ECOLOGY LETTERS

Ecology Letters, (2015) **18**: 779–789 doi: 10.1111/ele.12455

LETTER

Spatial structure, host heterogeneity and parasite virulence: implications for vaccine-driven evolution

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Abstract

Natural host-parasite interactions exhibit considerable variation in host quality, with profound consequences for disease ecology and evolution. For instance, treatments (such as vaccination) may select for more transmissible or virulent strains. Previous theory has addressed the ecological and evolutionary impact of host heterogeneity under the assumption that hosts and parasites disperse globally. Here, we investigate the joint effects of host heterogeneity and local dispersal on the evolution of parasite life-history traits. We first formalise a general theoretical framework combining variation in host quality and spatial structure. We then apply this model to the specific problem of parasite evolution following vaccination. We show that, depending on the type of vaccine, spatial structure may select for higher or lower virulence compared to the predictions of non-spatial theory. We discuss the implications of our results for disease management, and their broader fundamental relevance for other causes of host heterogeneity in nature.

Keywords

Dispersal, epidemiology, host-parasite interactions, kin selection, vaccination, virulence management.

Ecology Letters (2015) **18**: 779–789

INTRODUCTION

The rapid spatial spread of emerging pathogens, with major impacts on biodiversity, agroecosystems and human health, has recently emphasised the usefulness of spatial ecology for the management of diseases. Complex spatial dynamics have been demonstrated in diseases such as White-Nose syndrome in bats (Maher *et al*. 2012), sudden oak death (Filipe *et al*. 2012), foot-and-mouth diseases in cattle (Keeling *et al*. 2001), or pertussis in humans (Choisy & Rohani 2012). There is increasing evidence that disease spread is affected by changing patterns of mobility in hosts (e.g. airline traffic or farm animal transportation, Lemey *et al*. (2014), Choisy & Rohani (2012)). Climate change, habitat fragmentation and urbanisation also modify the ecology of host-parasite interactions, particularly affecting the distribution of vector-based diseases (Lafferty 2009; Magori *et al*. 2011). Another key factor affecting disease spread is parasite evolution. In particular, there is growing concern that pathogens evolve in response to treatments. A widely publicised example is the evolution of resistance to antibiotics (Restif 2009), but there is mounting theoretical and empirical evidence that vaccines may also impose selective pressures on parasite life-history traits, potentially selecting for more virulent pathogens (Gandon *et al*. 2001; Mackinnon & Read 2004; Gandon & Day 2008; Restif 2009; Barclay *et al*. 2012). Vaccine failure due to parasite evolution may cause the breakdown of control policies in humans and farm animals, but also of vaccine-based conservation programmes (Haydon *et al*. 2006). Other human interventions such as prophyllaxis or quarantine may also have short- or long-term evolutionary consequences.

From an ecological perspective, human interventions introduce variation in quality among hosts. There is a rich experimental literature demonstrating that heterogeneity in quality (or immune status) may be caused by a variety of mechanisms, such as genetic variation in resistance or tolerance (Råberg *et al*. 2007; Keith & Mitchell-Olds 2013), sex-based dimorphism in immunity (Nunn *et al*. 2009), and infection state or history (Sorci *et al*. 2013a,b). Other potential causes of host heterogeneity include nutritional status, immune senescence, spatial location, behavioural plasticity or division of labour, variation in offspring quality at birth, or environmental contamination. This has motivated theoretical work to understand how host heterogeneity may affect parasite evolution (Williams 2012).

Host and parasite dispersal is another key ecological factor affecting the structure and dynamics of the host population, with major consequences for host-parasite coevolution and local adaptation (Greischar & Koskella 2007; Tack & Laine 2014). Explicit spatial models of infectious diseases have shown that spatial structure introduces some important qualitative and quantitative deviations from the predictions of non-spatial models. For instance, low pathogen dispersal tends to select for less transmissible and less virulent parasites, although intermediate dispersal rates may also select for increased virulence (see Lion & Gandon (2015) for a recent review of coevolution in spatially structured host-parasite interactions). There is growing experimental support for the general theoretical prediction that parasites should exploit their host more 'prudently' in spatially stuctured than in well-mixed populations (Kerr *et al*. 2006; Boots & Mealor 2007; Berngruber *et al*. 2015).

How host heterogeneity and spatial disease dynamics interplay to affect disease ecology and evolution is still poorly understood. In particular, data documenting the joint impacts of spatial structure and treatments on disease evolution is still

Box 1 Empirical evidence

Vaccine-driven evolution and spatial spread of diseases Despite their success for disease control, there is growing evidence that vaccines may impose selective pressures on pathogens. Although most research has focused on 'escape mutants' (e.g. in HIV, Goulder & Watkins 2004), evolution of parasite life-history traits has also been reported (Gandon & Day 2008; Restif 2009). Earlier nonspatial theoretical (Gandon *et al*. 2001; Gandon & Day 2007; Atkins *et al*. 2013) and experimental studies in mice (Mackinnon & Read 2004; Barclay *et al*. 2012) have demonstrated that vaccination may select for increased virulence. Here, we focus on three examples that are highly suggestive of a complex interplay between vaccination, host and parasite dispersal, and virulence evolution.

- **Pertussis**. The recent resurgence of pertussis (whooping cough) is associated in many countries with the rise of strain *PtxP3* of *Bortedella pertussis*, which has a higher production of pertussis toxin (Mooi 2010). Evidence of vaccine-driven evolution is strong (Mooi 2010). Across-countries comparisons also show that pertussis evolution has been shaped by the advent of new vaccines with different modes of action (Mooi 2010; van Gent *et al*. 2014). Interestingly, phylogenetic studies show that the *PtxP3* strain has undergone a rapid global spread, mainly driven by vaccination (Bart *et al*. 2014). This is consistent with evidence that the recent pertussis epidemics does not present any particular spatial structure, in contrast with past epidemics, potentially reflecting changes in human movement (Choisy & Rohani 2012). Taken together, this data is suggestive of interactions between vaccination, spatial epidemiology and the evolution of *B. pertussis*.
- **Marek's disease**. Caused by an oncogenic virus, Marek's disease (MD) is an airborne poultry disease that has been successfully managed through vaccination. However, a continuous increase in MD virulence has been documented since the 1960s following vaccination (Witter 1997). There is clear evidence that successive vaccination campaigns have selected for viral strains causing more severe forms of the disease (Gimeno 2008; Atkins *et al*. 2013). Because this evolution is associated with the move to industrialised farming, the possibility exists that changes in parasite dispersal may also have contributed to the evolution of the disease. To our knowledge, however, there is little data on the spatial spread of Marek's disease in the wild and in small backyard chicken farms.
- **Avian influenza**. The pandemic threat of High Pathogenic Avian Influenza has recently highlighted the importance of bird and human migrations for the global spread of pathogens. Additionally, there is strong evidence of vaccine-driven antigenic drift (Escorcia *et al*. 2008) and of different evolutionary dynamics in countries with or without vaccination programs (Cattoli *et al*. 2011). However, how host and pathogen dispersal and vaccination strategies interplay is still poorly understood.

Vaccine mechanisms Perhaps surprisingly, the effects of vaccines on transmission, virulence, or recovery are only known for a few diseases (Gandon & Day 2008). Available data suggests that vaccines are usually imperfect and may act through a variety of mechanisms. Although some vaccines are designed to block infection (e.g. vaccines against the human papillomavirus, Barr & Sings 2008) or transmission (e.g. candidate vaccines against malaria, Nunes *et al*. 2014), most vaccines only alleviate the symptoms of the disease by reducing within-host parasite growth or toxic effects and increasing clearance. For instance, vaccines against Marek's disease are anti-toxin vaccines and do not block transmission nor infection (Gimeno 2008; Atkins *et al*. 2013). New acellular vaccines against pertussis also appear to be of the anti-toxin type, with no effect on transmission and susceptibility, although this needs to be confirmed by further studies (Warfel *et al*. 2014). In contrast, some vaccines jointly affect transmission, susceptibility and replication, as documented for vaccines against avian influenza (van der Goot *et al*. 2005).

scarce (but see Box 1). This calls for a general theoretical framework to provide clear predictions and guidelines for epidemiologists and field ecologists.

In this article, we first introduce a general model showing how spatial structure and heterogeneity in host quality interplay to affect the evolution of parasite life-history traits. We show how host heterogeneity alters previous inclusive fitness arguments for the evolution of parasite traits in spatially structured host populations (Lion & Boots 2010). Second, we illustrate the value of this general approach by analysing in detail the evolutionary impact of heterogeneity generated by vaccination, using a combination of analytical and simulation results. We review evidence of the joint effects of dispersal and vaccination on the evolutionary ecology of several infectious diseases, such as Marek's disease, pertussis, and avian influenza. Compared to previous non-spatial theory (Gandon *et al*. 2001, 2003), we show that local infections may select for either higher or lower virulence depending on vaccine type, efficacy or coverage. Finally, we discuss the potential practical consequences of our work, and the broader fundamental implications of our theoretical framework for other sources of host heterogeneity.

EPIDEMIOLOGICAL DYNAMICS

We first introduce a model of a spatially structured host population, with two classes of hosts. Throughout the manuscript, we use the terms 'naive' and 'treated' to describe the two classes of hosts, but our results apply more broadly, and the reader may more generally think of high-quality and low-quality hosts.

We consider a large regular network of sites. The life cycle of the host-parasite interaction is depicted in Fig. 1a. Each site is connected to n other sites and can be either empty (o) or occupied by one host. In the absence of treatment, hosts are said to be naive (N) and can be either susceptible (S_N) or

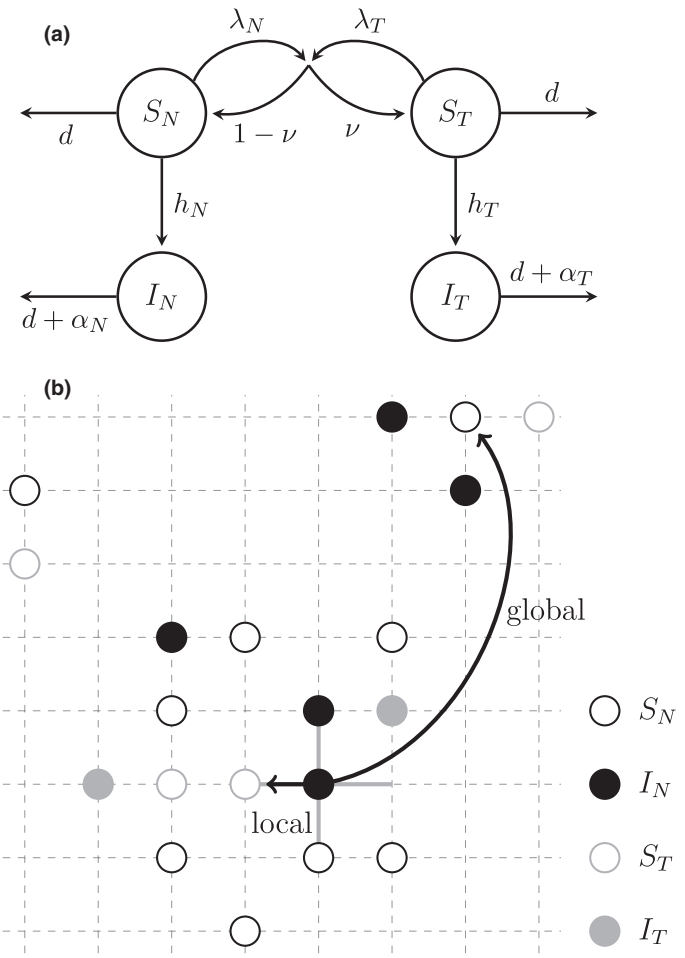

Figure 1 (a) Life cycle of the host-parasite interaction. (b) Diagram representing local and global infection routes on a square lattice. An infected individual may infect a random susceptible individual among its four neighbours (with probability $1 - g_P$), or a random susceptible individual in the population (with probability g_P). Note that, if the probability of finding a susceptible naive host around a focal site x is $Q_{S_N}(x)$, for the focal infected individual on the diagram we have $Q_{S_N}(x) = 1/4$. Averaging $Q_{S_N}(x)$ over all sites x in state I_N gives the average local density q_{S_N/I_N}.

infected (I_N). Treated individuals are identified by a T subscript (S_T, I_T). Infected hosts can transmit the disease at rates β_N or β_T respectively to a random neighbouring host with probability $1 - g_P$ (local transmission) or to a random host in the population with probability g_P (global transmission). The resulting force of infection on an average naive susceptible host is therefore

$$h_N = \beta_N[I_N|S_N] + \beta_T[I_T|S_N] \quad (1)$$

where $[I_i|S_j]$ is the average effective density of infected hosts in class i experienced by a susceptible host in class j. Hence, h_N measures the overall rate at which naive susceptible hosts may become infected. For our model, $[I_i|S_j] = g_P p_{I_i} + (1 - g_P)q_{I_i/S_j}$, where p_y is the global density of y individuals, and $q_{y/z}$ is the local density of y individuals in the neighbourhood of a z individual (Fig. 1b). In other words, q_{I_N/S_N} is the proportion of naive infected hosts in the neighbourhood of a susceptible naive host. Similarly, the force of infection on a treated susceptible host is

$$h_T = \sigma_T(\beta_N[I_N|S_T] + \beta_T[I_T|S_T]), \quad (2)$$

where σ_T is the relative susceptibility of treated hosts (naive hosts have a baseline susceptibility of 1). When $g_P = 1$ (fully global transmission), $h_T = \sigma_T h_N$ (Gandon *et al.* 2001). Note that this implies that the transmission rates between host types can be written as the product of transmissibility and susceptibility, but we relax this assumption in Appendix S1 in the supporting information.

Susceptible individuals die at rate d, and infected hosts at rates $d + \alpha_N$ (for naive hosts) and $d + \alpha_T$ (for treated hosts). The parameters α_N and α_T represent the virulence (disease-induced mortality) of the parasite in each class of hosts.

We assume that the parasite's strategy of host exploitation affects all epidemiological parameters: both transmission and virulence parameters are functions $\beta(x)$ and $\alpha(x)$ of the level of within-host exploitation x. For instance, increased parasite replication within the host may increase the number of propagules produced by an infected host (transmission benefit), but also decrease the host's life span (virulence cost). We represent this cost-benefit balance by a concave-down (saturating) trade-off between transmission and virulence (see Alizon *et al.* 2009 for a review).

We stress that the results of sections 'Evolution in homogeneous populations' and 'Evolution in heterogeneous populations' do not depend on the details of host reproduction, nor on the specific mechanism generating heterogeneity among susceptible hosts.

EVOLUTION IN HOMOGENEOUS POPULATIONS

For simplicity, we first examine a population where all hosts are naive. We consider the fate of a rare mutant parasite strain, with life-history traits β'_N, α'_N, in an endemic infection at equilibrium (Geritz *et al.* 1998).

Invasion fitness

The mutant parasite can invade if its lifetime reproductive output, $\mathcal{R}$, is greater than 1, with

$$\mathcal{R} = R'_N[S_N|I'_N] \quad (3)$$

where

$$R'_N = \frac{\beta'_N}{d + \alpha'_N}$$

is the individual reproductive value (Taylor 1990) of the mutant parasite in naive hosts. Hence, $\mathcal{R}$ measures the total number of secondary infections by the mutant strain.

Selection gradient

If mutations have small phenotypic effects (weak selection), we can take a further analytical step by computing the selection gradient, i.e. the partial derivative of invasion fitness with respect to the mutant trait, evaluated at neutrality (i.e. when the mutant has the same trait as the resident; Geritz *et al.* 1998). We then obtain

$$\partial\mathcal{R} = \frac{\partial R'_N}{R_N} + (1 - g_P) R_N \partial q_{S_N/I'_N} \tag{4}$$

Equation 4 partitions selection into direct and indirect fitness effects. The direct fitness effect is given by the marginal change in reproductive value, $\partial R'_N/R_N$. When dispersal is partly local ($g_P < 1$), selection also depends on how neighbouring parasites exploit the local supply of susceptible hosts. The quantity $\partial q_{S_N/I'_N}$ measures the local excess or depletion in susceptible hosts in the neighbourhood of a focal mutant parasite, compared to resident parasites. In other words, $\partial q_{S_N/I'_N}$ measures the local competition for susceptible hosts between parasite strains. This is an indirect fitness effect because it depends on the genotypes of neighbouring parasites. Indeed, it can be analytically shown that $\partial q_{S_N/I'_N}$ is proportional to the relatedness of parasites infecting neighbouring hosts and is therefore a measure of kin competition (Lion & Boots 2010; Lion & Gandon 2015).

Equation 4 can thus be interpreted as the inclusive fitness effect of a mutant parasite and shows that the outcome of selection in spatially structured population is determined by a balance between the direct fitness effect (change in reproductive value) and the indirect fitness effect (kin competition). In a well-mixed population, the optimal virulence for the parasite is to maximise its reproductive value. However, spatial structure may select for higher or lower virulence, depending on the kin competition effect. For our model, previous results have shown that evolutionarily stable virulence is maximal at intermediate dispersal (Lion & Boots 2010).

EVOLUTION IN HETEROGENEOUS POPULATIONS

Invasion fitness

When parasites can encounter both naive and treated hosts, the invasion fitness takes the following form (Appendix S1 in the supporting information):

$$\mathcal{R} = \left(R'_N[S_N|I'_N] + R'_T\sigma_T[S_T|I'_T]\right)\left(\frac{1}{2} + \frac{1}{2}\sqrt{1 - \frac{4\sigma_T R'_N R'_T}{\left(R'_N[S_N|I'_N] + R'_T\sigma_T[S_T|I'_T]\right)^2}C'}\right). \tag{5}$$

The first factor of eqn 5 is the sum of the lifetime productions of mutant propagules in naive and treated hosts, with

$$R'_N = \frac{\beta'_N}{d + \alpha'_N} \quad \text{and} \quad R'_T = \frac{\beta'_T}{d + \alpha'_T},$$

which are the individual reproductive values of the parasite in each type of host in the absence of cross-infections. Because of infections between hosts in different classes, simply summing the contributions in each class will either overestimate or underestimate the mutant's reproductive number. The second factor of eqn 5 introduces a correction that depends on the sign of the spatial correlation between treated and naive susceptible and infected hosts,

$$C' = [S_N|I'_N][S_T|I'_T] - [S_N|I'_T][S_T|I'_N].$$

If parasite dispersal is global, this correlation is always zero, but if dispersal is local, any correlation between the different types of habitats experienced by the parasite will affect parasite fitness. For instance, if hosts tend to interact more with hosts with the same treatment status, C' is positive.

Selection gradient

Under weak selection, we can compute the selection gradient as follows (Appendix S1 in the supporting information)

$$\partial\mathcal{R} = c_N\left[\frac{\partial R'_N}{R_N} + (1 - g_P)\left(R_N\partial q_{S_N/I'_N} + R_T\frac{\sigma_T h_T p_{S_T}}{h_N p_{S_N}}\partial q_{S_N/I'_T}\right)\right] \tag{6a}$$

$$+ c_T\left[\frac{\partial R'_T}{R_T} + (1 - g_P)\sigma_T\left(R_N\frac{h_N p_{S_N}}{\sigma_T h_T p_{S_T}}\partial q_{S_T/I'_N} + R_T\partial q_{S_T/I'_T}\right)\right] \tag{6b}$$

Equation 6 partitions the selection gradient as a sum of fitness effects in each class, weighted by the class reproductive values c_N and c_T (Taylor 1990). The class reproductive values are normalised such that $c_N + c_T = 1$, and have a useful interpretation in terms of the force of infection on each type of hosts. Indeed, c_N is proportional to the fraction of the force of infections on treated hosts that is caused by naive infected hosts: when most treated hosts get the disease through cross-infections, the class reproductive value c_N tends towards 1, and selection entirely operates in the naive class (Appendix S1 in the supporting information).

As in the homogeneous case, the fitness effect in each class can be further partitioned into direct and indirect fitness effects. The direct fitness effect is the first term between brackets on lines (6a) and (6b) and measures the marginal change in reproductive output in each class of hosts. The second terms between brackets give the indirect fitness effects, which measure the marginal effects on the local availability of susceptible hosts experienced by each class of host. The relative importance of each class of susceptible hosts for a focal parasite is quantified by the ratio of net infection rates, $\sigma_T h_T p_{S_T}/h_N p_{S_N}$. This generalises the kin competition term described in the section 3 to populations structured in classes (e.g. treatments, prophyllaxis, sex-based immunity).

In a well-mixed population, the kin competition terms vanish, and eqn 6 collapses to

$$\partial\mathcal{R} = (1 - c)\frac{\partial R'_N}{R_N} + c\frac{\partial R'_T}{R_T} \tag{7}$$

where $c \equiv c_T = 1 - c_N$ measures the relative value of treated hosts compared to naive hosts and is proportional to the frequency of treated hosts in the populations. When $c = 0$, selection acts to optimise the reproductive value of the parasite in naive hosts, while when $c = 1$, selection acts to optimise the reproductive value of the parasite in treated hosts.

Uncorrelated landscape

If variation in host quality is spatially uncorrelated for the parasite ($C' = 0$), eqn (5) simplifies to

$$\mathcal{R} = R'_N[S_N|I'_N] + R'_T\sigma_T[S_T|I'_T] \quad (8)$$

which is a straightforward spatial extension of Gandon *et al.* (2001)'s result (their eqn 7). This expression shows that the invasion fitness of a rare mutant parasite is the sum of the reproductive values of the mutant parasite in each class of hosts, weighted by the density of susceptible hosts experienced by the mutant parasite in each habitat. Furthermore, we show in Appendix S1 in the supporting information that the selection gradient can be written in the following compact form

$$\partial\mathcal{R} = (1-c)\left[\frac{\partial R'_N}{R_N} + (1-g_P)\frac{\partial q_{S_N/I'_N}}{[S_N|I_N]}\right] \quad (9a)$$

$$+c\left[\frac{\partial R'_T}{R_T} + (1-g_P)\frac{\partial q_{S_T/I'_T}}{[S_T|I_T]}\right] \quad (9b)$$

where $c = c_T$ is the reproductive value of the treated class.

Equation 9 provides an insighful partition of selective effects into direct and indirect fitness effects in each class. In Lion & Boots (2010), an analytical approximation of the kin competition term was obtained from the dynamics of pairs of sites. Here, however, further analytical progress is hampered by the higher dimensionality of the model. Nonetheless, we show in the following that we can use eqn 9 to understand the results of individual-based stochastic simulations of our model (see Appendix S1 in the supporting information for details).

EVOLUTIONARY CONSEQUENCES OF VACCINATION

To clarify the intertwined implications of host heterogeneity and spatial structure, we now apply the above general model to the specific example of vaccination. Interestingly, although data is still patchy, the rise of virulent strains in reponse to vaccination is often associated with changes in dispersal patterns, which suggests the need for an integrated study of spatial dynamics, vaccination policies, and parasite evolution (Box 1).

Vaccination

We assume density-dependent reproduction of hosts (Appendix S1 in the supporting information). Treatment is assumed to take the form of vaccination at birth: with probability ν, offspring are born in the treated class, and with probability $1-\nu$ they are born in the naive class. Thus, ν represents the proportion of vaccinated hosts at birth. Because vaccination coverage does not depend on spatial location, there is no correlation between treated and naive hosts from the perspective of the parasite.

Few studies have investigated in detail the effects of vaccines on epidemiological parameters, but available evidence suggests very diverse modes of action (Box 1). Gandon *et al.* (2001) have shown theoretically that different types of vaccines may have opposite evolutionary consequences in well-mixed populations. Following Gandon *et al.* (2001), we consider four main types of vaccines (see Table 1): (a) an anti-infection vaccine that reduces susceptibility to infection (with efficacy r_1); (b) an anti-growth vaccine that reduces within-host exploitation of the host by the parasite (with efficacy r_2); (c) an anti-transmission vaccine that reduces disease transmissibility (with efficacy r_3); and (d) an anti-toxin vaccine that reduces disease-induced mortality (with efficacy r_4). In the following, we measure virulence on naive hosts, i.e. we are interested in how the intrinsic strategy of host exploitation, x, evolves for various combinations of vaccine efficacy and coverage.

Anti-infection and anti-transmission vaccines

If there is no anti-growth nor anti-toxin vaccination component ($r_2 = r_4 = 0$), parasites in naive and vaccinated hosts have the following reproductive values $R'_N = \beta'/(d+\alpha')$ and $R'_T = (1-r_3)R'_N$. Hence, from eqn 7 the selection gradient in a well-mixed population takes the following simple form

$$\partial R = \frac{\partial R'_N}{R_N} \quad (10)$$

and the evolutionarily stable (ES) virulence is the value that maximises the reproductive output of the parasite in naive hosts. Hence, virulence depends neither on vaccine efficacy nor on vaccination coverage, unless other processes introduce an asymmetry in the reproductive values of the parasite in each class. For instance, Gandon *et al.* (2001, 2003) showed that, if superinfection occurs, higher vaccine efficacy selects for lower virulence.

When parasite dispersal becomes more local, additional selective pressures due to kin competition for susceptible hosts alter this result. Figure 2 shows that, when parasite dispersal is partly local ($g_P < 1$), an increase in vaccine efficacy selects for a decrease in parasite virulence for anti-infection vaccines. Furthermore, as vaccine efficacy increases, the relationship between virulence and parasite dispersal changes (Fig. 2a). For perfect anti-infection vaccines, parasite virulence monotonically increases with parasite dispersal. When vaccine efficacy increases, parasite evolution also leads to lower prevalence (Fig. 2c) and higher host density (Fig. S4). This is qualitatively similar to the predictions of non-spatial theory, but more local dispersal leads to lower prevalence. Anti-transmission and anti-infection vaccines have qualitatively similar evolutionary and epidemiological consequences (Appendix S3).

Table 1 Epidemiological parameters for naive and vaccinated hosts, as a function of vaccine efficacy. The function $\beta(z) = 20\ln(z+1)$ is used for all simulations

Trait (z)	Trait in naive hosts (z_N)	Trait in vaccinated hosts (z_T)
Susceptibility (σ)	1	$1-r_1$
Transmission (β)	$\beta(x)$	$(1-r_3)\beta([1-r_2]x)$
Virulence (α)	x	$(1-r_4)(1-r_2)x$

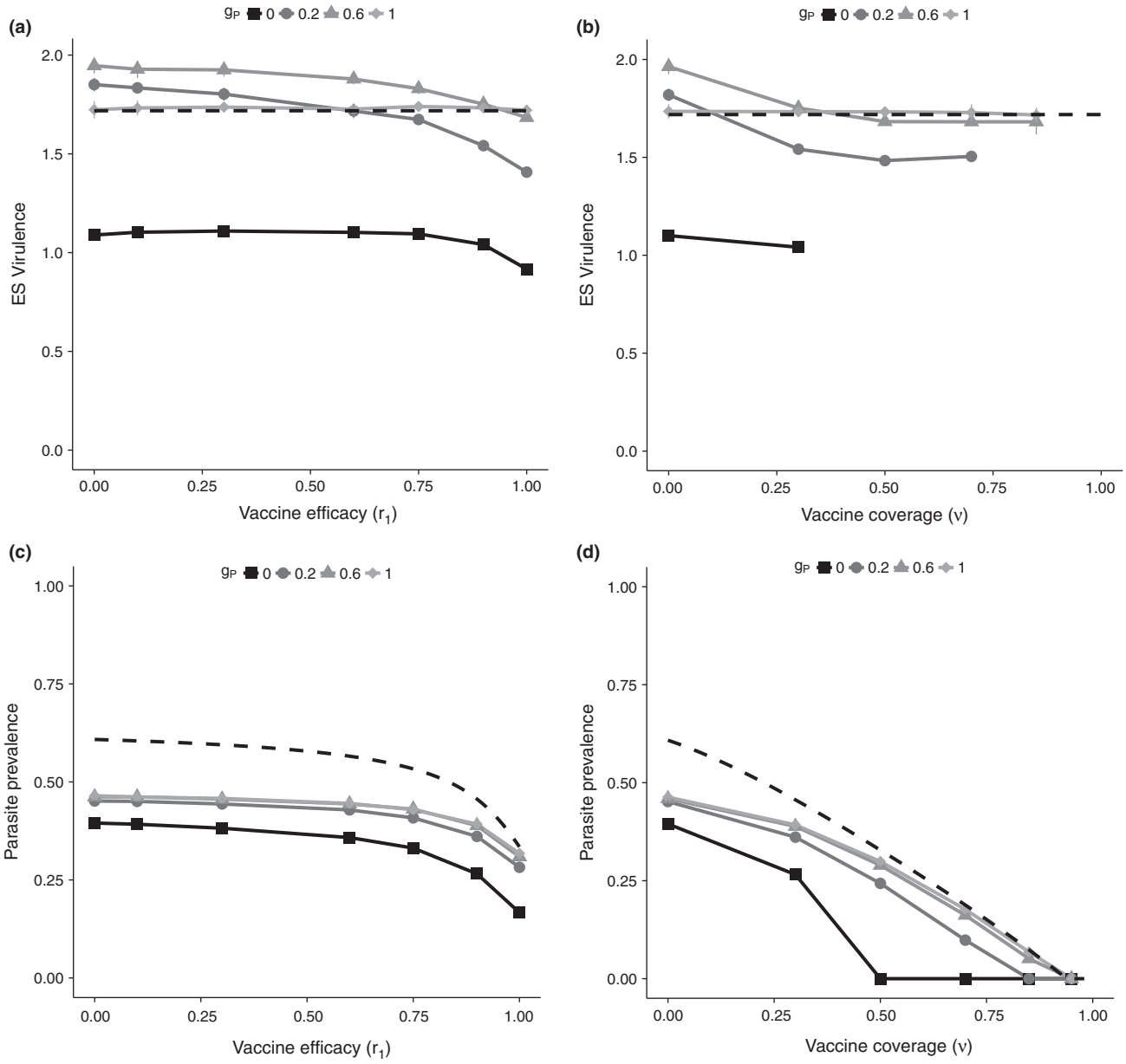

Figure 2 Anti-infection vaccine. The evolutionarily stable host exploitation (a,b) and prevalence (c,d) of the parasite as a function of parasite dispersal, vaccine efficacy (r_1), and vaccine coverage. The dashed lines indicate the predictions non-spatial theory. The dots indicate the mean and standard deviation for six runs of the stochastic process. For details of the simulations, see Appendix S1 in the supporting information. Parameters: $b = 8$, $d = 1$, starting from host exploitation $x = 1.25$. Other parameters: (a,c) $\nu = 0.3$, (b,d) $r_1 = 0.9$.

Equation 9 can help us understand this pattern. For an anti-infection and/or anti-transmission vaccine, eqn 9 can be rewritten as

$$\partial R = \frac{\partial R'_N}{R_N} \tag{11a}$$

$$+(1-g_P)R_N\left[\partial q_{S_N/I'_N} + (1-r_1)(1-r_3)\partial q_{S_T/I'_T}\right] \tag{11b}$$

Irrespective of vaccine efficacy, the direct fitness effects (11a) drive virulence to the optimal level in the naive class, $x_N^\star$, as predicted from non-spatial theory. Hence, the only effect of vaccine efficacy is through the kin competition terms (11b). As r_1 or r_3 increases, the contribution of competition for treated hosts diminishes. For perfect vaccines, what matters is the marginal effect of an increase in virulence on the availability of naive susceptible hosts experienced by naive infected hosts ($\partial[S_N|I'_N]$). Because of the presence of treated hosts, an increase in host exploitation will lead to even lower densities of naive susceptible hosts, compared to a population with zero vaccination coverage. Hence, one expects higher kin competition for naive susceptible hosts and, consequently, lower virulence. This explains why increasing vaccine efficacy leads to a decrease in virulence.

In contrast to non-spatial theory, increasing vaccination coverage leads to both lower prevalence and lower ES virulence (Fig. 2b,d). Importantly, the eradication threshold is lower when parasite dispersal becomes more local. Thus, in a spatially structured population, parasite evolution in response to an anti-infection vaccine may facilitate disease eradication, and even select for milder parasites as vaccination coverage increases.

Our simulations generally show that the ES virulence predicted by non-spatial theory (the dashed line in the figures) matches our simulation results when parasite dispersal is fully global ($g_P = 1$). However, there is a discrepancy for parasite prevalence. This can be explained by the pattern of host dispersal: in all our simulations, host dispersal is local, which creates spatial refuges for susceptible hosts and thus leads to lower disease prevalence. Simulations run for $g_H = g_P = 1$ give a perfect match with the non-spatial theory for both virulence and prevalence (results not shown). More generally, long-distance host dispersal tends to weaken the effect of spatial structure (Fig. S5 in the supporting information).

Anti-growth vaccines

For anti-growth vaccines, we recover Gandon *et al.* (2001)'s predictions when parasite dispersal is fully global ($g_P = 1$): increasing vaccination coverage never leads to disease eradication and selects for higher virulence (Fig. S2 in the supporting information), while more efficient vaccines select for higher parasite virulence (Fig. 3a). Furthermore, ES virulence is found to peak for near-perfect vaccines for any pattern of parasite dispersal (Fig. 3a). However, as parasite dispersal becomes more local, we show that parasite prevalence decreases, and even drops for high vaccine efficacy and very local dispersal (Fig. 3b). In addition, near-perfect vaccines select for maximal virulence when parasite dispersal is fully local (Fig. 3a).

As previously, eqn 9 helps to explain this pattern. For anti-growth vaccines, the marginal changes in reproductive output in naive vs. treated hosts are different. Hence, without kin competition, the direct effects of selection will select for an ES virulence between the optimum in the naive class, $x_N^\star$, and the optimum in the treated class, $x_T^\star = x_N^\star/(1 - r_2)$. The exact value depends on the class reproductive value c and on the marginal change in reproductive output in the treated class. When r_2 is low, c tends towards ν, but as r_2 increases, c decreases to zero because the transmissibility of treated infected hosts drops to zero. On the other hand, a higher vaccine efficacy leads to a higher marginal increase in reproductive output. These two effects combine to give the overall hump-shaped pattern of Fig. 3a.

Spatial structure quantitatively alters this pattern in two ways. First, even in a neutral model, parasite dispersal will affect the class reproductive value c, which is proportional to $[S_T|I_T]$. At equilibrium, the drop in reproductive value as vaccine efficacy increases is less pronounced when infections are local than when infections are global, which selects for higher virulence (results not shown). Second, an increase in vaccine efficacy will also tend to relax kin competition by decreasing the transmissibility of infected treated hosts and thereby increasing the local availability of susceptible hosts. Ultimately, the combination of these effects leads to a counter-intuitive pattern where, for near-perfect anti-growth vaccines, higher parasite dispersal leads to lower virulence (Fig. 3a).

Many human interventions for disease management in humans, farm animals, or wildlife endangered populations, aim at reducing parasite growth. For instance, trees are preventively treated against sudden oak death using fungicides. Our model shows that, when dispersal is local, anti-growth treatments with higher efficacy select for increased virulence (Fig. 3a), but also for lower prevalence (Fig. 3b). To evaluate the net effect on the population, we calculate the expected life spans of naive and treated hosts at birth (Gandon *et al.* 2003). Figure 3c shows that a higher efficacy increases the life expectancy of treated hosts (dashed lines), but decreases the life expectancy of naive hosts (plain lines), except when the vaccine is perfect. Spatial structure does not alter this pattern, but selects for higher life expectancy for any value of efficacy. In addition, parasite evolution leads to higher total host density when parasite dispersal is more local (Fig. S4 in the supporting information). Hence, our model suggests that, although spatial structure has negative effects at the individual level (higher virulence), it also has positive effects at the population level (lower force of infection, resulting in a higher host life expectancy and higher host density). Such 'dilemmas' are typical of virulence management programmes (van Baalen 2002), and reinforce the view that different measures of mortality may have different practical implications (Day 2002). It is difficult however to draw general recommendations from these results, because the precise relationships between dispersal, vaccination, and measures of disease severity are likely to depend on the specific form of the transmission-virulence trade-off.

Anti-toxin vaccines

Anti-toxin vaccines extend the host's lifespan and thus remove the cost of virulence, but without affecting parasite transmissibility. In a well-mixed population, increasing vaccine efficacy therefore selects for increased virulence (Gandon *et al.* (2001); Fig. 4). In a spatially structured host population, however, increased lifespan leads to higher local competition for susceptible hosts (eqn 9), and therefore ever-increasing virulence is selected against. Hence, for fully local parasite dispersal ($g_P = 0$), vaccine efficacy has only a mild impact on ES virulence (Fig. 4). This is reminiscent of earlier results showing that, in the absence of a trade-off between transmission and virulence, there is selection for intermediate transmission rates in spatially structured populations (Haraguchi & Sasaki 2000). The mechanism here is similar: ever-increasing levels of host exploitation are selected against in spatially structured populations because rapacious exploitation reduces the local availability of susceptible hosts, as captured by the kin competition terms of eqn 9. Note however that selection against highly transmissible or virulent strains in the absence of a transmission-virulence trade-off may depend on the underlying contact network of the

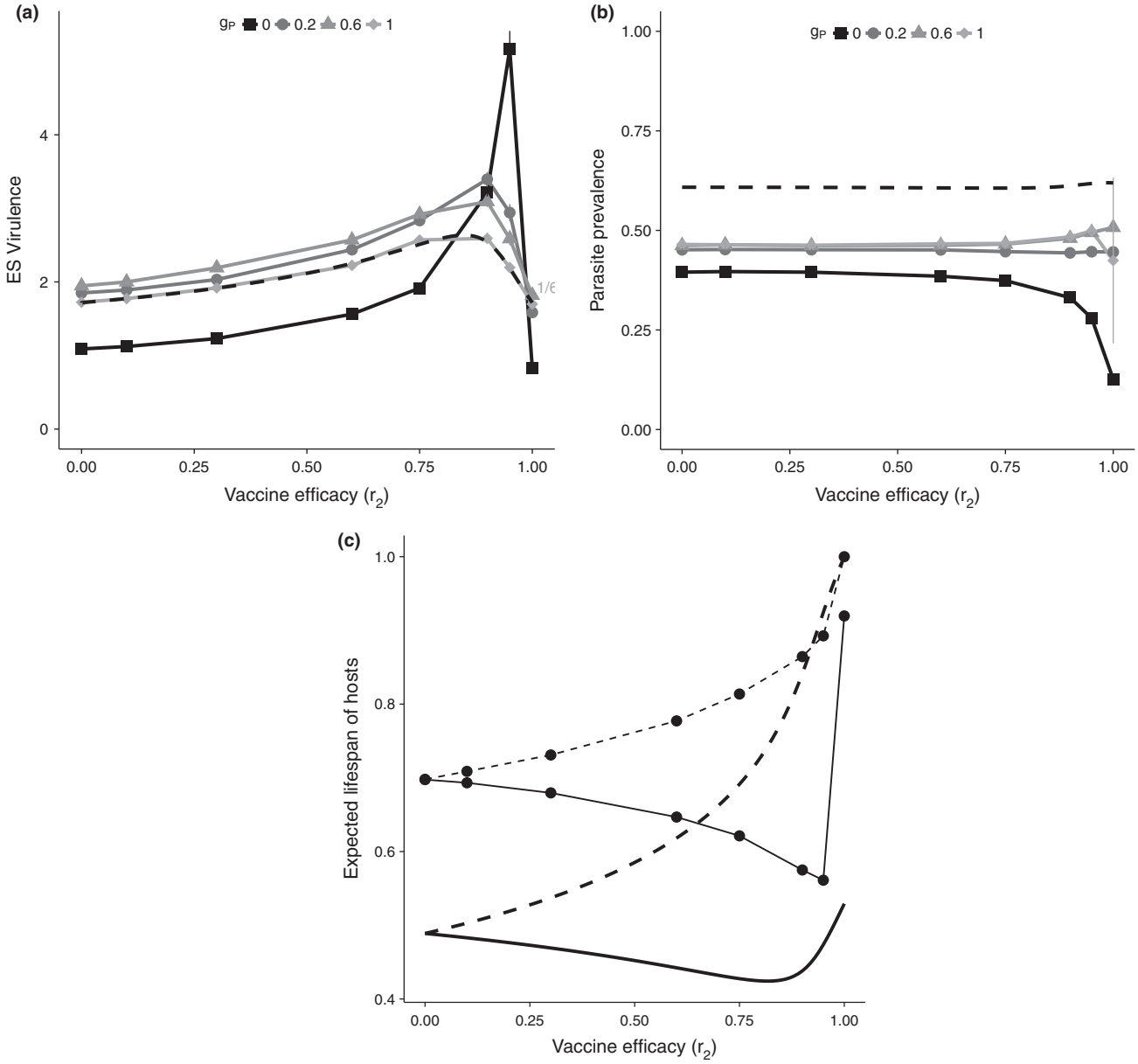

Figure 3 Anti-growth vaccine. The evolutionarily stable host exploitation (a) and prevalence (b) of the parasite as a function of parasite dispersal and vaccine efficacy (r_2). The fractions represent the number of runs that went extinct out of six runs. (c) Expected host life span as a function of vaccine efficacy (r_2). The expected life span of naive (plain line) and treated individuals (dashed lines) are compared. The dots indicate the results of stochastic simulations, and the lines are the predictions of non-spatial theory. – For other specifications and parameter values see Fig. 2.

infection. For instance, it has been shown that, on regular random networks, selection favours ever-increasing transmission (Lion & Boots 2010).

DISCUSSION

A key challenge for the population biology of infectious diseases is to understand the feedback between disease ecology and the evolution of host-parasite interactions (Restif 2009). In particular, how the structure of host populations shapes selective pressures on parasites is a question of growing fundamental and applied importance. Here, we present a theoretical framework to study the joint impact of two ecological factors affecting population structure: dispersal and heterogeneity in host quality.

We focus on the example of treatments for its applied and didactic value, but our results have broader implications for disease ecology. Our main result (eqn 6) does not depend on the mechanism generating variation in quality among hosts, although the specific predictions will depend on biological scenarios of interest. Nonetheless, a unifying conceptual framework is useful to unearth the common ecological processes among multiple causes of host heterogeneity. For instance, our model can be readily applied to sexual dimorphism in immunity, if we replace naive and treated hosts by males and females and interpret ν as the sex ratio of the

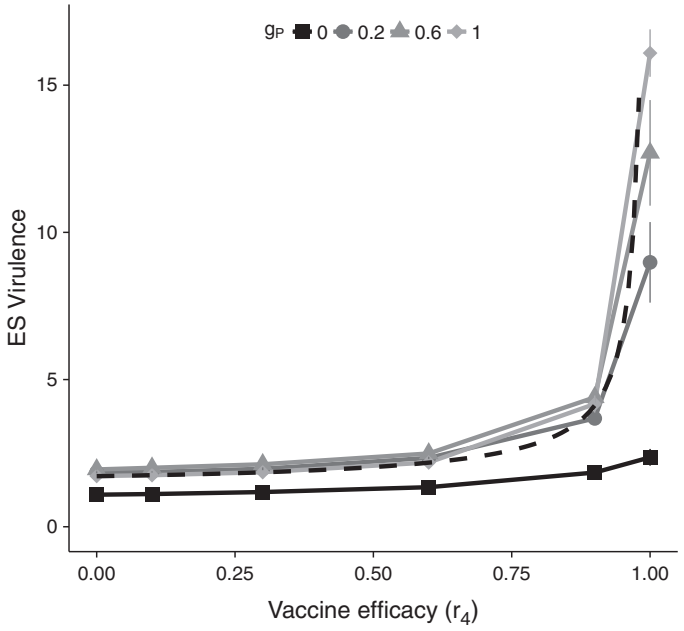

Figure 4 Anti-toxin vaccine. The evolutionarily stable host exploitation of the parasite as a function of parasite dispersal and vaccine efficacy (r_4). See Fig. 2 for further details.

population. Other sources of host heterogeneity can be similarly handled by modifying the birth terms in the dynamics of susceptible hosts.

Our study has implications for the management of infectious diseases. There is growing interest for the possibility that vaccines or drugs may favour pathogens strains with higher transmissibility or virulence ('life-history mutants', e.g. Gandon *et al*. 2001, 2003; Gandon & Day 2007; Allen *et al*. 2014). Here, we consider how different regimes of host and parasite dispersal may affect the evolution of parasites after vaccination. Due to habitat fragmentation, airline traffic and global trade, many host and parasite species tend to disperse both locally and globally (Keeling *et al*. 2001; Lemey *et al*. 2014). Our analysis highlights five potential consequences of increased parasite dispersal for parasite evolution in response to treatments. First, for anti-infection and anti-transmission vaccines, higher dispersal and lower vaccine efficacy select for higher prevalence and higher virulence. Second, the combination of evolution and higher dispersal causes the eradication threshold to increase for anti-infection or anti-transmission vaccines. Third, for anti-growth vaccines, higher dispersal selects for higher prevalence, but may also select for lower virulence for near-perfect vaccines: we find that parasite evolutionarily stable virulence monotonically decreases with increased parasite dispersal, in contrast to the classical prediction that parasites should be more prudent in spatially structured populations. Fourth, for anti-toxin vaccines, global infections can select for dramatically higher parasite virulence. Fifth, a mixture of local and global parasite dispersal, which is typical of many diseases, may select for maximal virulence for a broad efficacy range of all vaccine types.

From the perspective of virulence management, our results suggest that taking into account more realistic contact patterns is important when trying to make predictions on the evolutionary consequences of treatments. Our results show that, as long as some amount of local parasite dispersal exists, the evolutionary consequences of treatments cannot be ignored. For instance, imperfect anti-infection or anti-transmission vaccines tend to select for maximal virulence when parasite dispersal occurs both at local and global scales. This may be relevant for prospective transmission-blocking malaria vaccines (Box 1). Importantly, other factors may alter these general predictions, such as habitat fragmentation or heterogeneity, multiple infections, or the biology and dispersal of the vector for vector-borne diseases. Furthermore, vaccines combining several modes of action, such as vaccines against avian influenza (van der Goot *et al*. 2005), could lead to other evolutionary trajectories. In a well-mixed population, Gandon *et al*. (2003) have shown that the best vaccination strategy would be to maximise the anti-infection component (r_1), while choosing the anti-growth component to be either very low or very high. This reduces selection for increased virulence, while allowing vaccination coverage to be maximised, possibly leading to disease eradication. Further work is needed to elucidate how local host and parasite dispersal would affect these predictions.

For the sake of simplicity, we have restricted our attention to uncorrelated patterns of heterogeneity: offspring are born treated with a constant and uniform probability, and infection does not alter this pattern. Hence, we do not need to track the effect of parasite traits on the correlation between treated and naive hosts, C, which is always zero. However, many biological processes could lead to the build-up of spatial correlations in host quality. For instance, any heritable resistance trait will tend to generate correlations in the host landscape that may affect the selective pressures on parasite traits. Treatments that target specific groups in the population, or are geographically restricted, will also lead to correlations. In a human context, vaccine scares or other sociological factors can cause offspring from untreated individuals to be less likely to become treated than offspring from treated individuals. Our theoretical framework lays the groundwork for future studies of the evolutionary consequences of various strategies of treatment.

At a fundamental level, our results can be understood through an inclusive fitness framework, by decoupling the direct fitness effects of a trait (those acting on a focal parasite) and the indirect fitness effects (those acting on the focal parasite's neighbourhood). A key insight of our work is that different mechanisms of immunity do not have the same effect on direct and indirect fitness effects. When immunity decreases host susceptibility (r_1) or transmissibility (r_3), spatial structure only alters the indirect fitness effect through kin competition for susceptible hosts, as predicted by earlier theory (Lion & Boots 2010; Lion & Gandon 2015). On the other hand, when immunity targets the within-host growth or toxicity of the parasite, spatial structure affects both the direct and indirect fitness effects, leading to complex patterns of interaction between parasite dispersal and selective pressures due to host heterogeneity. We note that the magnitude of indirect

fitness effects depends on the network topology (more contacts will cause the population to be more well-mixed) and on the life cycle of the host-parasite interaction. In particular, kin competition may become negligible when the density of empty sites vanish, for instance when host fecundity increases (see Appendix S6 in the supporting information). This reiterates the important message that different assumptions on host demography may lead to divergent evolutionary predictions (Lion & Boots 2010).

We made a number of simplifying assumptions in this study. First, we assumed that infected individuals cannot recover. This allows comparisons with a large body of theory on parasite evolution in homogeneous spatially structured populations (reviewed in Lion & Gandon 2015). Previous studies have shown that increasing rates of recovery to an immune class tend to weaken the kin competition effect in the absence of treatments (Webb *et al*. 2013). It would be interesting to extend our results to account for the joint effect of natural vs. artificial immunity. Second, we assumed that treatment is only applied at birth and does not depend on the host or parasite traits, nor on the environment of the offspring. Spatial or temporal heterogeneities in vaccination coverage would introduce some correlations between naive and treated hosts that are likely to affect our results. Third, our predictions rely on an invasion analysis geared at predicting the long-term evolutionary outcomes, but give little insight on transient eco-evolutionary dynamics. Such short-term effects are of potential importance for disease management, because the speed of evolution can affect the probability of short-term disease eradication, and because highly virulent strains may be favoured transiently, with dramatic consequences for the host population (Gandon & Day 2007).

Data combining information on host quality and spatial structure is still limited, but recent advances give some hope for experimental tests of theoretical predictions. First, experimental evolution would in principle allow to study the evolution of parasites in heterogeneous populations, using farm animal populations, cultivated plants, or laboratory systems (see e.g. Hillung *et al*. 2014). Second, spatial variation in resistance, infectivity and local adaptation in natural populations has been extensively studied, especially in plants (Greischar & Koskella 2007; Tack & Laine 2014). Developing a fully epidemiological theory of host-parasite coevolution would allow a fruitful dialogue between theory and data (Lion & Gandon 2015). The present paper contributes to bridging this theoretical gap. Third, the joint effect of treatments and spatial structure on parasite evolution could be studied using recent phylogenetic methods that combine spatial epidemiology and evolution (see Bart *et al*. 2014 for an example on pertussis).

Testing our model predictions for specific diseases would require information on the effects of vaccines on transmission, virulence or recovery, which are known only for a few diseases (Gandon & Day 2008). Nonetheless, our results are consistent with data on pertussis: the emergence of the virulent *PtxP3* strain of *Bortedella pertussis* appears to be associated with a rapid global spread and a move to new vaccines with an anti-toxin action (Box 1). Similarly, our results suggest that selection for more virulent strains of Marek's disease virus may have been enhanced by the increase in pathogen dispersal caused by the move from fragmented metapopulations of small-scale chicken barns to large-scale, well-mixed warehouses. By combining anti-toxin vaccines with increased parasite dispersal, the poultry industry may have chosen the worst possible scenario for the evolution of more deadly strains of Marek's disease. This calls for further experimental and empirical work to analyse the spatial evolutionary dynamics of infectious diseases and the effects of different treatments on disease epidemiological parameters.

ACKNOWLEDGEMENTS

We thank S. Gandon and S. Alizon for discussions and comments. We thank John Drake and an anonymous reviewer for their insightful comments that greatly help to improve the article. Y.Z. thanks the Consejo Nacional de Ciencia y Tecnología (CONACyT), México, for financial support. This work was supported by CNRS and ANR 10-PDOC-017-01 SpatEvolEpid to S.L. Simulations were performed on the Montpellier Bioinformatics Biodiversity cluster.

AUTHORSHIP

YZ and SL performed the simulations, analysed the results and wrote the manuscript. SL designed the study and derived the analytical results.

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Editor, John Drake
Manuscript received 4 February 2015
First decision made 19 March 2015
Second decision made 25 April 2015
Manuscript accepted 29 April 2015