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Epidemiological, evolutionary, and economic determinants of eradication tails

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HIGHLIGHTS

- We provide a model-based analysis of eradication tails.
- For the first time, we quantitatively study the trade-off between infectivity and mobility.
- Eradication tails depend on how the extinction threshold is approached.
- Disease evolution counteracts eradication measures.
- The cost structure of eradication measures strongly shapes eradication tails.

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ABSTRACT

Despite modern medical interventions, infectious diseases continue to generate huge socio-economic losses. The benefits of eradicating a disease are therefore high. While successful with smallpox and rinderpest, many other eradication attempts have failed. Eradications require huge and costly efforts, which can be sustained only if sufficient progress can be achieved. While initial successes are usually obtained more easily, progress often becomes harder as a disease becomes rare in the eradication endgame. A long eradication tail of slowly decreasing incidence levels can frustrate eradication efforts, as it becomes unclear whether progress toward eradication is still being made and how much more needs to be invested to push the targeted disease beyond its extinction threshold. Realistic disease dynamics are complicated by evolutionary responses to interventions and by interactions among different temporal and spatial scales. Models accounting for these complexities are required for understanding the shapes of eradication tails. In particular, such models allow predicting how hard or costly eradication will be, and may even inform in which manner progress has to be assessed during the eradication endgame. Here we outline a general procedure by analyzing the eradication tails of generic SIS diseases, taking into account two major ingredients of realistic complexity: a group-structured host population in which host contacts within groups are more likely than host contacts between groups, and virulence evolution subject to a trade-off between host infectivity within groups and host mobility among groups. Disentangling the epidemiological, evolutionary, and economic determinants of eradication tails, we show how tails of different shapes arise depending on salient model parameters and on how the extinction threshold is approached. We find that disease evolution generally extends the eradication tail and show how the cost structure of eradication measures plays a key role in shaping eradication tails.

1. Introduction

While disease-control measures have saved and improved billions of lives, infectious diseases remain a substantial threat to human and animal health (Heesterbeek et al., 2015). Plans persist to eradicate the most dangerous diseases (Dowdle, 1998), but have so far been successful only for smallpox (Arita, 1980; Tomori, 2011) and rinderpest (Njeumi et al., 2012; Roeder et al., 2013). Many other eradication attempts have failed, most notably for malaria (Greenwood et al., 2008; Murray et al., 2012). Challenges to

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eradication attempts typically arise after early successes: once incidence levels have been markedly diminished, the marginal costs required to push the disease further toward extinction often steeply increase, while the remaining efforts are difficult to estimate (Klepac et al., 2013, 2015). In general, eradication attempts are huge and costly undertakings, which can be sustained only if donors and decision makers remain convinced that the target is within reach. To assess progress and estimate remaining efforts in a convincing manner, developing an understanding of how eradication tails are shaped is therefore of considerable importance.

From a modeler's perspective, pushing a disease toward extinction means altering the circumstances that allow the disease to persist in a fragmented host population in such a manner that it can no longer persist. Those circumstances are described by the parameters of a disease model. If we call the set of parameter combinations that allow a disease to persist its endemicity region, eradication amounts to identifying a trajectory that leaves this endemicity region and to pushing the disease along this trajectory through suitable interventions. As disease extinction is approached at the endemicity region's boundary, the disease's incidence level decreases, eventually dropping to 0 when the disease becomes extinct. In analogy to the eventual fading of an epidemic outbreak, often referred to as the epidemic tail, we call this decrease in incidence level before extinction the eradication tail. There are three major determinants of the shape of this eradication tail.

The first determinant of eradication-tail shape is the epidemiological dynamics. Of special interest here are disease models that go beyond the assumption of well-mixed host populations. Real host populations are often fragmented, in the sense that they consist of subpopulations that are more or less isolated, so that encounters within these subpopulations are much more frequent than encounters between individuals from different subpopulations. Such populations can be seen as inhabiting a network of patches connected by occasional host migration. The special challenge for epidemiological control measures resulting from such metapopulation structures is that local extinction does not imply global extinction; if the disease can survive in only one patch, it can re-infect other patches from there (Prothero, 1977). On the other hand, disease spread among patches may be limited by host mobility, even if host infectivity is high. Infection dynamics in fragmented host populations therefore strongly depend on the connectivity structure of the patch network, which, given a spatial arrangement, in turn depends on the inter-patch mobility of the individuals. To underscore the difference between a disease spreading in a fragmented host population or in a well-mixed host population, we refer to the 2014 Ebola outbreak in West Africa, which, unlike previous outbreaks that only spread from village to village in fragmented host populations, reached large cities that enabled disease spread in well-mixed host populations. For Ebola, this qualitative change led to “the largest outbreak in history” (Gatherer, 2014; Meyers et al., 2015).

Different network structures may be suitable for understanding disease spread, depending on the density and heterogeneity of host populations, and on the mode, range, and pace of disease transmission. Such network structures can differ widely with respect to the number of patches, the distribution of patch properties, and the connectivity among patches. Not all of such structures, however, are equally relevant as generic representations of real-world scenarios. In many cases, considering a large (in a model: infinite) number of similar (in a model: identical) patches is an acceptable first approximation of reality. Moreover, when dispersal occurs over far larger distances than to just a few neighboring patches, little biological information is lost by assuming equal connectance among patches.

The second determinant of eradication-tail shape is evolution. The rapid evolution of infectious diseases presents a challenge for eradication efforts, because disease agents may quickly adapt to eradication measures. Consequently, care must be taken not to create selection pressures favoring increasing virulence, or to promote adaptations that allow strains to become endemic under a wider array of circumstances, thereby newly exposing to infection risks hosts that were hitherto safe. Before implementing eradication measures, it should therefore be common practice first to analyze the evolutionary pathways that the targeted strains may follow, given the relevant intrinsic evolutionary constraints. The fact that this is rarely, if ever, done, is probably to a good part owed to the difficulties associated with identifying such constraints.

Evolutionary constraints arise when certain disease properties, or traits, cannot be realized independently of each other: a change in one trait may imply a corresponding change in another trait, so that adaptations can proceed only in a subset of the full trait space. The condition that evolutionary pathways remain constrained in this manner can be expressed as a functional relation between the involved traits, which leads to the notion of trade-off functions.

Famously, Anderson and May (1982) introduced trade-offs between disease infectivity and virulence, which have prominently featured in the literature ever since. Virulence as understood by Anderson and May is defined simply as the excess host mortality induced by the presence of a disease, and this definition has become widely adopted among modelers. However, as has been pointed out on occasion (e.g., Dieckmann et al., 2002), this particular notion of virulence captures only one aspect of what has traditionally been understood by this term, another being ease of transmission (a usage still common for plant diseases), and still another being the level of overall debilitation (a usage common in the medical profession). The strong traditional connotation of the term virulence with mortality and infectivity has led to the unfortunate misunderstanding in the minds of many that the two must be intimately related and imply one another – in other words, to the often unquestioned assumption of trade-off functions that let infectivity increase with mortality. This has thus become the most commonly studied trade-off, which is remarkable considering that there is no generic reason why these two properties should be related. Some would argue that the fact that both should be positively correlated to a disease agent's growth rate constitutes such a generic reason, but this assumes well-mixing within the host body. In fact, it is easy to find counter-examples for which this is not the case: one is provided by respiratory diseases, where more deeply seated strains tend to be both more lethal and less infective. In a similar vein, Ebert and Bull (2008) pointed out that disease-induced morbidity has other components besides mortality, and that the corresponding trade-offs should be analyzed systematically.

Here we focus on a trade-off that becomes important when the spatial structure of a host population cannot be neglected, namely, the trade-off between host infectivity and host mobility. High host infectivity and high host mobility both help spreading a disease and should thus be favored by natural selection. Interesting evolutionary dynamics are therefore only expected from negative trade-offs, which cause the mobility of infected hosts to decrease as their infectivity increases. One argument why such trade-offs may occur is that, all else being equal, a disease agent that multiplies more rapidly in a host's body may be expected to be more infective, as well as more debilitating. (Note the crucial proviso “all else being equal”: mortality in particular is often connected less with overall debilitation than with a disease's capacity to proliferate into additional body compartments; e.g., de Jong and Janss, 2002.) Another reason for considering trade-offs between infectivity and mobility is that these figure very prominently in inspiring and influential work by Ewald (1994), which is rooted in

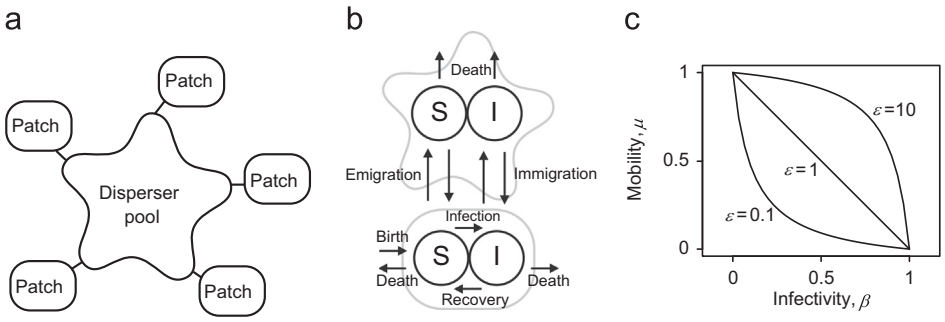

Fig. 1. The model combines a fragmented host population with standard disease dynamics within patches and includes a trade-off between infectivity and host mobility. (a) An infinite number of host patches is connected through a disperser pool, which contains individuals migrating among the patches. (b) Disease dynamics within patches follow an SIS-model. In addition to infection and recovery, birth of susceptible hosts, natural and disease-induced mortality, and migration are considered. (c) Infectivity (the probability with which an infected host transmits the disease upon contact with a susceptible host) and mobility (the probability with which an infected host leaves a patch when it would if it were not ill) are linked by a trade-off defined by the marginal mobility loss (measured by the trade-off function's slope $-\varepsilon$ at $\beta = 1$).

concrete disease ecology. In Ewald and De Leo (2002), such a trade-off was made to act through a non-monotonic mortality-dependent infectivity. Here we develop a framework in which host infectivity and host mobility initially occur as separate model ingredients and subsequently are linked by a trade-off.

As evolution through natural selection proceeds in the direction of increasing fitness, the need arises to find a suitable proxy for the fitness of a disease strain of given infectivity in a host population with given structure. In commonly considered spatially unstructured epidemiological models, the basic reproduction ratio R_0 serves this purpose. For populations spread over a large number of small, equally connected patches, Metz and Gyllenberg (2001) showed that a suitable fitness proxy is provided by R_m, the number of secondary patch invasions resulting from a single primary patch invasion. This fitness proxy is obtained as the dominant eigenvalue of a transition matrix describing the complete reinvasion cycle from patch to patch via a disperser pool. Jesse et al. (2011) discussed the application of this idea to general epidemiological models and introduced a framework for calculating R_m for such models in a straightforward manner (for related approaches to this problem, see, e.g., Ball et al., 1997; Pellis et al., 2012).

Before there can be an evolutionary play, there needs to be an ecological stage, that is, a viable host population and an endemic resident strain. While this seems self-evident, it may happen that a disease-free host population cannot survive for certain model parameters or that a disease cannot become endemic in a viable host population for certain other model parameters. It is therefore important to assess, before considering disease evolution, the parameter ranges enabling viability and endemicity for the disease traits under consideration (here: host infectivity and host mobility, linked by the aforementioned trade-off). Viability and endemicity can be assessed by calculating the invasion fitness for uninfected hosts in an empty host habitat, or for infected hosts in a disease-free host population, respectively (Jesse et al., 2011).

Finally, the third determinant of eradication-tail shape is the economics of eradication measures. A decreasing incidence level is usually considered as a function of time, but is really a function of investments that are made over time. Investments come in two basic forms: one-time investments that have a lasting effect, and investments that need to be sustained over time to retain their effect. As investments into eradication push a disease along a trajectory through the disease model's parameter space, it is this mapping of investments to steps along that trajectory that finally produces the observed eradication tail, which underlies the assessment of past progress and the expectation of future progress toward eradication. Assuming that progress can be made through the accumulation of one-time investments is a first approximation of more realistic investment structures.

In this study, we disentangle the aforementioned three determinants of eradication-tail shape by analyzing the endemic states of a simple infectious disease in a fragmented host population distributed over a large number of equally connected patches, considering evolutionary responses under an infectivity–mobility trade-off, and combining this with a generic model of geometrically increasing one-time investments needed for a succession of steps toward disease eradication.

2. Methods

Utilizing a standard SIS model in the framework of Jesse et al. (2011) allows us to assess viability and endemicity, analyze the stationary state, and understand the action of selection on disease traits. To evaluate the effects of eradication costs, we make some simple additional assumptions.

2.1. Endemicity and the stationary state

The framework of Jesse et al. (2011) requires us to specify the population size of host patches, all possible host states involved in the disease dynamics, all relevant transitions between host states, and the corresponding transition rates (which may be state-dependent).

Our model assumes equally connected host patches and host mobility among these patches via a disperser pool (Fig. 1a), combined with a variant of the common SIS model (Fig. 1b). We thus discern three host states: susceptible hosts, hosts infected with a resident strain, and hosts infected with a mutant strain. Hosts are always born susceptible. Co-infections or immunity are not considered, and recovered hosts revert to being susceptible. With patch-state frequencies described by a vector $\mathbf{p}$ and the disperser-pool states described by a vector $\mathbf{d}$, the dynamical equations take the following pseudo-linear form (Jesse et al., 2011),

$$\dot{\mathbf{p}} = \mathbf{A}(\mathbf{d})\mathbf{p},$$
$$\dot{\mathbf{d}} = \mathbf{B}(\mathbf{p})\mathbf{d} + \mathbf{C}\mathbf{p}, \quad (1)$$

in which the matrices on the right-hand sides are constructed from the transition rates. All relevant transitions (Fig. 1b) are listed in Table 1 together with their rates. For a list of all model parameters, see Table 2.

We apply the procedure Jesse et al. (2011) recommend for studying the invasion of diseases:

1. Write down the dynamical equations for the disease-free host population.
2. Calculate R_m for the disease-free host population (termed host

Table 1
Epidemiological transitions and their rates.

Event	Affected hosts	Patch-state change	Per capita transition rate
Involving only susceptible hosts ("s")			
Death	s	$s \to s-1$	d
Birth	s	$s \to s+1$	$b\ \max(0, 1-N/K)$[a]
Emigration	s	$s \to s-1$	m
Immigration	s[b]	$s \to s+1$	e
Involving hosts infected by a resident strain ("i", with trait values μ and β)			
Death	i	$i \to i-1$	$d+\alpha$
Birth	i	$s \to s+1$	$b\ \max(0, 1-N/K)$[a]
Emigration	i	$i \to i-1$	$m\mu$
Immigration	i[b]	$i \to i+1$	e
Infection	s	$s, i \to s-1, i+1$	$c\beta(i/N)$[a]
Recovery	i	$s, i \to s+1, i-1$	γ
Involving hosts infected by a mutant strain ("j", with trait values μ' and β')			
Death	j	$j \to j-1$	$d+\alpha$
Birth	j	$s \to s+1$	$b\ \max(0,\ 1-N/K)$[a]
Emigration	j	$j \to j-1$	$m\mu'$
Immigration	j[b]	$j \to j+1$	e
Infection	s	$s, j \to s-1, j+1$	$c\beta'(i/N)$[a]
Recovery	j	$s, j \to s+1, j-1$	γ

[a] In which N is the total patch occupation.
[b] From the disperser pool.

Table 2
Model parameters.

Natural host mortality	d	1
Birth rate	b	5
Disease-induced mortality	α	2
Recovery rate	γ	1 – 1000
Contact rate	c	1 – 150
Emigration rate	m	0.1 – 1
Patch carrying capacity	K	15
Marginal mobility loss	ε	0.1 – 10
Immigration rate	e	100
Step factor	f	0.9, 1.1
Cost increase	y	5 %, 10 %

R_m), to assess the host's viability.
3. If the host $R_m > 1$, find the non-trivial equilibrium of the disease-free host population, which in this case exists (the trivial equilibrium of hosts being extinct always exists).
4. Augment the dynamical equations by incorporating host states and host interactions required to describe infection dynamics.
5. Using the non-trivial host equilibrium from step 3, calculate R_m for the disease (termed disease R_m), to assess the disease's endemicity.

If the disease $R_m > 1$, a non-trivial equilibrium of the disease exists and can be calculated. From this endemic stationary state we extract the incidence level shown in Figs. 2–4, defined as the fraction of host patches among all occupied host patches that contain at least one infected host.

2.2. Selection and the evolution of disease properties

Calculating the non-trivial disease equilibrium is the first step of the full evolutionary analysis, for which we proceed as follows:

6. If the disease $R_m > 1$, find the non-trivial equilibrium of the disease.
7. Augment the dynamical equations by incorporating host states and host interactions required to describe the infection dynamics of a mutant strain in addition to the infection dynamics of a resident strain.
8. Using the disease equilibrium from step 6, calculate R_m for the mutant strain (termed mutant R_m), to assess the mutant's invasibility (which implies its endemicity).
9. If the mutant $R_m > 1$, replace the resident strain with the mutant strain and loop from step 6 (with step 7 only requiring a change in trait values) until invasions are no longer possible.
10. Ascertain that the final strain from step 9 corresponds to an evolutionarily steady state – conventionally called a continuously stable strategy, or CSS – and not to an evolutionary branching point.

While this description is conceptually accurate, in practice a problem arises in step 7, where we repeatedly have to choose trait values for the mutant strain. To avoid accidentally jumping over the CSS, we construct a function that (numerically) evaluates the local gradient of the invasion fitness $w(x, y) = \log R_m(x, y)$ of the mutant trait value y as a function of the resident trait value x, and then find a candidate CSS x^* as the root of $g(x) = [\partial^{(0,1)} w](x, x)$, i.e., instead of the standard adaptive dynamics we implement a so-called best-response dynamics. For step 10, we ascertain that x^* is a CSS by confirming the conditions $[\partial^{(0,2)}w](x^*, x^*) < 0$ and $[\partial^{(0,2)}w](x^*, x^*) < [\partial^{(2,0)}w](x^*, x^*)$ (Metz et al., 1996; Geritz et al., 1998).

After the dynamical equations are augmented as described in step 7, resulting in Eq. 1 with transition rates according to Table 1, the equilibria in step 6 are naturally obtained by solving for the equilibrium states of reduced dynamical equations with all mutant-related host states and host interactions removed. Thus, these equilibrium states $(\hat{\mathbf{p}}, \hat{\mathbf{d}})$ are the solutions of

$$0 = \mathbf{A}'(\mathbf{d})\mathbf{p},$$
$$0 = \mathbf{B}'(\mathbf{p})\mathbf{d} + \mathbf{C}'\mathbf{p}, \qquad (2)$$

where the prime indicates the reduced matrices, following the notation in Jesse et al. (2011). We numerically solve these nonlinear equations by iterative substitution: with an initial guess for $\hat{\mathbf{d}}$, we solve the first equation to find a corresponding trial value for $\hat{\mathbf{p}}$, which in turn serves to improve the guess for $\hat{\mathbf{d}}$ by multi-dimensional minimization, $\hat{\mathbf{d}} = \arg\min |\mathbf{B}'(\hat{\mathbf{p}})\mathbf{d} + \mathbf{C}'\hat{\mathbf{p}}|^2$. We alternate between these two steps until convergence is reached. The minimization step is made feasible by the fact that the dimension of the disperser-pool state vector is equal to the number of host states, and thus relatively low: for an SI or SIS model, $\mathbf{d}$ has merely two components. Figs. 2–4 are based on implementing the described model in R (RCore Team, 2012).

On a general note, the substantial – and, in our experience, sometimes under-appreciated – challenge when working with complex epidemiological models is the construction of the transition matrices needed for the calculations, because identifying the relevant interaction terms is an error-prone process (not in theory, but in practice) and the correctness of the resulting matrices is not easy to guarantee, if their elements are manually devised. For the present study, we have circumvented this problem via an automated generation of the needed transition matrices from simple descriptions of the epidemiological processes (as in Table 1), which, we feel, is really the only way to reliably explore model variants and parameter effects in complex models of this kind.

2.3. Trade-off and choice of parameters

As mentioned in the Introduction, we consider a disease to be characterized, in general, by its effects on host mortality, host

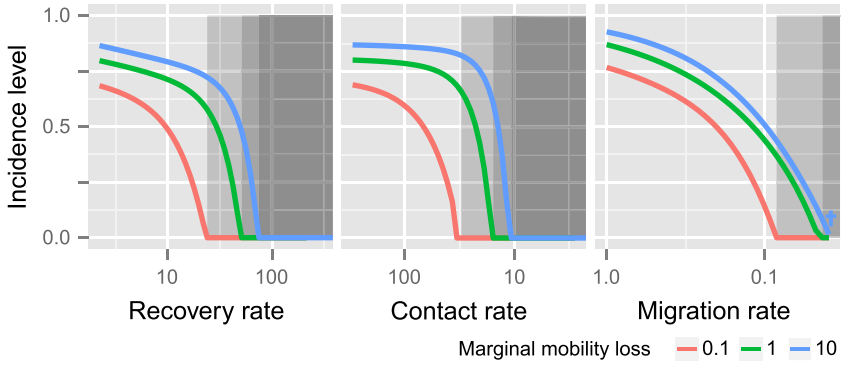

Fig. 2. Eradication tails depend on the epidemiological rate through which the extinction threshold is approached. Panels show the incidence level L_{evo} for three different values of the marginal mobility loss ε (measuring the negative slope of the trade-off function at $\beta = 1$) as the extinction threshold is approached through increasing recovery rate, decreasing contact rate, or decreasing migration rate. Shading indicates the thresholds for disease extinction. With decreasing migration rate and high marginal mobility loss, the host population becomes extinct before the disease, indicated by the cross. Other parameters: $K = 15$, $d = 1$, $b = 5$, $e = 100$, $\alpha = 2$, and $m = 0.5$.

mobility, and host infectivity. Here we study diseases for which increasing host infectivity implies decreasing host mobility, resulting from an immobilizing effect the disease has on its host. We assume a, presumably fairly representative, monotonic relationship between host mobility μ and host infectivity β of the form

$$\mu(\beta) = (\beta - 1)/((1 - 1/\varepsilon)\beta - 1), \tag{3}$$

in which the parameter ε determines the shape of the trade-off. Specifically, it equals the negative slope of this function at maximum infectivity, which we call the marginal mobility loss, $[D\mu](1) = -\varepsilon$. A high marginal mobility loss implies that mobility remains high for a relatively wide range of infectivities, while a low marginal mobility loss implies that mobility is low for a wide range of infectivities. A marginal mobility loss of $\varepsilon = 1$ corresponds to a linear decrease of mobility with increasing infectivity (Fig. 1c).

Other model parameters are the natural host mortality d and birth rate b, the disease-induced host mortality α, the recovery rate γ, the contact rate c, the emigration rate m, the immigration rate e, and the patch carrying capacity K. The recovery rate could be understood as another disease trait, but may additionally describe extrinsic influences, such as the level of medical treatment. One can interpret c as the average contact rate among hosts within a patch and β as the probability for an infected host to transmit the disease upon contact with an uninfected host, but also more generically as the maximum infection rate of a single infected host and a discounting factor describing any disease properties preventing its full realization. Similarly, μ can be understood as a discounting factor describing any disease properties that prevent a host from realizing its normal emigration rate m from patches.

We choose parameters so as to represent typical circumstances occurring in extended families or larger households in pre-modern agricultural societies (Table 2). In this way, the natural mortality rate, the birth rate, and the patch carrying capacity can all be roughly fixed at plausible values. Since we neglect infection dynamics during dispersal and assume that most of the host population is found in patches at any point in time, as seems realistic, the immigration rate at which hosts re-enter into patches from the disperser pool (termed the patch-encounter rate in Jesse et al., 2011) must be high, and we have confirmed numerically that under these conditions its specific value has little effect. For the disease-induced mortality, we choose a value that describes a tripling of natural mortality in infected hosts, which characterizes diseases that are relatively dangerous. Based on these considerations, we can focus on exploring the effects of the remaining model parameters: recovery rate, contact rate, and migration rate. These can also be influenced in a straightforward way by health interventions (e.g., through improved treatments, better hygiene, and isolating patients, respectively).

2.4. Eradication and effects of the cost structure

As shown in Section 3, disease eradication can be achieved by increasing or decreasing the aforementioned three focal model parameters. Here we assume that lasting changes can be made by one-time investments, that is, after an investment to change the environment of the disease made at time t, the value of the

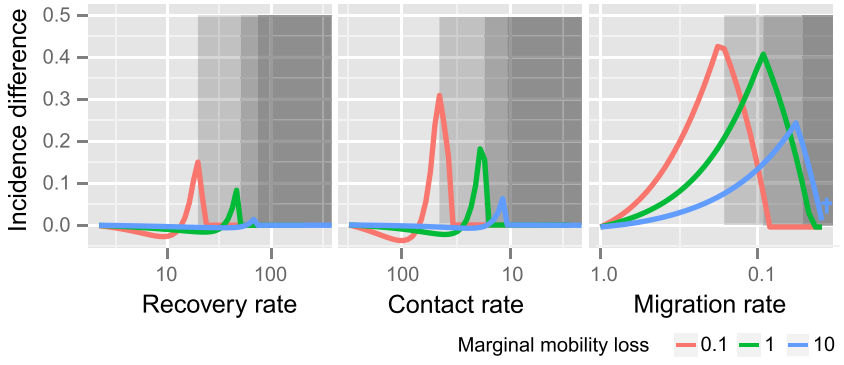

Fig. 3. Disease evolution counteracts eradication measures. Panels show the difference in incidence levels with and without disease evolution, $L_{evo} - L_{noevo}$, for three different values of the marginal mobility loss ε (measuring the negative slope of the trade-off function at $\beta = 1$) in the same layout as in Fig. 2. The infectivity assumed for the non-evolving disease agent is the evolutionarily steady infectivity on the far left side of the extinction threshold (where the difference in incidence levels consequently equals 0). As the extinction boundary is approached the incidence level caused by the evolving disease agent increases relative to that caused by the non-evolving disease agent. Farther away from the boundary, the incidence level initially decreases with increasing recovery rate or decreasing contact rate. Shading indicates the thresholds for disease extinction without disease evolution. The cross indicates extinction of the host population. Parameters as in Fig. 2.

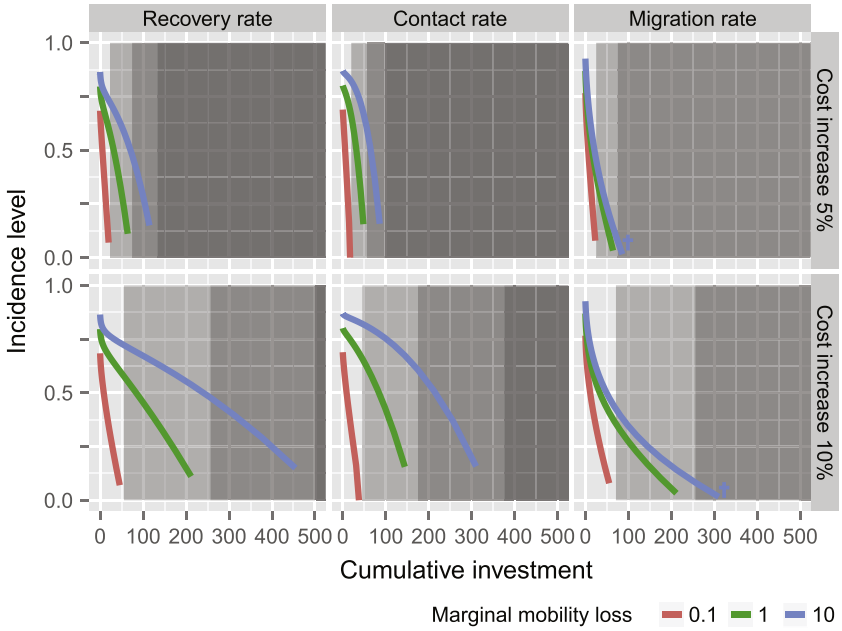

Fig. 4. Costs of eradication measures strongly shape eradication tails. In practice, eradication tails are observed as functions of time, although they are really functions of the cumulative investments made into eradication measures. For the three approaches to the extinction boundary shown in Figs. 2 and 3 (columns), as well as for the three trade-off shapes (defined by their marginal mobility loss ε, measuring the negative slope of the trade-off function at $\beta = 1$) considered there, panels show incidence levels as functions of cumulative investments into eradication, under the assumption that the costs for each subsequent intervention toward extinction increase by 5 % times (upper row) or 10 % (lower row). Relatively minor differences in this cost structure can result in large differences in the total investments needed for eradication. Shading indicates the thresholds for disease extinction. Crosses indicate extinction of the host population. Other parameters as in Fig. 2.

associated disease parameter permanently changes from x to fx after a relaxation period that is short compared to the time between subsequent investments. Furthermore, we assume that investments have to increase geometrically in order to achieve the same relative change as the disease's extinction boundary is approached (such growing costs will arise, for example, if it becomes more and more costly to identify any remaining cases as the disease becomes rarer and rarer). Consequently, making i investments changes the considered parameter from an initial value x_0 to a value $x_i = x_0 f^i$ with associated costs $c_i = c_1 y^{i-1}$; in this sense, we say that costs for subsequent interventions increase by $y/f - 1$. The cumulative investment after k such one-time investments equals $c_1(y^k - 1)/(y - 1)$.

3. Results

Below we examine the shape of eradication tails resulting from approaching a disease's extinction boundary through changes in disease parameters, also looking at the influence of disease evolution. As a direct measure of disease presence, we use the incidence level $L_x = \sum_{i\sim\text{infected}} \hat{p}_i / \sum_{j\sim\text{occupied}} \hat{p}_j$, defined as the fraction of infected patches among all occupied patches, where the subscript x indicates whether disease evolution is considered ($x = \text{evo}$) or not ($x = \text{noevo}$). We concentrate on the case of fast disease evolution, as disease agents tend to have short generation times and high mutabilities.

3.1. Eradication tails depend on how the extinction threshold is approached

We begin our analysis of eradication tails by considering three simple trajectories that lead from a point well within the endemicity region, where the incidence level is consequently relatively high, to the extinction boundary: firstly, through increasing the recovery rate, secondly, through decreasing the contact rate, and thirdly, through decreasing the migration rate. Fig. 2 shows how incidence levels decrease for different trade-off shapes as the extinction boundary is approached. While the overall appearance is similar, the location of the extinction boundary depends on trade-off shape. Trade-offs with higher marginal mobility loss (Eq. 3; Fig. 1c) generally lead to higher incidence and prolonged persistence. The endemic stationary states are determined for the evolutionarily steady trait values: this accounts for the evolutionary response through which a disease reacts to the eradication efforts, assuming that enough time passes between interventions to allow the needed evolutionary adjustments.

3.2. Disease evolution counteracts eradication measures

To highlight the importance of accounting for disease evolution, we look at eradication-tail shapes when evolution is neglected. We repeat the calculations described above for the endemic stationary states, now calculated not for the evolutionarily steady trait values, but for the evolutionarily steady trait values for the first point of the eradication trajectory, that is, for a point well within the endemicity region. Incidence decreases in a manner overall similar to the case with evolution, but disease extinctions can be achieved earlier. Since differences mostly occur in the steep part of the eradication tail, where they are difficult to see, Fig. 3 shows the difference between incidence levels with and without evolution, $L_{\text{evo}} - L_{\text{noevo}}$, which initially equals 0 by construction, and drops to 0 again when extinction has occurred for both cases, in the same layout as in Fig. 2. With evolution, extinction is generally delayed, giving rise to characteristic peaks in Fig. 3. That these peaks are largest when varying the migration rate indicates that migration among patches is indeed the most important determinant for disease incidence in the host metapopulation, which evolution can in this case fine-tune directly. Interestingly, we also observe that disease evolution can cause an initial decrease in incidence level. Both this decrease and the general delay of extinction result from the disease's evolutionary response to the

extinction threat. Responding to increasing recovery rate or decreasing contact rate, disease evolution increases infectivity and thus roughly maintains within-patch success; this in turn decreases host mobility and thus negatively affects the disease's ability to colonize uninfected patches, resulting in an initial decrease of its incidence level. Responding to decreasing migration rate, disease evolution increases host mobility and thus roughly maintains between-patch success; therefore no decrease in incidence level is observed. In all of these cases, disease evolution counters the eradication measure in the most direct manner available.

3.3. Costs of eradication measures strongly shape eradication tails

Finally, we show how eradication tails look when observed as functions of cumulative investments (which is also how they look as functions of time when cumulative investments linearly increase with time). This generally requires knowledge about how the costs of pushing a disease toward its extinction boundary change as the boundary is approached. Here we simply assume that costs to effect a given relative change toward the extinction boundary increase geometrically, and compare two small (arbitrarily chosen) cost factors. The resulting eradication tails are shown in Fig. 4. As can be seen, the shapes of the eradication tails when shown in dependence on epidemiological parameters (Figs. 2, 3) are qualitatively transformed when shown in dependence on cumulative investments, even for very simple cost structures. This highlights the strong influence eradication costs, which often are hard to assess when eradication efforts are started, can have on the shape of eradication tails.

4. Discussion

Here we have presented a model-based analysis of the determinants of eradication tails of generic SIS diseases. To account for spatial structure and disease evolution – two major factors that complicate real-world eradication efforts – we have employed the modeling framework of Jesse et al. (2011), which allows to extend standard epidemiological models formulated for well-mixed host populations to fragmented host populations spread over networks of equally connected patches, while providing a conceptually straightforward approach to assessing the viability of host populations, the endemicity of resident strains, and the invasibility of mutant strains by using the R_m fitness proxy of Metz and Gyllenberg (2001). We have chosen parameters that roughly describe, for example, populations fragmented into large households or extended families in pre-modern societies (Table 2).

4.1. A modeler's perspective on eradication

From a modeler's perspective, disease eradication means pushing a disease along a trajectory that eventually leaves the disease's endemicity region. As the extinction boundary is approached, the incidence level decreases, resulting in an eradication tail. Since the current position of a disease within its endemicity region, and consequently its distance from the extinction boundary, is rarely well known in advance, observing this eradication tail is the only practical way to assess if and how progress toward extinction is being made. To interpret this information correctly, a good understanding of what determines the shapes of eradication tails is necessary.

We have shown how the incidence level decreases as the disease is pushed to extinction in various ways (Fig. 2), and how disease evolution counteracts such eradication attempts (Fig. 3). In this way, disease evolution generally extends the endemicity region (that is, the range of parameters that allow disease persistence in the fragmented host population) and may in extreme cases even prevent disease extinction (Fig. 3). In reality, however, decreases in incidence level as a function of disease parameters are not observed directly. Eradication tails result from the changes in the circumstances that affect disease persistence (which are described by the disease parameters) being effected through investments into health interventions, which typically are spread out over time. This makes the cost structure of eradication measures a key determinant of eradication-tail shape, with the consequence that small uncertainties about this cost structure can result in large mis-estimations of the necessary total investments (Fig. 4). These qualitative insights are generic, and hence widely applicable, and largely independent of the specific model assumptions that we have made to illustrate them.

We have assessed incidence levels at disease equilibrium, which assumes that epidemiological dynamics settle to new attractors relatively fast after a health intervention. Whether or not this is a valid assumption must be decided on a case-to-case basis. We believe that with interventions coming in five- or ten-year plans and responses to diseases manifesting over single seasons, this assumption will often hold in practice. In any case, single interventions will typically be designed to have noticeable effects, while not completely changing the disease environment, which implies that the initial change toward the new equilibrium should be relatively fast at first and make the equilibrium an acceptable estimate of the real transitory state.

Concerning our definition of incidence level, as the fraction of infected host patches among occupied host patches, the question may arise whether empty patches should not also be considered, and if so, how. Empty patches are certainly disease-free, but in practice they may not be counted together with the uninfected patches, be it because they are not even noticed (as, e.g., in the case of a wandering tribe that is no longer there), or because observers may be reluctant to report a village as uninfected where a disease has just killed every last inhabitant. In any case, the fraction of empty patches is very low in the parameter ranges investigated here, and the overall picture does not change if they are included.

4.2. Spatial structure and trade-offs

We have assumed patches to be equivalent, while patches in real fragmented host populations may often appear heterogeneous to at least some extent. Apparent heterogeneity may, however, also result from the underlying population dynamics, which is fully accounted for in our model. Stronger patch heterogeneity can partly be accounted for through multiple levels of mixing, instead of the two levels included here, and applications of the fitness proxy of Metz and Gyllenberg (2001) may be extended to multiple levels of mixing with some effort (Britton et al., 2011; for a discussion of issues related to mixing, see also Verboom et al., 1991; Parvinen, 2002). However, modeling localized interventions (e.g., ring vaccinations etc.) would require a different approach. Patches are also assumed to be equally connected to each other. This represents the limit in which host dispersal beyond the spatially nearest neighbors is common, or patch connections are frequently rearranged, which is nearly the norm with current means of transportation and modern travel habits.

The trade-off between host infectivity and host mobility, assumed here to constrain evolution, links the primary determinant of a disease's within-patch success with the primary determinant of its among-patch success, respectively. The function in Eq. 3 has a shape very similar to that of the more traditional trade-off function $\mu^{1/s} + \beta^{1/s} = 1$, with the advantage that our parameter ε has a straightforward interpretation as the trade-off function's negative slope at infectivity 1, whereas the parameter s of the traditional function regulates trade-off strength, but offers no such

useful interpretation. A second disadvantage of the traditional function results from its slopes at $(\beta, \mu) = (0, 1)$ and $(1, 0)$ abruptly jumping from 0 to infinity as s crosses 1.

There are ways to attempt eradication not discussed here. In fact, a very common strategy might be to attempt local eradication in as many patches a possible. This would, in our model-based perspective on eradication, amount to including local-eradication events among the events listed in Table 1 and just introduce another parameter and another dimension along which we can push the disease to extinction, resulting in eradication tails similar to the ones shown. Including such an event type would, however, not well match our parameter assumptions, which are meant to describe extended households, whereas local-eradication efforts would typically be undertaken on a province or country level. Our approach could be extended to modeling vaccination campaigns: this would require including immune hosts; otherwise, the analysis would proceed in the same way.

4.3. Importance of cost structure

Even with our very simplistic assumptions of progress toward eradication being made through successive one-time investments, relatively minor uncertainties about how costs increase can result in substantial factors in the estimation of the total investments required for eradication (Fig. 4). In reality, necessary investments come both as one-time investments and as investments that need to be sustained, and the distribution of investments of either sort over time may be uneven. As a result, the cost structure will generally not be well known, resulting in much uncertainty in estimating the eradication tail, and hence in assessing achieved progress and remaining effort. Our analysis thus highlights the need to understand and estimate the cost structure of eradication measures as carefully as possible.

5. Conclusions

We have disentangled the epidemiological, evolutionary, and economic determinants of eradication tails. While evolutionary responses generally counteract eradication measures, this is a relatively weak effect and can be overcome by sustaining eradication measures just a little longer. Our study demonstrates how the shapes of eradication tails, on which assessments of achieved progress and remaining effort must in practice be based, are strongly influenced by the cost structure of the eradication measures and by the resultant distribution of interventions over time. Modeling endgame scenarios thus requires a thorough understanding not only of the evo-epidemiological, but also of the socio-economic aspects of eradication. With good intervention models that clearly link investments made over time to their effects on disease parameters, such analyses can become valuable tools in support of eradication plans.

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