The population ecology of infectious diseases: pertussis in Thailand as a case study

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SUMMARY

Many of the fundamental concepts in studying infectious diseases are rooted in population ecology. We describe the importance of population ecology in exploring central issues in infectious disease research including identifying the drivers and dynamics of host-pathogen interactions and pathogen persistence, and evaluating the success of public health policies. The use of ecological concepts in infectious disease research is demonstrated with simple theoretical examples in addition to an analysis of case notification data of pertussis, a childhood respiratory disease, in Thailand as a case study. We stress that further integration of these fields will have significant impacts in infectious diseases research.

Key words: Population ecology, spatio-temporal dynamics, persistence, pertussis.

INTRODUCTION

While they may superficially appear to be distantly related, research on the epidemiology of infectious diseases encompasses a wide range of concepts from population ecology, which is concerned with the abundance of organisms in space and time, arising from both biotic interactions and with their environment. Since the classic work of Anderson and May (1979), the link between ecology and epidemiology has been increasingly recognized and the cross-talk has been mutually beneficial. Epidemiology has benefited from the adaptation of concepts and analytical tools developed in population ecology, while providing some of the most exciting test-beds of ecological theory (May and Anderson, 1977; Earn *et al*. 1998).

We begin by describing some of the key concepts from population ecology and discuss their relevance to infectious disease systems, with emphasis on persistence mechanisms and spatio-temporal population dynamics. This description is coupled with simple theoretical models to demonstrate the applicability of some of the key concepts from population ecology. Finally, we describe several metrics derived from ecology that have been used in recent years to interrogate infectious disease data; we provide empirical examples of these methods using time series incidence data for pertussis, or whooping cough, in Thailand.

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CONCEPTS FROM POPULATION ECOLOGY

Temporal dynamics and periodicity

The pattern of temporal changes in, for example, species abundance in a given region can provide insight into the underlying drivers of population dynamics. A historically important demonstration of this claim comes from the study of measles. While studying the case reports of measles in Glasgow in early 20th Century, Soper (1929) noted a striking contrast. On the one hand, the theoretical constructs proposed to explain measles transmission within a population predict an equilibrium prevalence in the long run (Hamer, 1906). On the other hand, the epidemiological data from Glasgow and other locations exhibited large amplitude fluctuations. This discord led Soper to examine the data in a bid to identify the key, missing ingredient in mathematical models. He concluded that measles transmission is strongly seasonal, with most transmission occurring during the autumn/winter months and that annually occurring factors, such as the congregation of children in schools, were the most likely explanations for such a 'seasonal influence'.

Since the classic work of Soper, the contribution of seasonality to the transmission dynamics of infectious

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diseases has become well established (London and Yorke, 1973; Dietz, 1976; Altizer *et al*. 2006; Grassly and Fraser, 2006). A variety of mechanisms may lead to seasonality in transmission. In directly transmitted infectious diseases, for example, seasonal variation in social behaviours can generate temporal patterns in host contact rates (Fine and Clarkson, 1982; Finkenstädt and Grenfell, 2000; Ferrari *et al*. 2008; Metcalf *et al*. 2009; Mantilla-Beniers *et al*. 2010; Bharti *et al*. 2011). Vector-borne diseases, on the other hand, commonly exhibit seasonal variation resulting from changes in vector biology. For example, climatic factors including rainfall and temperature may affect mosquito (1) abundance, (2) the gonotrophic cycle, or (3) the extrinsic incubation period, thereby shaping seasonal trends in the transmission of pathogens such as malaria and dengue (Watts *et al*. 1987; Hoshen and Morse, 2004). In other infectious disease systems, seasonality may be generated via differential pathogen survival (e.g. influenza viruses circulating in humans; Shaman *et al*. 2010), pulsed host breeding (avian influenza viruses; Breban *et al*. 2009) or host susceptibility, perhaps modulated by photoperiod (Dowell, 2001).

In addition to varying incidence seasonally, a number of infectious disease systems exhibit multi-year inter-epidemic periods – defined as the time between successive large epidemics (Cummings *et al*. 2004; Metcalf *et al*. 2010; Rohani and King, 2010). For example, prior to mass immunization programmes, measles incidence in England and Wales exhibited a biennial period (Bolker and Grenfell, 1996; Rohani *et al*. 1999; Earn *et al*. 2000). Similarly, pertussis incidence is usually characterized by multi-ennial fluctuations with inter-epidemic periods ranging from 2–5 years (Hethcote, 1998; Rohani *et al*. 1999; Broutin *et al*. 2005). To demonstrate the epidemiological processes generating these multi-ennial periods, we used a simple seasonally forced deterministic model following the Susceptible (S)-Infected (I)-Recovered (R) framework (Dietz, 1976; Anderson and May, 1991; Keeling and Rohani, 2008) with parameters that loosely correspond to pertussis. A schematic diagram of this model is provided in Fig. 1. From theory, we know that epidemic growth requires the fraction of the population in the susceptible pool to be greater than a critical threshold, given by the inverse of the basic reproduction number, R_0 (Anderson and May, 1991; Keeling and Rohani, 2008). In Fig. 1A, we observed the transient dynamics beginning when the fraction of susceptibles (grey line) falls above its critical threshold (thin black line), thereby allowing epidemic take-off. While the fraction susceptible individuals remains above the threshold, prevalence continues to increase and peaks at the point in which the susceptible fraction (S/N) intersects its threshold level. The epidemic depletes the susceptible pool, and with replenishment, via susceptible births, takes longer than one year, thereby generating multiennial cycles (Keeling and Rohani, 2008).

Epidemiological theory has also shown that the time between each epidemic, or the inter-epidemic period, increases following the roll-out of immunization (Anderson and May, 1991; Keeling and Rohani, 2008). This is because immunization programmes effectively slow down the rate at which the susceptible class is replenished, resulting in a longer waiting time before the susceptible threshold is reached. This concept is demonstrated in Fig. 1B, where we examined the same model as in Fig. 1A, but introduced vaccination with uptake of 50%, implemented by simply discounting the birth rate accordingly. In the absence of vaccination, an inter-epidemic period of $\sim$3·1 years is observed and following the introduction of vaccination, the inter-epidemic period rises to $\sim$4·4 years; a result that has been confirmed empirically. For example, Broutin *et al*. (2010) showed that in a number of countries for which incidence data are available prior to and after the introduction of routine infant immunization programmes that, on average, the inter-epidemic period of pertussis increases by 1·27 years.

Anticipating our analysis of pertussis in Thailand as a case study, we point out that periodicity in infectious disease systems is determined by a combination of the amplitude of seasonality β_1 the vaccination coverage p and the pathogen transmission potential, as quantified by the basic reproductive ratio, R_0, (Bailey, 1975; Anderson and May, 1991; Bauch and Earn, 2003; Keeling and Rohani, 2008). Focusing on the former two, we used global wavelet analysis (described in greater detail in subsequent sections) to determine the dominant, statistically significant period of model output over various values of p and β_1 (Fig. 2). For low levels of seasonality, as vaccine uptake increases, there is a clear increase in the inter-epidemic period, consistent with empirical observations (Rohani *et al*. 2000; Grenfell *et al*. 2001; Broutin *et al*. 2005, 2010). Importantly, when seasonality is strong, multiennial epidemics give way to annual outbreaks, providing an example of 'harmonic oscillation'.

Understanding the periodicity of infectious diseases has clear public health implications – the timing of epidemics could directly affect the design and effectiveness of vaccination programmes. In the model presented in this section, we considered only routine vaccination such that some fraction p of newborns were vaccinated. An alternative method that has been proposed is pulsed vaccination, which recommends episodic vaccination campaigns that ensure the fraction susceptible is always below the epidemic threshold. This approach has been discussed as a potential strategy for eliminating diseases including measles and polio (Nokes and Swinton, 1997) and the current World Health Organization strategies for controlling polio are heavily centered

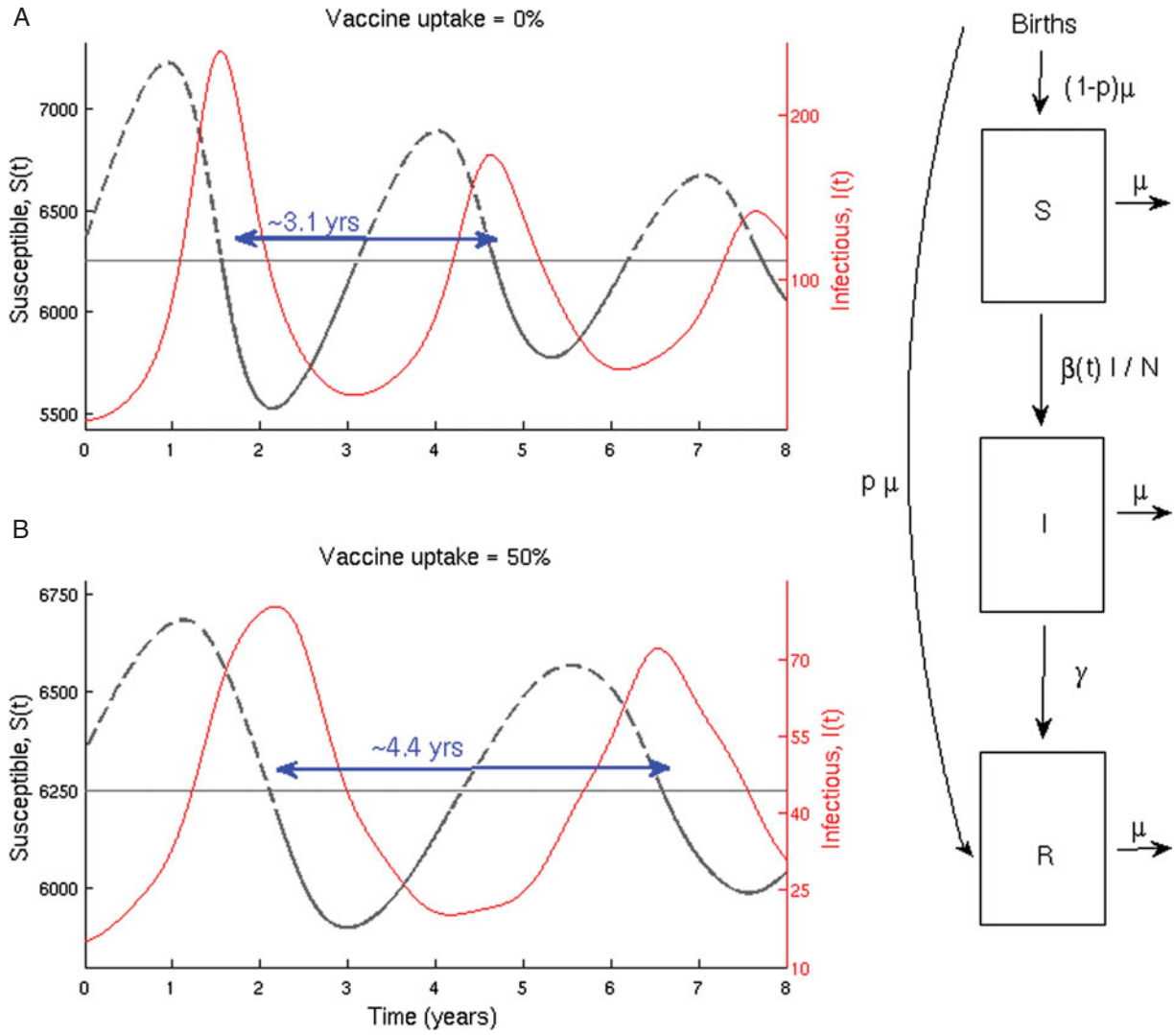

Fig. 1. A. The number of susceptible (grey) and infectious individuals (red) with vaccine uptake $P=0$, generating an interepidemic period of ~3·1 years. B. Same as A but with $P=0{\cdot}5$, increasing the interepidemic period to ~4·4 years. In both, the thin black line is the mean critical threshold for S to allow epidemic growth, or N/R_0 where $R_0=\beta(t)/\gamma$ and γ is the duration of the infectious period. The number of susceptibles is indicated by a dashed line when S falls above the threshold and solid elsewhere. We note that this represents the transient stage of the deterministic dynamics, resulting in a damping of the oscillations. A schematic representation of the *SIR* model used is provided on the right; parameters roughly correspond to pertussis with weak seasonality where seasonality is modeled as a sinusoidal curve $\beta_0(1+\beta_1\sin(2\pi t))$ (parameters are day^{-1}): $\gamma=1/21$, $\beta_0=1$ (corresponding to an R_0 of 16), $\beta_1=0{\cdot}01$, $N=1\times10\text{^}5$, $\mu=1/(60*365)$ (i.e. mean lifespan is 60 years).

on administering vaccines annually on a designated national immunization day (Heymann and Aylward, 2004). However, as shown by Choisy *et al.* (2006), under some circumstances, a pulse vaccination strategy can result potentially in increased numbers of infectious individuals. Further, these authors stress the importance of accounting for many aspects of the disease dynamics, including seasonal transmission.

Pathogen persistence, synchrony and spatial interactions

Persistence is a fundamental concept in population ecology, with long-standing contentious debates on the central determinants of population regulation. This concept is especially important in applied ecology, where conservation biologists aim to understand those factors that promote the persistence of endangered populations, or may limit the spread of invasive species in their non-native habitats. Therefore, commonly addressed questions in many ecological contexts include the determinants of persistence, the relevant spatial scale of dispersal and the appropriate spatially structured intervention strategies to ensure conservation of endangered species and the management of pest or invasive species. There is an obvious connection between spatial ecology and infectious disease systems (Nee, 1994; Grenfell and Harwood, 1997). Studies

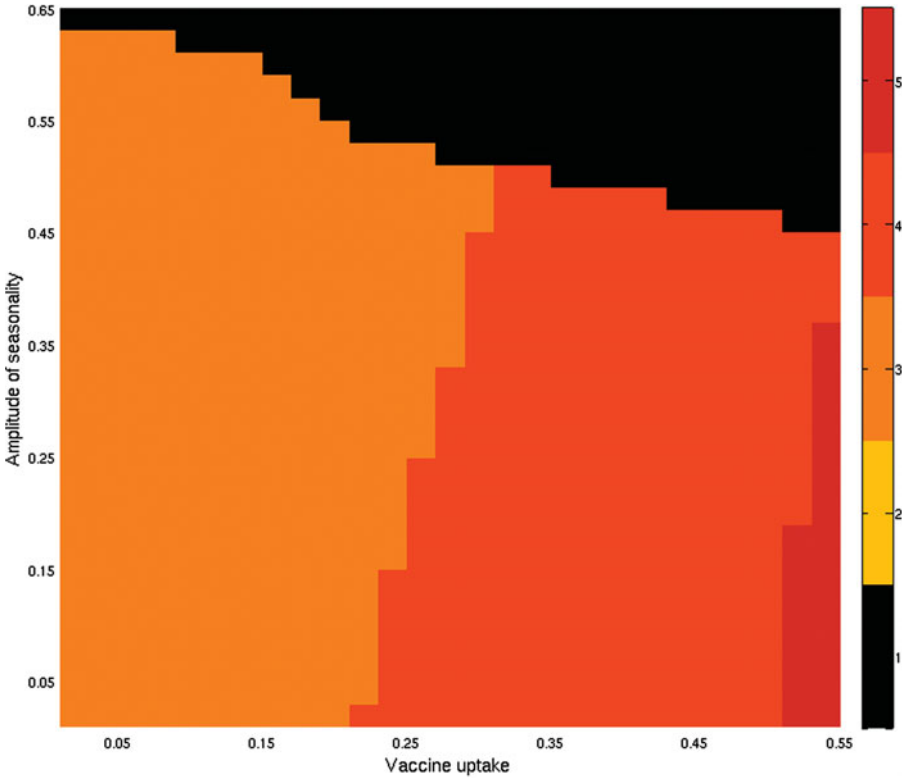

Fig. 2. Dominant statistically significant multiennial period from the global wavelet spectrum for various levels of vaccine uptake and amplitude of seasonality. Black regions indicate that the only significant period is annual, and in this example there are no parameter combinations that result in a dominant 2-year signal. The model is the same used in Fig. 1 with $\gamma = 1/21$ and the initial number of susceptible individuals (S_0) chosen to fall above its critical threshold.

of infectious diseases have a central goal of finding determinants of pathogen persistence within a host population and ultimately utilizing these findings to attempt to prevent epidemics and control the pathogen. Further, host-pathogen interactions operate on multiple spatial scales, making it essential to consider persistence dynamics at the appropriate scales.

First introduced in 1957 by Bartlett, the *Critical Community Size* (CCS), or the population size below which a particular pathogen exhibits frequent extinctions, is a central concept in disease persistence (Bartlett, 1957). The CCS is expected to increase following the onset of vaccination, indicating frequent extinctions in large populations as a consequence of reduced pathogen transmission. For example, Rohani *et al*. (2000) demonstrated that following the onset of pertussis immunization programmes in England and Wales, there was a dramatic increase in the observed CCS. Similar findings have been documented for pertussis in Niakhar, Senegal (Broutin *et al*. 2004). Importantly, estimating the CCS can identify populations that are less likely to exhibit stochastic extinctions and consequently inform vaccination strategies (Grenfell *et al*. 2001).

One method of quantifying the CCS is by identifying the relationship between population size and the mean number of fade-outs, or stochastic extinctions, per year. Stochastic *SIR*-type models provide a means to estimate the CCS; however, the resulting CCS will vary depending on model assumptions and parameters (Conlan *et al*. 2010). We illustrate these concepts by implementing a simple *SIR* model with stochastic infectious imports for three different levels of vaccine uptake. Defining a fade-out is disease specific and depends on the characteristic generation length (the time to recovery once an individual contracts an infection) of that pathogen. Pertussis, for example, has a latent period of $\sim$8 days followed by a mean infectious period of 14–21 days (Crowcroft *et al*. 2003; Wearing and Rohani, 2009). Here, it is reasonable to assume that a fade-out had occurred and the chain of transmission was broken when no cases were reported for at least one month. Averaging over 100 stochastic realizations of the model, we estimate the mean number of fade-outs per year over 50 years for various different population sizes. To obtain an approximation of the CCS, an exponential curve is fitted to the output and in the absence of vaccination it is estimated that the CCS is $\sim$600,000 for the specified *per capita* birth rate (Fig. 3, black line). When vaccine uptake reaches 40%, the CCS increases to $\sim 8 \times 10^5$ (Fig. 3, red line) and when vaccine uptake is increased to 80% the CCS is in excess of 10^6 (Fig. 3, blue line).

Importantly, in the absence of importation of infectious individuals, the pathogen would remain

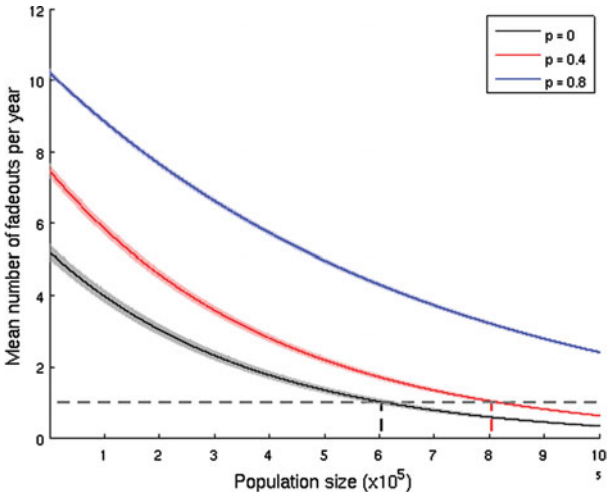

Fig. 3. Mean number of disease extinctions per year over 100 realizations of 50 years using Gillespie's algorithm to simulate a basic SIR model. Parameters are identical to those used in Fig. 1 with transmission held constant at β_0 and a stochastic import rate of 2 per 10^5 individuals per year. Black holds vaccine uptake p at 0, red at 0·4, and blue at 0·8. The lines represent the best fit exponential curve and the shading indicates the standard errors. The horizontal grey dashed line is the extinction threshold and the vertical black and red dashed lines represent the CCS for $P=0$ and $P=0{\cdot}4$, which are found to be $\sim 6\times 10^5$ and $\sim 8\times 10^5$, respectively. The CCS when $P=0{\cdot}8$ is greater than 10^6.

extinct. This highlights the importance of understanding the patterns of spatial synchrony. Crucially, *asynchrony* in the timing of epidemics between neighbouring populations facilitates this reseeding of infections to prevent local extinction, known as the rescue effect in ecology (Brown and Kodric-Brown, 1977). The importance of synchrony and the rescue effect is demonstrated in measles dynamics in England and Wales. Prior to vaccination, fade-outs were only observed in rural communities, with a critical community size of 250,000–300,000. In this era, there was also strong spatial synchrony in measles epidemics across England and Wales (Bolker and Grenfell, 1996; Rohani *et al*. 1999). The introduction of national pediatric vaccination led to a dramatic decline in measles incidence, but, paradoxically, did not increase the critical community size as would be expected from theory (Bolker and Grenfell, 1996). A potential explanation for this surprising phenomenon lies in the spatial ecology of measles. Specifically, it has been shown that the onset of immunization coincided with a significant decline in spatial synchrony across populations (Bolker and Grenfell, 1996; Rohani *et al*. 1999), which may have promoted the persistence of measles at the national scale (Earn *et al*. 1998; Rohani *et al*. 1999; Grenfell *et al*. 2001). This example demonstrates that patterns of synchrony can shed light on important though paradoxical behaviour of infectious disease dynamics. Moreover, it stresses the importance of spatial synchrony in the context of disease control and eradication.

The rescue effect falls under the umbrella of *metapopulation* dynamics and these concepts are tightly bound to understanding the drivers of movement of individuals between populations, which, in turn, allows for local persistence via the rescue effect. Incidence of dengue virus in Thailand, for example, is characterized by strong annual variability (Cummings *et al*. 2004). It is likely shaped by several interacting factors including climatic patterns which influence vector dynamics, thereby initially complicating the identification of clear spatio-temporal patterns. Cummings *et al*. (2004) however, analysed the spatial synchrony of multiennial epidemics finding that spatial synchrony largely declined with distance. This decline in synchrony with distance indicated diffusive spread originating in Bangkok, the country's capital and largest city. Such spatial hierarchies have also been observed in other contexts. For example, spatial signatures may arise from gravity coupling or the concept that the degree of host migration is proportional to the product of the population density of their locations divided by the square of the distance between them. This is parallel to the concept of *source-sink* dynamics in that high-density population centres (or sources) can reseed infection in low-density populations (or sinks). Work-flow patterns, rather than geographical distance, have been demonstrated to exhibit this type of gravity coupling with seasonal influenza spread significantly correlated with work-flow (Viboud *et al*. 2006). Clearly, understanding these dynamics has implications in both predicting and targeting high-risk regions in vaccination programs.

PERTUSSIS IN THAILAND AS A CASE STUDY

Pertussis is a highly infectious respiratory disease caused by the Gram-negative bacterium *Bordetella pertussis* and is transmitted directly via aerosol droplets between infected and susceptible individuals. Pertussis vaccination programmes were introduced in many developing countries in the 1940s and 1950s, leading to a substantial decline in incidence. However, a rise in incidence has been recently reported in many highly vaccinated countries, including the United States and several European countries (Bass and Stephenson, 1987; Celentano *et al*. 2005). Moreover, the burden of pertussis remains significant and is a major public health priority accounting for nearly 300,000 pediatric deaths worldwide, primarily in developing countries (Crowcroft and Pebody, 2006).

In the following sections, we apply several metrics founded in the ecological concepts outlined in the previous sections to a high-resolution dataset of pertussis incidence in Thailand from 1981–2000. The data were obtained from the Ministry of Public

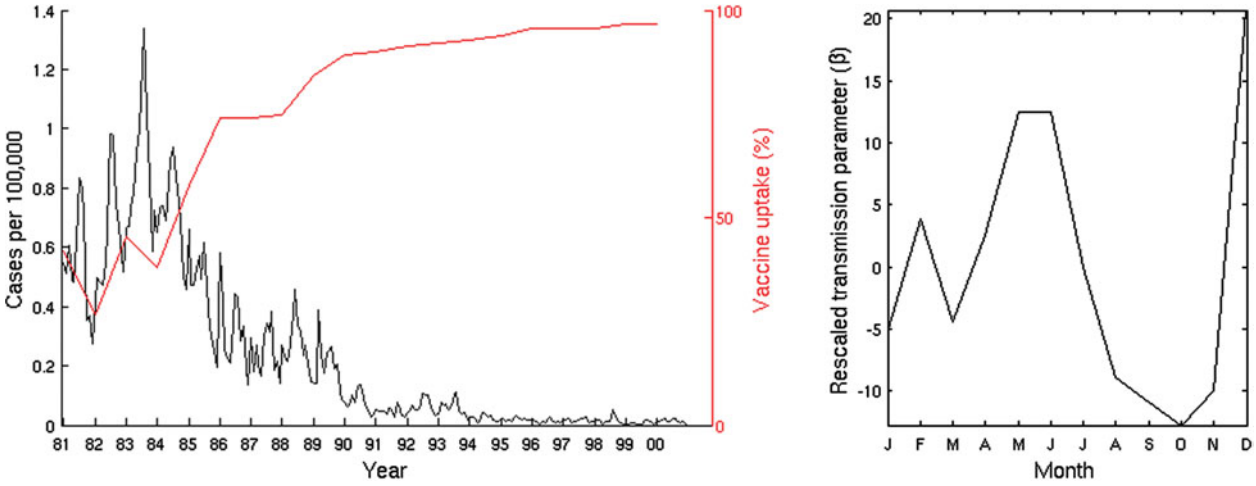

Fig. 4. A. Time series of pertussis incidence in Thailand (black) and annual vaccine uptake (red). B. Monthly transmission parameters estimated using the TSIR framework. Parameters are normalized to have zero mean.

Health and are comprised of monthly case reports over the duration of the time period for each of Thailand's 72 provinces. We additionally utilize population data obtained from the National Statistical Office of Thailand (1980, 1991, 2001).

In Thailand, mass vaccination efforts began in 1977 with the National Expanded Programme on Immunization (EPI) (Bhunbhu, 1989). We separate the data into two distinct vaccine periods: from 1981–1989 where vaccine uptake had a low of 26% in 1982 and continued to rise throughout the decade, and from 1990–2000 when vaccine uptake maintained levels greater than 90%. This level of vaccine uptake was maintained across all provinces. Over the duration of these two eras, pertussis incidence declined at the national level (Fig. 4A) as well as the provincial level (Fig. 5). This dataset allows for a comparative analysis of pre-vaccine versus vaccine era dynamics.

Temporal dynamics and periodicity

Seasonal transmission patterns have clear implications in infectious disease research, as described in previous sections. Given a time series of incidence data, a time series *SIR* (*TSIR*) model has been proposed as a method of estimating seasonal transmission parameters $\beta(t)$ (Finkenstädt and Grenfell, 2000; Finkenstädt *et al*. 2002). These methods have been used to determine seasonal transmission rates in several other infectious diseases, including measles, mumps and pertussis (Finkenstädt *et al*. 2002; Metcalf *et al*. 2009; Mantilla-Beniers *et al*. 2010). Using similar methods, Fig. 4B displays the estimated seasonal transmission of pertussis in Thailand (see ESM for details). Interestingly, the Thailand data exhibit very strong seasonality, as characterized by the high estimated seasonal amplitude. This strong seasonality is evident by observing the incidence dynamics during the 1980s (Fig. 4A). The peak of transmission occurs between May and June, which corresponds to both the beginning of the rainy season in addition to the start of the school year and consequently, one of these factors may drive this seasonal pattern.

We explore the periodicity of pertussis in Thailand using the Fourier transform (Chatfield, 1996). Here, a time series is transformed into its frequency domain and the power at a particular frequency (the inverse of the period) can be quantified. This approach assumes that the time series is stationary, or that a particular periodic signal remains constant throughout the course of a time series. Infectious diseases, however, generally exhibit non-stationarity, especially when comparing pre- and post-vaccination eras. For example, pre-vaccine measles in England and Wales was characterized by a biennial period but in the post-vaccine era the epidemics were significantly smaller with a longer multiennial period (Bolker and Grenfell, 1996; Rohani *et al*. 1999). As previously discussed, the onset of vaccination usually corresponds to an increase in the interepidemic period by depleting susceptible recruitment, resulting in a longer waiting time before a successive epidemic. Such increases in inter-epidemic period have previously been reported in pertussis dynamics (Rohani *et al*. 2000; Broutin *et al*. 2005, 2010; Wearing and Rohani, 2009).

To account for non-stationarity in disease dynamics, wavelet analysis is a popular alternative approach and has been used to study periodicity in many infectious diseases including dengue fever, measles and pertussis (Broutin *et al*. 2005; Johansson *et al*. 2009; Mantilla-Beniers *et al*. 2010; Thai *et al*. 2010). In summary, wavelet analysis uses a family of functions to decompose the time series into time-frequency space so that local variation in periodicity can be studied. Furthermore, analogous to the Fourier transform, the *global* wavelet spectrum can be computed by averaging the wavelet spectrum over

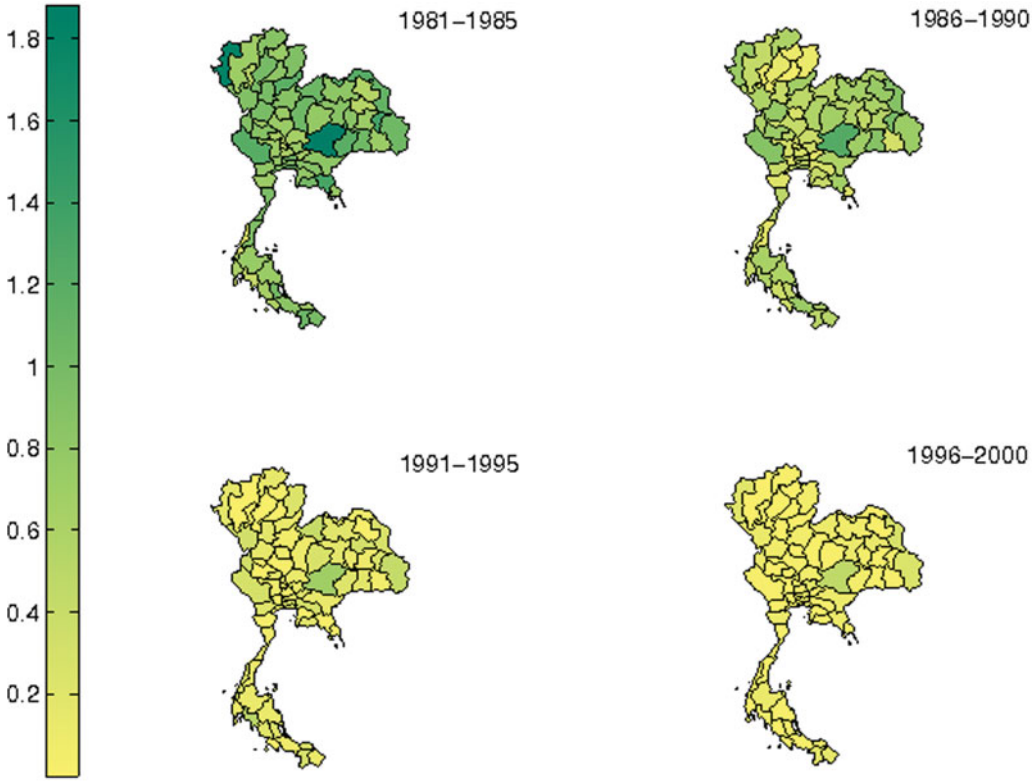

Fig. 5. Log transform of mean annual incidence in each of Thailand's provinces from 1981–1985 (top left), 1986–1990 (top right), 1991–1995 (bottom left), and 1996–2000 (bottom right). This demonstrates a decline in incidence across all provinces corresponding the increases in vaccine uptake.

time. We perform wavelet analysis by implementing the methodology and wavelet software provided by Torrence and Compo (1998*a*, *b*).

Fig. 6 provides a wavelet analysis of the national incidence time series in Thailand, with thick black lines identifying statistically significant periods. From this, it becomes evident that there were only significant annual epidemics prior to 1990. After this period (and after vaccine uptake reached levels >90%), the annual periodicity is no longer significant. Importantly, there are no significant multiennial periods. We submit that this is a direct consequence of the high amplitude of seasonality observed in Fig. 4B. As demonstrated in Fig. 2, when the seasonal amplitude is large the epidemiological dynamics are characterized by annual outbreaks.

Pathogen persistence, synchrony and spatial interactions

The CCS is an important metric used to determine the population size below which a pathogen exhibits frequent extinctions. Using the same definition of a fade-out as that used in Fig. 3, we estimated a CCS of $\sim 7{\cdot}7 \times 10^5$ in the beginning years of immunization programmes in Thailand from 1981–1989 (Fig. 7). In contrast, from 1990–2000 the CCS cannot be identified because frequent extinctions occur for all population sizes of provinces in Thailand. This indicates a much larger CCS, providing indication that increased vaccine uptake has successfully reduced transmission.

Several mechanisms can drive spatio-temporal patterns in disease incidence and synchrony plays a large role in identifying these spatial patterns. A commonly used indicator of spatial synchrony is through the non-parametric spatial covariance function, which provides a quantitative measure of spatio-temporal dependence between time series when plotted against distance between locations (Bjørnstad and Falck, 2001). We determined the synchrony of pertussis in Thailand using the time series of pertussis case notification for each of Thailand's 72 provinces (Fig. 8). The figure displays a smoothed spline fit to the correlation coefficients, with the 95% confidence region in blue and a correlation coefficient of one corresponds to strong synchrony and a value of zero indicates no correlation. Here there is initially a small decline in synchrony with distance – which can indicate diffusive spread – but more critically there is a strong baseline synchrony between provinces in that, regardless of distance, provinces maintain roughly the same level of synchrony. Moreover, the baseline level of synchrony is higher than previous studies of pertussis. Specifically, we documented a baseline synchrony of 0·28, while the comparable value was only 0·14 in the pre-vaccine era in England and Wales

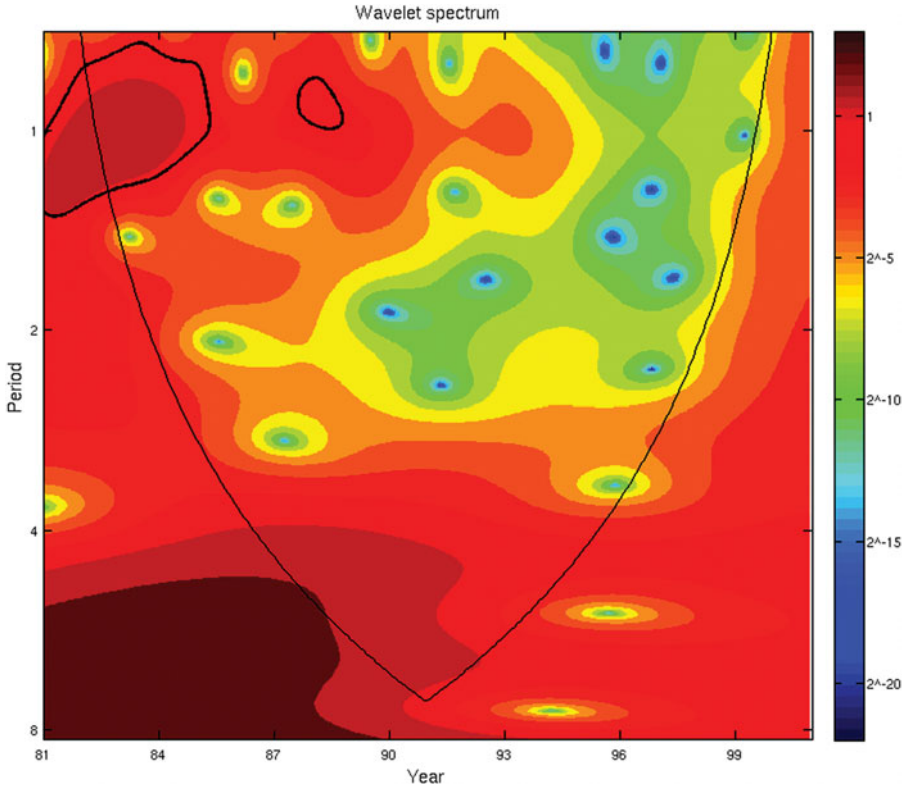

Fig. 6. Wavelet analysis of pertussis in Thailand. The thin black line indicates the 'cone of influence', regions inside of which are not influenced by edge effects (a consequence of using a finite time series) (Torrence and Compo, 1998*b*). The thick black circles indicate statistical significant periods, and the colour map indicates power with dark red representing the highest observed power. Periods are statistically significant if their power falls above the red noise spectrum. A significant annual period is observed in the early 1980s and becomes damped following the onset of vaccination.

(Rohani *et al*. 1999). Again, we consider this to be due to the strong seasonal forcing of pertussis transmission in Thailand (Fig. 4B) – the seasonality generates epidemics throughout the provinces of Thailand that peak in similar months. This consistency throughout Thailand diminishes the impact of spatial interactions.

As described in previous sections, it has also frequently been found that diffusion emanating from large population centres can promote global persistence. Declining synchrony with distance from a population centre can indicate this type of spatial spread (e.g. Grenfell *et al*. 2001; Cummings *et al*. 2004; Viboud *et al*. 2006). To determine the presence of this type of spatial hierarchy, we additionally determined synchrony as a function of distance from Bangkok, which is the capital of Thailand and also has the largest population. Again we see a similar pattern to that observed in Fig. 8, indicating that highly synchronized annual epidemics limit the existence of spatial hierarchies (Blackwood *et al*. unpublished data).

DISCUSSION

Integrating concepts from population ecology into infectious disease research has led to a large body of literature dissecting the determinants of observed host-pathogen spatio-temporal dynamics. Importantly, a mechanistic understanding of epidemiological dynamics permits inferences to be made about the potential impacts of changes, be they the implementation of novel vaccination schemes, secular trends in population demography or pathogen biology. We have attempted to motivate the use of ecological concepts in disease research through simple theoretical explorations in addition to empirical examples of ecological metrics applied to case notification data of pertussis in Thailand. Importantly, each of the described concepts has implications in evaluating immunization programmes and minimizing the mortality and morbidity associated with disease.

While we have emphasized the spatio-temporal patterns that shape pathogen persistence and the periodicity of epidemics, other population-level facets affect disease dynamics. For example, demographic changes directly affect the recruitment rate of susceptibles which, in turn, affects the force of infection by modulating the proportion of the population in the immune class. These impacts of birth rate on the force of infection have been shown to have important consequences on the transmission of dengue in Thailand, which underwent a demographic transition to lower birth rates resulting in a lower force of infection (Cummings *et al*. 2009).

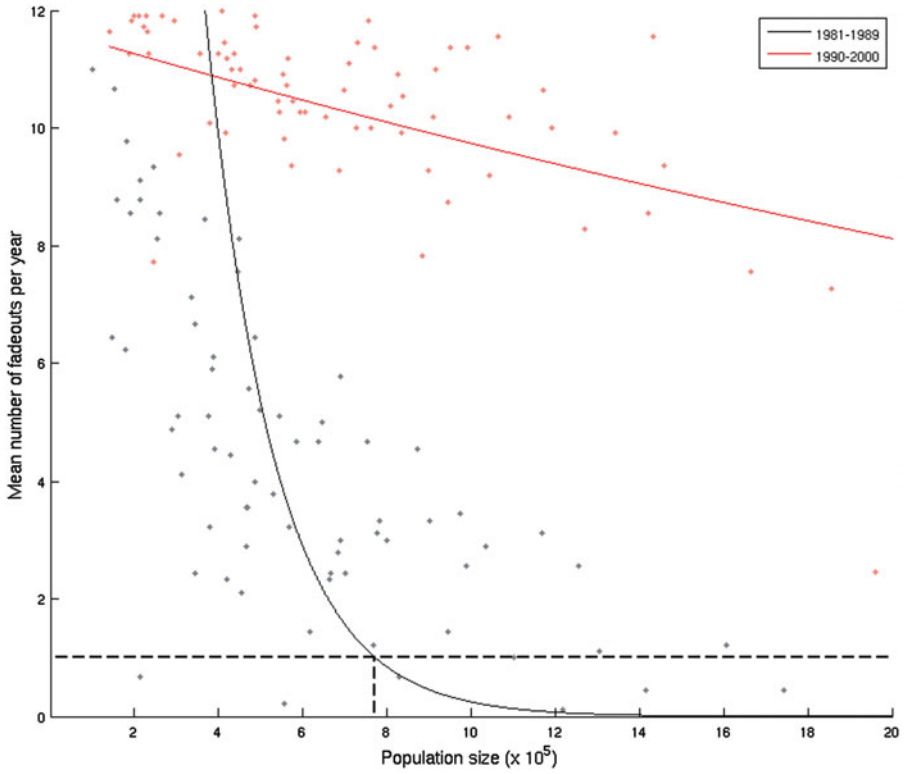

Fig. 7. Mean number of fade-outs per year in each of Thailand's provinces with exponential curves fit to the data. Bangkok is included in the fit but not shown in the figure, as its population size is much larger than the other provinces. Black is over the time period of 1981–1989 and red is 1990–2000. The horizontal dashed line indicates the fadeout threshold and the vertical line indicates the critical community size. A CCS of approximately $7{\cdot}7 \times 10^5$ is observed prior to 1990 and after 1990 the CCS is greater than 2×10^6.

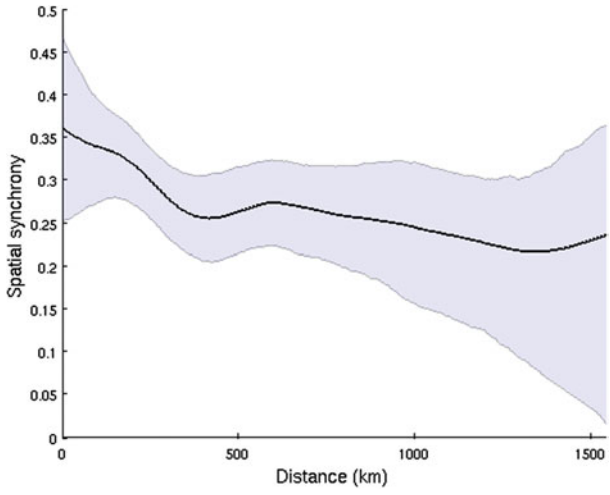

Fig. 8. Spatial synchrony of pertussis incidence between each of Thailand's provinces. The dark black line is a smoothed spline to the output and the blue shading indicates 95% confidence intervals.

Furthermore, integration of ecology and epidemiology is not limited to well-established infectious diseases of humans as we emphasize here; the threat of emerging and re-emerging infectious diseases in humans and wildlife poses challenges to our current understanding of host-pathogen interactions. Ecological mechanisms driving 'emergence events' are largely unknown, presenting unpredictable threats to human health. It is therefore a public health priority to identify these mechanisms, illustrating the urgency in fostering collaboration between ecologists and epidemiologists.

Multidisciplinary approaches to deciphering infectious disease dynamics have successfully improved our understanding of host-pathogen interactions, but infectious diseases remain a major source of mortality and morbidity worldwide. Collaboration will help to break new ground and confront future challenges caused by both pre-existing and emerging infectious diseases. Concerted efforts are required to obtain the necessary data (e.g. high resolution case notification and demographic data) to identify patterns and trends in the dynamics of host-pathogen interactions. This provides a test-bed for ecological theory, and importantly also provides a means to develop our understanding of the consequences of vaccination or other control measures on disease. Many challenges remain in infectious disease research, and we stress that the integration of ecology and epidemiology has critical implications in public health.

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SUPPLEMENTARY INFORMATION

Supplementary information includes technical details of the susceptible reconstruction and TSIR estimation methods for seasonal transmission rats. See Cambridge Journals On-Line, Parasitology.

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