a new model for a potential population-level (non-immunological) interaction between two infectious diseases. The aim has been to explore whether the temporary removal of susceptibles for the 'competing' disease has an important dynamic effect on the persistence and dynamics of a community of childhood diseases.

We have concluded that two diseases with differing infectious periods can potentially interfere strongly at the population level. The dynamics of the disease with the shorter infectious period (likened in this paper to measles) is not dramatically affected but is slightly 'stabilized', with a reduced likelihood of exhibiting chaotic dynamics. However, the disease with the longer infectious period (e.g. whooping cough) is coerced by the other disease to show a mostly biennial epidemic pattern, whereas it is strictly annual in isolation. Our most straightforward prediction is that epidemics of the two infections are likely to be negatively correlated (when the dynamics are not rigidly annual).

Our comparison with the time-series data for the incidence of measles and whooping cough in England was suggestive but not conclusive. There seems to be no unique pattern of interaction between these two infections; there are qualitative differences between cities in both the individual dynamics of measles and whooping cough and in the relationship between the two. As we have stressed, the differences may in part be due to some of the complications of pertussis which may mean that using the simple SEIR framework is inappropriate. In addition, the time-series are very short and contaminated both by a transient demographic disruption caused by the second world war and sporadic pertussis vaccination.

Another limitation of our study is that we have considered the interaction between only two diseases. Population-dynamic interference may occur quite generally. Once diagnosed, infected children are isolated from other children and our model predicts that this should affect the frequency of epidemics and extinction probability. Evidence may exist for interference among diseases such as measles, mumps and chicken pox, though currently we do not have access to the relevant time-series.

Elsewhere, we have shown that epidemiologic interference can potentially have important consequences for the design of effective immunization schemes (Rohani *et al.* 1999). Our results imply that interference is potentially a very important factor to bear in mind when multiple vaccines are being developed. In particular, they point towards careful timing of vaccinations to make full use of potential interference effects. Currently, both the measles and whooping cough vaccines also vaccinate against other infections; since 1988, the measles vaccine has also immunized against mumps and rubella (MMR vaccine), while the whooping cough vaccine is combined with tetanus and diphtheria (DTP vaccine). There are immunological and economic reasons why some vaccines are grouped together; our work suggests that epidemiological factors should also be taken into account (Rohani *et al.* 1999).

It is a pleasure to thank Jonathan Swinton, Matt Keeling, Mike Bonsall and four anonymous reviewers for their comments on this paper. P.R. is supported by a NERC Postdoctoral Research Fellowship. D.J.D.E., B.F. and B.T.G. are supported by the Wellcome Trust.

## REFERENCES

Agur, Z., Cojocaru, L., Mazor, G., Anderson, R. M. & Danon, Y. L. 1993 Pulse mass measles vaccination across age cohorts. *Proc. Nat. Acad. Sci.* **90**, 11 698–11 702.

Anderson, R. M. & May, R. M. 1991 *Infectious diseases of humans*, Oxford University Press.

Andreasen, V., Lin, J. & Levin, S. A. 1997 The dynamics of co-circulating influenza strains conferring partial cross-immunity. *J. Math. Biol.* **35**, 825–842.

Bartlett, M. S. 1957 Measles periodicity and community size. *J. R. Statist. Soc.* **120**, 48–70.

Bolker, B. M. 1993 Chaos and complexity in measles models: a comparative numerical study. *IMA J. Math. Appl. Med. Biol.* **10**, 83–95.

Clarkson, J. A. & Fine, P. E. M. 1985 The efficiency of measles and pertussis notification in England and Wales. *Int. J. Epidemiol.* **14**, 153–168.

Diekmann, O. & Kretzschmar, M. 1991 Patterns in the effects of infectious diseases on population growth. *J. Math. Biol.* **29**, 539–570.

Dietz, K. 1979 Epidemiologic interference of virus populations. *J. Math. Biol.* **8**, 291–300.

Earn, D. J. D., Rohani, P. & Grenfell, B. T. 1998 Persistence, chaos and synchrony in ecology and epidemiology. *Proc. R. Soc. Lond.* B **265**, 7–10.

Feng, Z. & Thieme, H. R. 1995 Recurrent outbreaks of childhood diseases revisited: the impact of isolation. *Math. Biosci.* **128**, 93–130.

Finkenstädt, B. & Grenfell, B. T. 1998 Empirical determinants of measles metapopulation dynamics in England and Wales. *Proc. R. Soc, Lond.* B **265**, 211–220.

Finkenstädt, B., Keeling, M. J. & Grenfell, B. T. 1998 Patterns of density dependence in measles dynamics. *Proc. R. Soc. Lond.* B **265**, 753–762.

Gilbert, S. C., Plebanski, M., Gupta, S., Morris, J., Cox, M., Aidoo, M., Kwiatkowski, D., Greenwood, B. M., Whittle, H. C. & Hill, A. V. S. 1998 Association of malaria parasite population structure, HLA, and immunological antagonism. *Science* **279**, 1173–1177.

Grenfell, B. T. 1992 Chance and chaos in measles dynamics. *J. R. Statist. Soc.* B **54**, 383–398.

Grenfell, B. T. & Anderson, R. M. 1989 Pertussis in England and Wales: an investigation of transmission dynamics and control by mass-vaccination. *Proc. R. Soc. Lond.* B **236**, 213–252.

Grenfell, B. T. & Harwood, J. 1997 (Meta)population dynamics of infectious diseases. *Trends. Ecol. Evol.* **12**, 395–399.

Grenfell, B. T., Kleckowski, A. & Bolker, B. M. 1995 Seasonality and extinction in chaotic metapopulations. *Proc. R. Soc. Lond.* B **259**, 97–103.

Gupta, S., Trenholme, K., Anderson, R. M. & Day, K. 1994 Antigenic diversity and the transmission dynamics of *Plasmodium falciparum*. *Science* **263**, 961–963.

Hethcote, H. W. 1988 Optimal ages of vaccination for measles. *Math. Biosci.* **89**, 29–52.

Hethcote, H. W. 1997 An age-structured model of pertussis transmission. *Math. Biosci.* **145**, 89–136.

Hodder, S. L. & Mortimer, E. A. Jr 1992 Epidemiology of pertussis and reactions to pertussis vaccine. *Epidemiol. Rev.* **14**, 243–267.

Kuznetsov, Y. A. & Piccardi, C. 1994 Bifurcation analysis of periodic SEIR and SIR epidemic models. *J. Math. Biol.* **32**, 109–121.

Levin, S. A. & Durrett, R. 1996 From individuals to epidemics. *Phil. Trans. R. Soc. Lond.* B **351**, 1615–1621.

Li, M. Y. & Muldowney, J. S. 1995 Global stability for the SEIR model in epidemiology. *Math. Biosci.* **125**, 155–164.

London, W. P. & Yorke, J. A. 1973 Recurrent outbreaks of measles, chickenpox and mumps. I. Seasonal variations in contact rates. *Am. J. Epidem.* **98**, 453–468.

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

May, R. M. & Anderson, R. M. 1984 Spatial heterogeneity and the design of immunization programs. *Math. Biosci.* **72**, 83–111.

Nokes, D. J. & Swinton, J. 1997 The control of childhood viral infections by pulse vaccination. *IMA J. Math. Appl. Med. Biol.* **12**, 29–53.

Renshaw, E. 1991 *Modelling biological populations in space and time*. Cambridge University Press, Cambridge.

Rohani, P., Earn, D. J. & Grenfell, B. T. 1999 Vaccination implications of disease interference. (In preparation.)

Schaffer, W. M. & Kot, M. 1985 Nearly one-dimensional dynamics in an epidemic. *J. Theor. Biol.* **112**, 403–427.

Schenzle, D. 1984 An age-structured model of pre- and post-vaccination measles transmission. *IMA J. Math. Appl. Med. Biol.* **1**, 169–191.

Scott, P. T., Clark, J. B. & Miser, W. F. 1997 Pertussis: an update on primary prevention and outbreak control. *Am. Fam. Phys.* **56**, 1121–1128.

Stone, L., Shulgin, B. & Agur, Z. 1998 Theoretical examination of the pulse vaccination policy in the SIR epidemic model. *Math. Comp. Model.* (In the press.)

Taylor, L. H., Walliker, D. & Read, A. F. 1997 Mixed-genotype infections of malaria parasites: within-host dynamics and transmission success of competing clones. *Proc. R. Soc. Lond.* B **264**, 927–935.

As this paper exceeds the maximum length normally permitted, the authors have agreed to contribute to production costs.