(Meta)population dynamics of infectious diseases

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The metapopulation concept provides a very powerful tool for analysing the persistence of spatially-disaggregated populations, in terms of a balance between local extinction and colonization. Exactly the same approach has been developed by epidemiologists, in order to understand patterns of diseases persistence. There is great scope for further cross-fertilization between these areas. Recent work on the spatiotemporal dynamics of measles illustrates that the large datasets and rich modelling literature on many infectious diseases offer great potential for developing and testing ideas about metapopulations.

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The metapopulation concept has been extremely influential in theoretical ecology and conservation biology[1]. Essentially, it assumes that the distribution of many species can be described as a system of local populations, each of which may be subject to turnover as a result of extinction and subsequent recolonization by dispersing individuals. Most developments in this field have been theoretical rather than empirical. This is mainly because of the difficulties in obtaining sufficient spatiotemporal data, in systems where the underlying biology is well enough understood to produce realistic metapopulation models. Recently, long-term studies of invertebrate populations, which meet these criteria[2–4], have generated important findings about metapopulation dynamics. However, there is still a pressing need for new data sets, particularly from longitudinal studies spanning many population generations.

Some authors[5] have suggested that the influence of metapopulation theory is unjustified and others[6,7] have questioned whether many real populations actually conform to the metapopulation model. However, recent extensions[8] of Levins' original formulation of the metapopulation concept[9], have provided a powerful tool for testing model predictions using data on the presence or absence of species in suitable habitat patches.

Since the 1960s, a number of authors (reviewed in Begon *et al.*[10]) have recognized that epidemiological theory has also addressed exactly this question: of population persistence in a set of host 'patches'. Lawton *et al.*[11] point out that, if the species of interest is a parasite, each host organism can be considered as a habitat patch containing a local population of the parasite. Infection is equivalent to colonization, and death or recovery of the host is equivalent to local extinction. Indeed, the derivation of the formula for the minimum amount of suitable habitat (MASH)[12], required for metapopulation persistence, is identical to that used to determine the proportion of a host population which must be vaccinated in order to eradicate a parasite[11,13]. In fact, the relationship between metapopulation and epidemiological theories is even more extensive.

Metapopulations of parasites

In classic metapopulation theory, a patch is available for colonization after it is emptied by extinction. This is not always the case for parasite metapopulations. Parasites can be divided[14] into those which produce lifelong immunity or kill their host (for example measles and other related viruses such as Rinderpest, rabies and insect baculoviruses) and those in which hosts can re-acquire infection after losing it (the case in many other microparasites and most macroparasitic worms). At one extreme, an infection such as gonorrhoea (which does not result in host immunity[15]) exists as a classic metapopulation, with each individual host forming a patch. On the other hand, an infection which immunizes or kills the host renders the host-patch indefinitely unsuitable for recolonization. Thus measles, along with many of the other great microparasitic infections of childhood (pertussis, mumps, etc.), does not form a true metapopulation at the individual host level.

However, if we consider *groups* of hosts as patches, the metapopulation analogy applies very well to parasites that invoke life-long host immunity. In particular, the spatial organization of human hosts into well-defined social units – families, villages, towns and cities – produces well-defined patches of resource for their microparasites[16,17]. Because of the economic and medical importance of these diseases, their occurrence is often officially notifiable in many countries. Disease incidence is routinely recorded in official statistics at a geographical scale which coincides with patch boundaries, and on a time scale (weekly or monthly) that is close to the generation time of measles and the other childhood microparasites[18–20]. This process results in large spatiotemporal data sets, which are highly suitable for metapopulation analyses (Box 1).

However, an extensive data set is only part of the story; we also ideally need a tractable model framework for the metapopulation. Measles is especially suitable, since the underlying population process – essentially a predator–prey interaction between infectious and susceptible individuals[15] – is relatively simple and well understood. Epidemiologists have developed a family of models of measles dynamics, whose parameters can be estimated from the available data. These range in complexity from simple aggregate models for the dynamic impact of vaccination[15] and the nonlinear dynamics of infection[19] to those that explicitly model the age-structured dynamics of the host[21–25] and complex spatial structures[26–28].

Measles metapopulation dynamics

Box 2 describes the biology of measles epidemics using a simple deterministic model. The best ecological metapopulation analogy is with the well-documented example of butterfly species, which rely on specific host plants as resources (e.g. Ref. 2). For measles metapopulations, patch 'resources' are determined by the density of susceptible hosts.

In terms of classical metapopulation theory, we are interested in the local presence or absence of infection.

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Box 1. Features of the available data on notifiable diseases of childhood which make them especially suitable for metapopulation analyses

- Extensive time series for individual patches which document extinction and recolonization events, with information on the internal patch dynamics of the parasitic colonizer.
- A parallel time-series of data on other important ecological variables – such as birth rate and population size (i.e. essentially resource dynamics) – which relate to long-term changes in the state of the system.
- Heterogeneity in patch sizes which leads to extinction and recolonization in small patches and persistence in large ones.
- Different metapopulation structures often occur in different geographical areas.
- Substantial, quantifiable changes in metapopulation structure with time as a result of manipulation (mass vaccination).

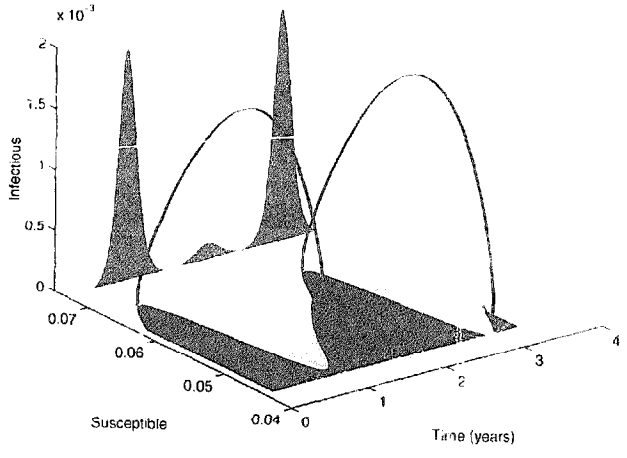
Box 2. Measles dynamics

A combination of relatively large data sets and simple natural history makes measles among the best understood childhood diseases[16]. We focus on the best-documented case: measles in developed countries, though the infection is much more important in public health terms in developing countries[5]. In developed countries, measles occurred in relatively violent epidemics, generally at a biennial frequency in large conurbations. Measles dynamics have been the subject of much modelling, from simple formulation which assume a homogeneous population with deterministic dynamics to complex age- and spatially-structured stochastic formulations[26].

We can illustrate the essentials of measles dynamics with a simulation of the simple seasonally-forced SEIR model. The host population is divided into four compartments denoting the proportions of susceptible (previously uninfected) individuals S, exposed (infected but not yet infectious) individuals E, infectious individuals I, and recovered individuals R. The model assumes that susceptibles pick up the infection by contact with infectious individuals, harbour the infection for a few weeks, then become immune for life.

The figure shows a simulation of a simple 4-compartment measles model, with seasonal forcing of the infection parameter; because S + E + I + R = N (the total population), we only need to consider S, E and I. Hosts have a natural death rate, m, but are assumed not to die from the infection. The system $dS/dt = m(1 - S) - bc(t)IS$; $dE/dt = bc(t)IS - (m + a)E$; $dI/dt = aE - (m + g)I$ was solved iteratively with the following illustrative parameter values $m = 0.02$, $a = 48.67$, $g = 56.19$, $b = 1010.7$ (all per day; b per infective per day): a and g control the movement of individuals out of the Exposed and Infectious classes and b is the infection parameter. We modelled seasonality in b [$c(t)$] by a simple cosine wave {$c(t) = 1 + 0.25\cos(2\pi t)$}; the amplitude of 25% gives a biennial epidemic pattern. Parameter values were taken from Olsen *et al.*[19] S, E and I are expressed as proportions of N.

Epidemics (shown in red) extinguish themselves by depleting the susceptible population (blue), which is then replenished back to the epidemic threshold, precipitating another epidemic after about two years. Seasonality in infection rate (yellow) resonates with this timescale to promote the persistence of epidemics. In small host populations, the troughs between epidemics can be sufficiently deep to cause a high probability of local extinction of infection, which then needs to be reintroduced before the next epidemic can occur. Reintroduction of infection cannot succeed until the density of susceptibles has risen above the epidemic threshold[15].



'Colonization' therefore corresponds to the establishment of measurable infection in an uninfected patch; colonizers here are infected individuals. We can therefore measure the success of a particular colonization event by the size of the ensuing epidemic – itself a major preoccupation of stochastic epidemic theory[29]. Epidemic size depends on the level of susceptible resources and hence on the epidemic history of the patch. This dependence is illustrated by the epidemic sequence in Box 1.

The epidemic phase

If the susceptible density is high (the blue shaded curve near time zero in Box 1), the number of infectives within the patch (the red shaded curve) increases roughly exponentially, following colonization. During this major epidemic phase, the dynamics of the system are predominantly deterministic and the metapopulation analogy is relatively weak. As the epidemic progresses, it depletes the level of resources in the patch (blue curve), which in turn acts as a density-dependent brake on the increase in infectives.

Extinction: the epidemic trough

Very quickly, the (susceptible) resource density drops below a deterministic invasion threshold and the density of infectives begins to fall. This threshold is determined by that mystical epidemiological quantity, the basic reproduction ratio of infection, R_0 (Refs 15,30,31). Local persistence of infection is now prey to stochastic events and, in small patches the infection tends to 'fade out' (see below and the small towns in Figs 1 and 2b). During this phase, the system most closely resembles a classical metapopulation. Susceptibles are then gradually topped up by births over several infective generations, until the invasion threshold is passed and a further epidemic can occur (Box 1).

In broad terms, this alternation of deterministic and stochastic phases makes measles similar to a natural enemy metapopulation[32], which periodically outstrips its local resources. As with many ecological metapopulations, seasonality (here associated with school transmission) is also an important force in dynamics and persistence (Box 1).

Of course, the disease metapopulation is distinct from more familiar ecological ones in other important respects. A fundamental difference is the question of patch dynamics – for viral infections such as measles, 'empty' patches suitable for colonization arise from existing patches by births. This potentially adds another layer of metapopulation complexity, depending on the degree of pathogenicity of the parasite. For very pathogenic agents such as phocine distemper virus infecting harbour seals[33], epidemics with high fatality rates may affect the local persistence of the *host* metapopulation, as well as reducing the subsequent net recruitment of new patches for the parasite.

Another distinction of measles from the classical metapopulation paradigm is that we can consider the absolute population dynamics of colonists in patches explicitly, rather than simply their presence/absence. This allows us to develop an accurate empirical picture of the forces that shape persistence.

Persistence of measles metapopulations: the critical community size

One of the major achievements of epidemiological theory has been the quantification of the Critical Community Size (CCS): the (generally urban) population size, below which measles tends to die out in the troughs between epidemics. The CCS was first defined for British and American cities in the seminal work of Bartlett[34], though the concept also applies to

the more isolated communities on islands[35]. Although these studies used data from a variety of sources and demographic situations, they indicate a remarkably consistent CCS, of around 250–400 000 individuals.

The CCS can be deduced from a plot of the degree of 'fadeout' of infection (where fadeout is defined as three or more consecutive weeks without cases[34]) against population size (Fig. 1). However, to explore the metapopulation implications of the CCS, we need to look at the temporal pattern of fadeouts in more detail. Figure 2 summarizes the spatiotemporal persistence of measles in England and Wales over the last 50 years as a function of urban population size. Before the vaccine era (1944–66), measles persisted in the troughs between epidemics in cities with a population size of more than 300–500 000. Epidemics in large centres were highly synchronized[36–38]. Most local extinctions occurred in relatively small towns, below the CCS; these communities also showed much more irregular episodic epidemic patterns.

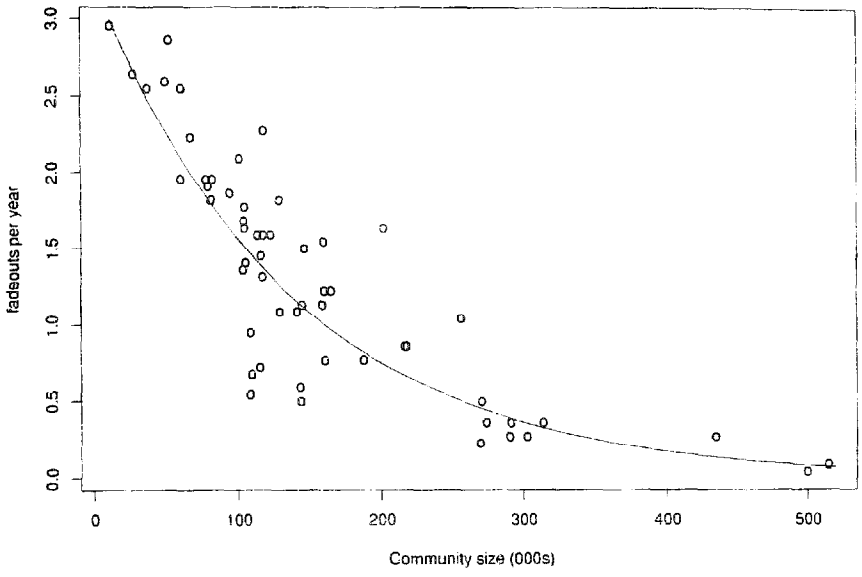


Fig. 1. Persistence of measles in 60 towns and cities in England and Wales in the pre-vaccination era (1944–67), as a function of population size in 1960. Persistence is measured inversely by the proportion of weeks with 'fade-outs' (three or more weeks without infection, to allow for under-notification of cases[34]). The curve is a simple least-squares exponential fit. The figure clearly shows the CCS – a population threshold of 300–500 000 – above which measles persists.

This combination of endemic persistence in large communities and fadeout in small ones corresponds crudely to a mainland-island metapopulation[6].

The full data set provides a large sample of colonization and extinction events (with replicates for individual patches)

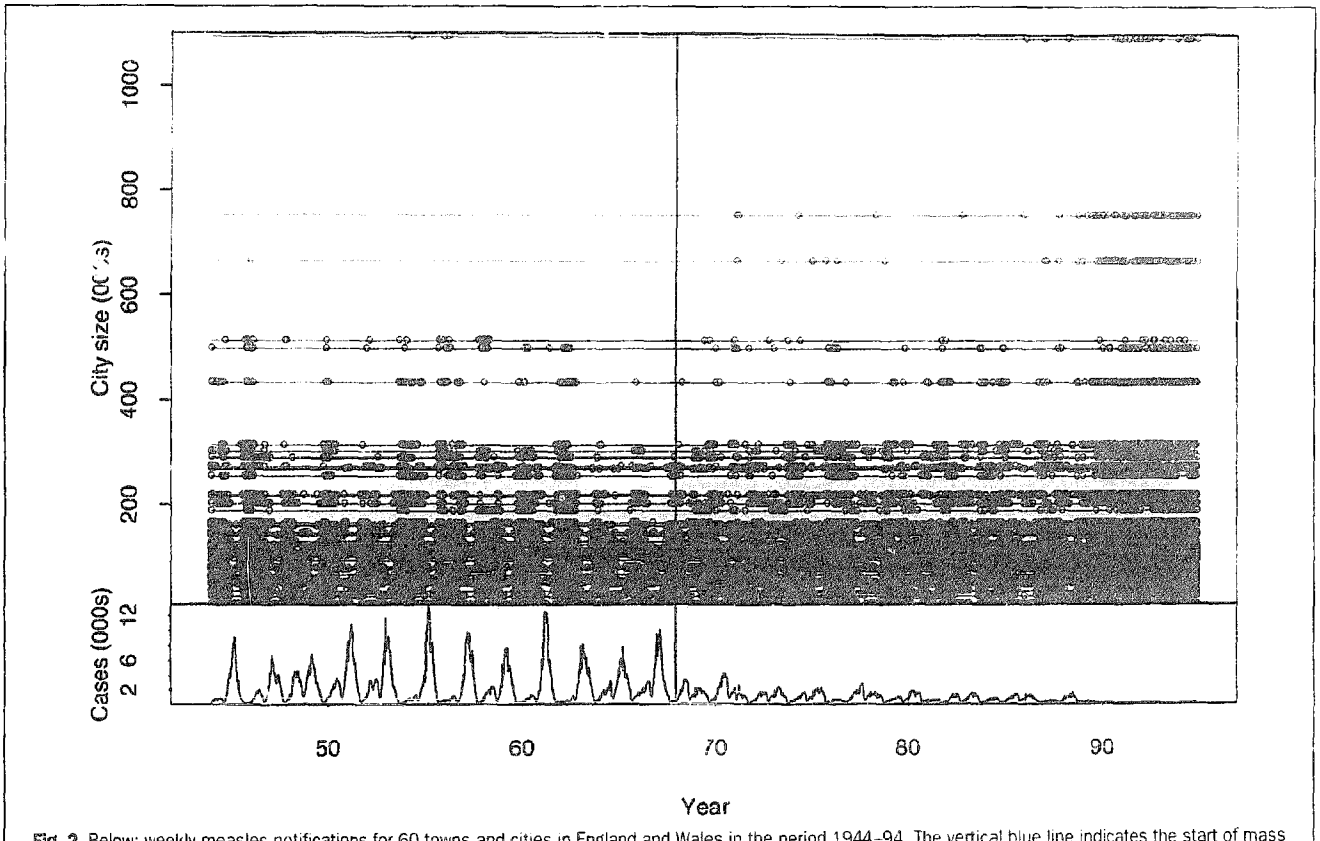


Fig. 2. Below: weekly measles notifications for 60 towns and cities in England and Wales in the period 1944–94. The vertical blue line indicates the start of mass vaccination in around 1968. Above: equivalent persistence of measles as a function of population size and time, in towns and cities up to the size of Birmingham. Population size of individual centres is shown by horizontal green lines and the red dots show weeks without notifications – note that this slightly overestimates the degree of fadeout (and therefore overestimates the CCS, compared to Fig. 1), because of under-notification[34].

which can be used to estimate the relationship between patch size (as measured by the number of human hosts) and persistence time. The relationship between colonization events and distance from the various 'mainland' cities can also be analysed in detail. Work in progress here indicates that the main effect of geographic isolation is – unsurprisingly – to reduce the incidence of infection in the troughs between major epidemics.

The Minimum Viable Population (MVP) of metapopulation theory is – like the CCS – a measure of the number of individuals required for an isolated population to have a given probability (usually 95%) of surviving for a finite period (generally 100 years). In general, the MVP depends in a complex way on the nature and size of the stochastic variations to which the population is subject, and on its long-run growth rate[39]. As noted above, measles reflects a relatively simple population process. This raises the question: can epidemiological theory shed light on the dynamic processes that determine the persistence of measles metapopulations?

Because we are considering the persistence of infection in epidemic troughs, this is a question for stochastic rather than deterministic arguments. The essential point is that there must be enough susceptible individuals ('resources') to maintain a chain of transmission. In terms of comparisons between infections, this depends primarily on the infectious period[40]. For infections with very long infectious periods, the chain of transmission is so well maintained that we do not see non-seasonal epidemics with deep troughs[15]. By contrast, the short infectious period of measles predisposes it to cycles and metapopulation behaviour.

The absolute level of the CCS has only recently been clarified by modelling. Seasonality in transmission resonates with the epidemic process to produce very deep troughs in incidence (Box 1). Simple homogeneous models predict many more extinctions than we observe[18]. The introduction of realistic heterogeneities in transmission – with host age[24] and the spatial arrangement of hosts[26] – alleviates this problem somewhat. However, these refinements cannot reduce the model CCS below one million.

Recent modelling work shows that, as well as the mean infectious period, the variance in the duration of infection may also be important for determining persistence[41]. Stochastic epidemiological models for measles have tended to assume that the statistical distribution of residence times in disease categories, such as the infectious period, follow an exponential distribution. This implies relatively variable incubation and infectious periods with, in particular, a relatively high probability of very short or long infection times. In fact, Keeling and Grenfell[41] show that a more constant (and biologically correct) infectious period can bring the model CCS down to a realistic level of 300–500 000. These results stress the importance of looking at the distribution of survival rates in natural enemy metapopulations.

Vaccination: a natural experiment

Mass measles vaccination in the UK began in the late 1960s, causing a significant decrease in disease incidence (Fig. 2). Vaccine uptake stayed at around 60% until the late 1980s, when it increased to around 90%. Mass vaccination reduces the rate at which new susceptible humans are recruited to the population and therefore increases the inter-epidemic interval[42]. In metapopulation terms, this corresponds to a decrease in the rate of replenishment of resources for colonizers.

How did vaccination affect the persistence and spatial dynamics of measles in the troughs between epidemics? In the period 1968–87 (Fig. 2b), fadeouts in smaller patches were spread much more evenly through the year than in the pre-vaccination era. However, surprisingly, the CCS stayed roughly the same, even though vaccination reduced average measles incidence significantly[27,43].

This may well be a manifestation of emergent metapopulation behaviour. In the pre-vaccination era, epidemics in major centres appeared to synchronize disease incidence throughout the country. However, vaccination tends to decorrelate local epidemics, by reducing their amplitude[27,44]. Such asynchronies can increase the persistence time of spatially-structured populations[45,46], via local 'rescue effects'[47].

The high vaccination levels during the 1990s have reduced the incidence of measles to very low levels and appear to have increased the CCS (Fig. 2). As a result, there are now fewer 'mainland' patches in the disease metapopulation. The consequences of this for the metapopulation dynamics of measles are still unclear, but the impact of desynchronization on disease persistence in the vaccine era seems to be a fruitful area for future research. In particular, the current vogue for regular 'pulses' of vaccination could have the unexpected benefit of re-synchronizing epidemics in the disease metapopulation[48]. This could, in turn, decrease the possibility of rescue effects promoting disease persistence and improve the prospects of large-scale disease eradication. Exploring the full spatiotemporal impact of vaccination will ultimately require a new generation of models, which explicitly allow for hierarchical spatial heterogeneity.

Conclusion: synthesizing ecological and epidemiological approaches

Epidemiological and metapopulation theory share a common concern with the way in which the balance between extinction and recolonization affects the persistence of a patchily-distributed species. There is clearly enormous potential for cross-fertilization between these disciplines. Epidemiological studies have generated long time series of data on patch occupancy, which provide excellent material for understanding the mechanisms that underlie extinction within small populations. They are also suitable for examining how colonization probabilities are affected by the spatial arrangement of patches. A fruitful avenue for future work here is the analysis of *hierarchical* spatial data. For example, measles appears to correspond to a mainland-island metapopulation at the between-city level shown in Fig. 1. However, at the individual borough level within large cities, we frequently see local fadeout but global persistence[16]. The form of metapopulation behaviour we see depends on the level in the patch network at which we look[1].

A key to understanding metapopulation dynamics is quantifying the migration rate of individuals between patches. For infections like measles, there is often a mass of relevant demographic data on human movement patterns – however, arguably the best systems for quantifying movement are animal metapopulations where marked individuals can be experimentally released. This is a growth area in insect metapopulation studies[49], which has interesting parallels in the study of dispersal of insect disease vectors by mark–recapture[50]. Given the advent of molecular ecological methods, genetic variation in pathogens themselves provides another potential measure of the previous contact rate – and therefore dispersal – of hosts in many systems. This looks to be an exciting area for future studies of both human and animal disease metapopulations.

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