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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.
- Pathogen evolution counteracts eradication measures.
- The cost structure of eradication measures strongly shapes eradication tails.

Abstract

Infectious diseases still generate huge socio-economic costs and many people would like to see them gone entirely. While success stories like with smallpox and rinderpest give hope that this may be possible, many other eradication attempts have failed. Eradication requires huge and costly efforts, which can only be sustained if sufficient progress can be reported. While initial successes are usually easily obtained, progress often becomes harder as the disease becomes rare (during the "endgame"). Often a long "eradication tail" of slowly decreasing incidence level frustrates eradication efforts, as it becomes unclear whether

progress towards eradication is still made and how much more needs to be invested to push the disease beyond the extinction threshold. Realistic disease dynamics are complex, generally involving dynamics on several temporal and spatial scales, and evolutionary responses to interventions. Models that account for these complexities can serve to understand the eradication tails of diseases as they are pushed to extinction; that is, they allow predicting how hard or costly eradication will be, and may even inform in which manner progress has to be assessed during the endgame. Here, we outline a general procedure by analyzing the eradication tail of a generic SIS disease, taking into account two major ingredients of realistic complexity; namely, a spatially-structured host population where contacts within groups are much more likely than contacts between groups, and virulence evolution, with a trade-off linking local infectivity and host mobility among groups. Disentangling the epidemiological, evolutionary, and economic determinants of the eradication tail, we show that different tails result depending both on parameters and on how the extinction threshold is approached. Specifically, we find that pathogen evolution generally extends the eradication tail. Finally, we show how the cost structure of eradication measures shapes eradication tails in a major way.

Keywords

evolutionary disease control; virulence management; meta-population; endemicity; household

1. Introduction

Despite successful control measures having saved and improved billions of lives, infectious diseases still remain a substantial threat to human and animal health (Heesterbeek et al., 2015). Plans to eradicate the most dangerous diseases persist (Dowdle, 1998), but were so far 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). The challenge to eradication attempts typically comes after early successes when the incidence level has already been markedly decreased,

because costs to push the disease further to extinction then often steeply increase, while the remaining effort is difficult to estimate (Klepac et al., 2013, 2015). Eradication attempts are huge and costly undertakings, and can only be sustained if donors and decision-makers can be convinced that the target is within reach. To assess progress and estimate the remaining effort in a convincing manner, understanding how exactly a disease becomes extinct is therefore of paramount importance.

From a modeler's perspective, pushing a disease toward extinction means altering the circumstances that allow the disease to persist in the fragmented global host population, in such a manner that it can no longer persist. Those circumstances are expressed through the parameters of a disease model. If we call the set of parameter combinations that allow persistence the "endemicity region", eradication amounts to identifying a trajectory that leaves this endemicity region, and then pushing the disease along this trajectory through suitable interventions. As the boundary to extinction is approached, the incidence level decreases, eventually dropping to 0 when the disease becomes extinct. In analogy to the eventual fizzling-out of an epidemic outbreak, 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 the occasional migration of individuals. The special problem for epidemiological control measures resulting from this structure is that local extinction does not imply global extinction; if the disease can survive in only one patch, it can re-infect the other patches from there (Prothero, 1977). On the other hand, spreading of the disease among patches may be limited by host mobility, even if infectivity is high. Infection dynamics in fragmented host populations therefore strongly depends 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 illustrate the difference between a disease spreading in a fragmented population or a well-mixed population, we refer to the Ebola outbreak 2014 in West Africa, which unlike previous outbreaks that only hopped from village to village (spreading in a fragmented population) has reached large cities (now spreading in a well-mixed population) and thus became "the largest outbreak in history" (Gatherer, 2014; Meyers et al., 2015).

There are many possible network structures, differing with respect to number of patches, distribution of patch properties, and connectivity among patches. Not all of them, 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. Since, moreover, dispersal often occurs over far larger distances than to just a few neighboring patches, little biological information is lost by assuming equal connectance.

The second determinant of eradication-tail shape is evolution. The rapid evolution of infectious diseases presents a challenge for eradication efforts, not only because pathogens quickly adapt to counteracting measures, but also because care must be taken not to inadvertently create selection schemes favorable to increasing virulence, or to promote adaptations that allow strains to become endemic under a wider array of circumstances, thereby newly exposing to infection risks host populations that were hitherto safe. Before acting, it should therefore be common practice first to analyze the evolutionary pathways that the targeted strains may follow, given the 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 relevant constraints.

Evolutionary constraints arise when certain disease properties, or traits, cannot be realized independently of each other, but a change in one implies a corresponding change in the other, and so adaptation can only proceed 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 agent infectivity and "virulence", which have pervaded the literature ever since.

Virulence as understood by Anderson and May simply meant host mortality induced by the presence of the agent, and this definition was widely adopted among modelers. However, as has been pointed out on occasion (Dieckmann et al., 2002), this 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 overall debilitation (a usage common among the medical profession). The strong traditional connotation of the term "virulence" with "mortality" and "infectivity" has led to the unfortunate conclusion in the minds of many that the two must be intimately related and imply each other – in other words, to the often unquestioned assumption of trade-off functions which let infectivity increase with mortality. This has thus become the most commonly studied trade-off, which is quite 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 parasite growth rate constitutes such a generic reason, but this assumes well-mixing within the host body. It is in fact easy to find counter-examples where this is not the case; one such example 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 (2006) 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 the host population cannot be neglected, namely, the trade-off between infectivity and host mobility. High infectivity and high host mobility both help spreading the disease and should thus be selected for. Interesting evolutionary dynamics are therefore only expected from negative trade-offs, where the mobility of infected hosts decreases as their infectivity increases. One argument why such a trade-off may occur is that, all other things being equal, a disease organism that multiplies more rapidly in the body may be expected to be more infective as well as more debilitating. (Note the crucial phrase "all else being equal"; in

particular mortality often is connected less with overall debilitation than with the disease proliferating into additional body compartments; e.g., de Jong and Janss, 2002.)

Another reason for considering a trade-off between infectivity and mobility is that such trade-offs figure heavily in the inspiring work of Ewald (1994) rooted in concrete disease ecology. In Ewald and De Leo (2002) such a trade-off was made to act through a non-monotone mortality-dependent infectivity. Here, we develop a framework in which infectivity and larger-scale mobility occur as separate model ingredients, which can subsequently be connected by trade-offs.

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 strain of given infectivity. In the common spatially-unstructured epidemiological models, the basic reproduction ratio R_0 serves this purpose. For our case of populations spread over a large number of small, equally-connected patches, Metz and Gyllenberg (2001) showed that a suitable fitness proxy is found in R_m, the number of secondary patch invasions resulting from a single primary patch invasion, obtained as the dominant eigenvalue of a 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 compartment models as used in epidemiology and introduced a calculation framework to obtain R_m values for such models in a straight-forward 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, given all other parameters, even a disease-free host population cannot survive, or that with a viable host population, the disease still cannot become endemic for the adaptive trait under consideration (here: infectivity and host mobility as linked by the trade-off function). Viability and endemicity can be assessed by calculating the invasion fitness for hosts in an empty landscape, or of strains 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. The 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 the effect. As the investments into eradication push the disease along a trajectory through the 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 and the expectation of future progress toward eradication. Assuming that progress can be made through the cumulation of simple one-time investments is a first approximation of more realistic investment structures.

In this study, we disentangle the 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 subsequent steps toward extinction.

2. Methods

Plugging a standard SIS model into the framework of Jesse et al. (2011) allows us to assess endemicity, analyze properties of the stationary state, and the action of selection on disease properties. To speak about the effect of investment cost structure, 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 compartments, the patch size, all relevant transitions and all corresponding transition rates (which may be state-dependent). The full model used here combines the equally-connected patch structure with disperser pool (Fig. 1a) with a variant of the common SIS model (Fig. 1b) and has three compartments to discern between: susceptible hosts, hosts infected with the resident strain, and hosts infected with the mutant strain. Hosts are always born susceptible. Co-infections or immunity are not

considered; recovered hosts become susceptible again. 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 pseudo-linear form (Jesse et al., 2011)

$$\begin{aligned} \dot{\mathbf{p}} &= \mathbf{A}(\mathbf{d})\mathbf{p} \\ \dot{\mathbf{d}} &= \mathbf{B}(\mathbf{p})\mathbf{d} + \mathbf{C}\mathbf{p} \end{aligned} \tag{1}$$

in which the matrices on the right-hand sides are constructed from the transition rates; the relevant transitions (Fig. 1b) together with their rates are listed in Table 1. For the patch size, see Table 2. Jesse et al. (2011) then put forward the following procedure 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 to assess its viability.
3. If this $R_\mathrm{m} > 1$, find the non-trivial equilibrium of the disease-free host population, which in this case exists (the trivial equilibrium of being extinct always exists).
4. Augment the dynamical host equations by incorporating compartments and interactions required to describe infection dynamics.
5. Using the non-trivial host population equilibrium from step 3, calculate R_m for the disease to assess endemicity.

If $R_\mathrm{m} > 1$, a non-trivial equilibrium of the disease exists and can be calculated. From this stationary endemic state we then extract the summary statistic shown in the result figures (see section 3): the "incidence level" as the fraction of patches containing at least one infected host among all occupied patches.

2.2 Selection and the evolution of disease properties

The step of calculating the non-trivial disease equilibrium is also the first step of the full evolutionary analysis, which proceeds as follows:

6. If its $R_\mathrm{m} > 1$, find the non-trivial equilibrium of the disease.

7. Augment the dynamical equations by incorporating compartments and interactions required to describe the infection dynamics of a mutant strain in addition to the infection dynamics of the resident strain.
8. Using the equilibrium from step 6, calculate R_m for the mutant strain to assess invasibility (which also implies endemicity).
9. If this $R_\mathrm{m} > 1$, replace the resident strain by the mutant 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 state", CSS) and not a 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 $w(x,y) = \log R_\mathrm{m}(x,y)$ as a function of the resident trait value x, then find a candidate CSS trait value 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-reply dynamics. For step 10, we calculate $[\partial^{(0,2)} w](x^*,x^*)$ to exclude the possibility of a branching point and ascertain that x^* corresponds in fact to a CSS, which is the case if this second derivative is smaller than 0 and additionally $[\partial^{(2,0)} w](x^*,x^*) > [\partial^{(0,2)} w](x^*,x^*)$ (Metz et al., 1996; Geritz et al., 1998).

The resident equilibria underlying the R_m calculations are obtained by solving for the stationary case reduced dynamical equations with all invader-related compartments and interactions removed; that is, the equilibrium states $(\hat{\mathbf{p}}, \hat{\mathbf{d}})$ are the solutions of

$$\begin{aligned} \mathbf{0} &= \mathbf{A}'(\mathbf{d})\mathbf{p} \\ \mathbf{0} &= \mathbf{B}'(\mathbf{p})\mathbf{d} + \mathbf{C}'\mathbf{p} \end{aligned} \tag{2}$$

where the prime symbol indicates the reduced equations, following the notation in Jesse et al. (2011). Given the nonlinearities in this equation system, we resort to numerical solution 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, i.e., let $\hat{\mathbf{d}} = \arg\min |\mathbf{B}'(\hat{\mathbf{p}})\mathbf{d} + \mathbf{C}'\hat{\mathbf{p}}|^2$ etc. The minimization step is made feasible by the fact that the dimension of the disperser-pool state vector is equal to the number of compartments, that is to say, relatively low; for example, $\mathbf{d}$ is a 2-vector for an SI or SIS model. We implement the procedure outlined above in R (R Core Team 2012).

On a general note, the substantial, and, in our experience, sometimes under-appreciated, problem when working with epidemiological compartment 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 this is programmed by hand. We have circumvented this problem via automatic generation of the involved matrices from simple descriptions of the involved processes (as in Table 1), which, we feel, is really the only way to reliably explore model variants and parameters.

2.3 Trade-off and choice of parameters

As mentioned in the Introduction, we consider a disease to be characterized by its effect on host mortality, its effect on host mobility, and its infectivity. Here, we study the case where increasing infectivity implies decreasing host mobility, that is, where the disease has an immobilizing effect on its host. We assume a presumably fairly representative monotone relationship between host mobility μ and infectivity β of the form

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

in which the additional parameter ε defines 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": $[\mathrm{D}\mu](1) = -\varepsilon$. A high marginal mobility loss also 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 $\varepsilon = 1$ corresponds to a simple 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 mortality α, the recovery rate γ, the contact rate c, the emigration rate m and the

patch carrying capacity K. The recovery rate could be understood as another disease trait, but may additionally describe extrinsic influences, e.g., treatment etc. One can interpret c as the average contact rate among hosts within a patch and β as the probability to transmit the disease upon contact, 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 encountered in extended families or larger households in pre-modern agricultural societies (Table 2).

Of the available model parameters (Table 2), birth rate and carrying capacity are already mostly fixed through our assumptions of extended families, and anyway are generally beyond control, except possibly in totalitarian states. Since we neglect infection dynamics during dispersal and assume that most of the population is found in patches at any point in time, as seems realistically to be the case, the patch encounter rate becomes a technical device to keep the dispersal pool mostly empty. Given these constraints, we may expect that the limited freedom that we have to change the encounter rate will have little effect. While reducing disease mortality may be a strategy, it would – if it were possible – make the disease harmless and alleviate the need for eradication altogether. Consequently, we focus on the remaining parameters: recovery rate, contact rate, and migration rate, which can also be influenced in a straight-forward way (through improved treatment options, better hygiene, and isolation of patients).

2.4 Eradication and effects of the cost structure

As shown in section 3, eradication can be achieved by increasing or decreasing certain parameters. Here, we assume that lasting changes can be achieved by one-time investments, that is, after an investment to change the environment of the disease made at time t, the value of the associated disease parameter permanently changes from x to fx after a relaxation period which is short compared to the time between subsequent investments.

Furthermore, we assume that investments have to increase geometrically to achieve the same relative change as the extinction boundary is approached (for example, it may become more costly to identify any remaining cases as the disease becomes rarer). Consequently, i investments change the value 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 $C_k = c_1(y^k - 1)/(y - 1)$.

3. Results

Below, we present an analysis of the eradication tail as it results from approaching the extinction boundary through changes in disease parameters, also looking at the influence of pathogen evolution. As a direct measure of disease presence we use the "incidence level" L_x, here defined as the fraction of infected patches among all non-empty patches ($L_x = \sum_{i\sim\text{infected}} \hat{p}_i / \sum_{j\sim\text{not empty}} \hat{p}_j$) with the subscript indicating whether pathogen evolution is considered ($x = \text{evo}$) or not ($x = \text{noevo}$). We here concentrate on the case where evolution is fast, on the assumption that this case is more common, due to the short generation time and high mutability of most pathogens.

3.1 Eradication tails depend on how the extinction threshold is approached

We begin our analysis of eradication tails by constructing 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 within-patch contact rate, and thirdly, through decreasing the inter-patch migration rate. Figure 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 prolong persistence. The underlying stationary endemic states are calculated at the evolutionarily

stable trait values and so account for the evolutionary response to the eradication attempt. This also assumes that enough time passes between interventions to allow evolutionary equilibration.

3.2 Pathogen evolution counteracts eradication measures

To highlight the importance of accounting for trait evolution, we now look at eradication tail shapes when evolution is neglected. We repeat the calculations above for underlying stationary endemic states calculated not at the evolutionarily stable trait value for the respective parameter combination, but at the evolutionarily stable trait value of the first point of the trajectory, that is, the point well within the endemicity region. Incidence decreases in a manner overall similar to the case with evolution, but shifted to the right. Since differences mostly occur in the steep part where they are difficult to see, Figure 3 shows directly 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 where extinction has occurred for both cases, in the same layout as used in Fig. 2. With evolution, extinction is generally delayed by two or three interventions, giving rise to characteristic peaks in this difference plot. That these peaks are largest when varying the migration rate indicates that migration among patches is indeed the most important determinant for incidence in the metapopulation, which evolution can in this case fine-tune directly. Interestingly, an initial decrease in incidence level with evolution can also be noticed. This indicates that close to extinction, evolution "delays" extinction by increasing a strains ability to colonize empty patches (which become more frequent as the extinction threshold is approached), sacrificing within-patch success in the process. This explanation is consistent with the observation that the effect is more pronounced with lower marginal mobility losses, where the infectivity penalty for increasing mobility is higher.

3.3 The cost structure of eradication measures strongly shapes eradication tails

Finally, we show how eradication tails look when observed as a function of cumulative investments (which is also how they look as a function of time when cumulative investments

increase linearly with time). This generally requires knowledge about how costs to push the disease toward the extinction boundary change as the boundary is approached. Here, we simply assume that costs to effect a 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 appearance of the eradication tails expected in the epidemiological models (Figs. 2, 3) can be completely transformed even with very simple cost structures. This highlights the strong influence these often unknown or neglected cost structures have on eradication tails.

4. Discussion

Here, we have presented a model-based analysis of the determinants of the eradication tail of a generic SIS disease. To account for spatial structure and pathogen evolution – two major factors that also enormously complicate real-life eradication efforts – we have employed the modeling framework of Jesse et al. (2011), which allows to extend standard compartment models formulated for well-mixed systems easily to fragmented host populations spread over equally-connected patches, and provides a conceptually straight-forward recipe for assessing endemicity and invasibility of mutant strains using the R_m fitness proxy of Metz and Gyllenberg (2001). We have chosen parameters that would describe, for example, populations fragmented into large households or extended families (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 endemicity region. As the extinction boundary is approached, the incidence level decreases, resulting in an "eradication tail". Since the exact location of a disease in its endemicity region, and consequently its distance from the extinction boundary, is rarely known in advance, observing this eradication tail is the only real way to assess if and how progress toward extinction is being made. To interpret this information correctly, a good understanding of what determines the shape of eradication tails is necessary.

We have shown how the incidence level decreases as the disease can be pushed to extinction in various ways (Fig. 2), and how pathogen evolution acts against eradication attempts by generally extending the endemicity region, that is, the range of parameters that allow disease persistence in the fragmented host population (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, which themselves are spread out over time. This makes the cost structure of eradication measures the ultimate 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 made to illustrate them.

We have assessed disease incidence levels at equilibrium, which assumes that dynamics settle to their new attractor fast enough after each 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 in practice often be good enough. In any case, single interventions will often be designed to have noticeable effects, but not completely change 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 among occupied 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 reporters 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 strictly equivalent, while patches in real-life fragmented 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 the fitness concept of Metz and Gyllenberg (2001) may be extended to multiple levels of mixing with some effort (Britton et al., 2011; for a discussion of mixing-related issues 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 where 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 infectivity and mobility, assumed here to constrain evolution, links the primary determinant of within-patch success with the primary determinant of between-patch success. The functional form (Eq. 3) has an appearance very similar to the more traditional trade-off shape $\mu^{1/s} + \beta^{1/s} = 1$ with the advantage that its parameter ε has a straight-forward interpretation as the negative gradient at infectivity 1, whereas the trade-off strength parameter s of the traditional form offers no such useful interpretation.

There are ways to attempt eradication not discussed here. In fact, the most common strategy is probably 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 push the disease to extinction, resulting in eradication tails similar to the ones shown. Including such an event type would, however, push our parameter assumptions a bit, which supposedly describe extended households, while such local eradication efforts would typically be undertaken on a province- or country-level. Modeling

vaccination campaigns – another common strategy – would require an additional "immune" compartment; otherwise, the analysis would proceed in the same way.

4.3 Importance of the cost structure

Even with our very simplistic assumptions of progress toward eradication made through nicely parceled one-time investments, relatively minor uncertainties about how costs increase can result in a substantial factors in the estimation of the total investment necessary 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 be much less clear, resulting in a lot of uncertainty in the final estimate of the eradication tail, and therefore a lot of uncertainty in the assessment of the current state and the remaining effort. Our analysis thus highlights the need to understand and estimate the cost structure of eradication measures as precisely as possible.

4.4 Conclusion

We have disentangled the epidemiological, evolutionary, and economic determinants of the eradication tail. 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 also clearly demonstrates that the overall shape of eradication tails, on which assessments of progress and remaining effort are based, is strongly influenced by the cost structure of the eradication measures and distribution of interventions over time. Modeling endgame scenarios thus requires a thorough understanding not only of the 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, analyses of this sort can become a valuable tool to support eradication plans.

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Tables

Table 1 **Patch transitions and their rates.**

Event	Affected	Patch state change	Per capita transition rate
Dynamics involving only susceptible ("s") hosts			
Death	s	$s \to s-1$	d
Birth	s	$s \to s+1$	$b\max(0,1-N/K)^{\dagger}$
Emigration	s	$s \to s-1$	m
Immigration	s^{*}	$s \to s+1$	e
Dynamics involving hosts infected with the resident strain ("i")			
Death	i	$i \to i-1$	$d+\alpha$
Birth	i	$s \to s+1$	$b\max(0,1-N/K)^{\dagger}$
Emigration	i	$i \to i-1$	$m\mu$
Immigration	i^{*}	$i \to i+1$	e
Infection	s	$s,i \to s-1,i+1$	$c\beta(i/N)^{\dagger}$

Recovery	i	$s, i \to s+1, i-1$	γ

Dynamics involving hosts infected with the mutant strain ("j")

Death	j	$j \to j-1$	$d+\alpha$
Birth	j	$s \to s+1$	$b\max(0,1-N/K)$ †
Emigration	j	$j \to j-1$	$m\mu'$
Immigration	j *	$j \to j+1$	e
Infection	s	$s, j \to s-1, j+1$	$c\beta'(i/N)$ †
Recovery	j	$s, j \to s+1, j-1$	γ

† In which N is the total patch occupation.

* Disperser pool compartment.

Table 2 **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	$0.1-10$ *
Patch encounter rate	e	100
Step factor	f	$0.9, 1.1$ *
Cost increase	y	$5\%, 10\%$ *

* Ranges shown in figures.

Figures

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

Figure 2 **Eradication tails depend on how the extinction threshold is approached.** Panels show the incidence level L_{evo} for three different values of the marginal mobility loss ε (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 extinction. Other parameters: $K = 15$, $d = 1$, $b = 5$, $e = 100$, $\alpha = 2$, $m = 0.5$.

Figure 3 **Pathogen evolution counteracts eradication measures.** Panels show the difference in incidence levels with and without pathogen evolution, $L_{\text{evo}} - L_{\text{noevo}}$, for three different values of the marginal mobility loss ε (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 pathogen is the evolutionarily stable infectivity on the far side of the extinction threshold (where the difference consequently equals 0). The incidence level caused by the evolving pathogen at first decreases as the extinction boundary is approached through increasing recovery rate, decreasing contact rate, or decreasing migration rate. Parameters as in Fig. 2.

Figure 4 **The cost structure of eradication measures strongly shapes eradication tails.** In practice, eradication tails are observed as a function of time, although they are really a function of cumulative investments into eradication measures. For the three approaches to the extinction boundary and the three trade-off shapes (defined by their marginal mobility loss ε, the negative slope of the trade-off function at $\beta = 1$) also shown in Figs. 2 and 3 (columns), panels show the incidence level as a function of investment into eradication, under the assumption that costs for each subsequent intervention toward extinction (subsection 2.3) 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 investment needed for eradication. Other parameters as in Fig. 2.

4. Figure 1

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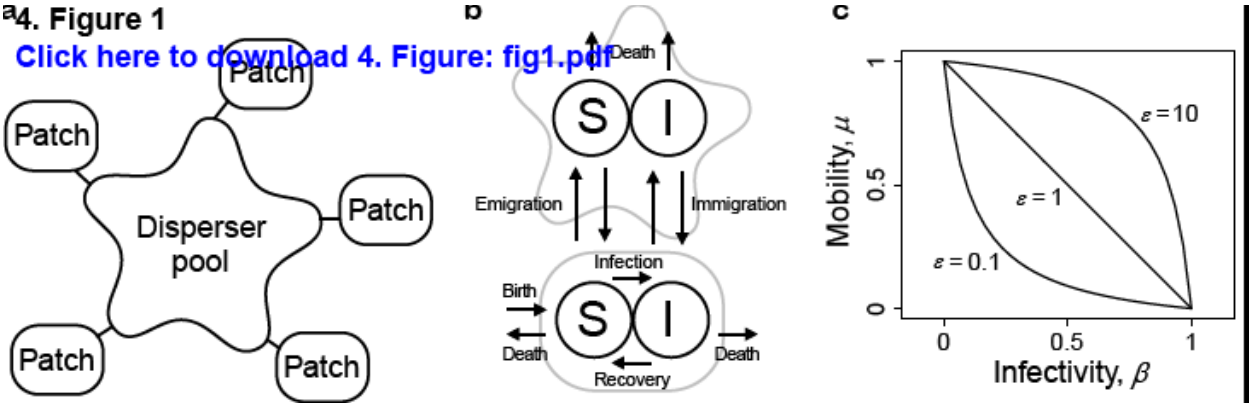

4. Figure 2

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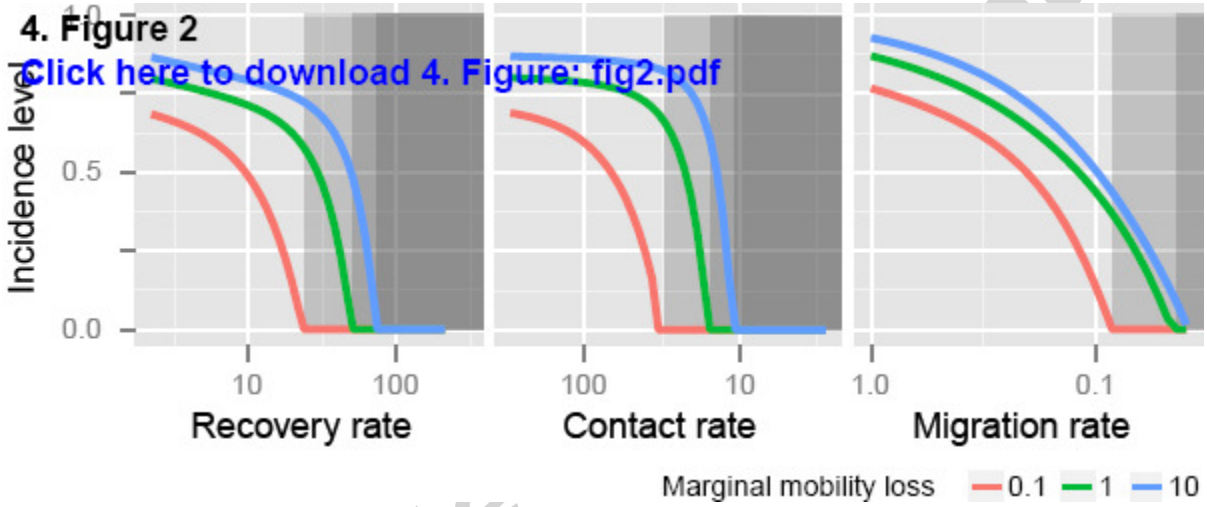

4. Figure 3

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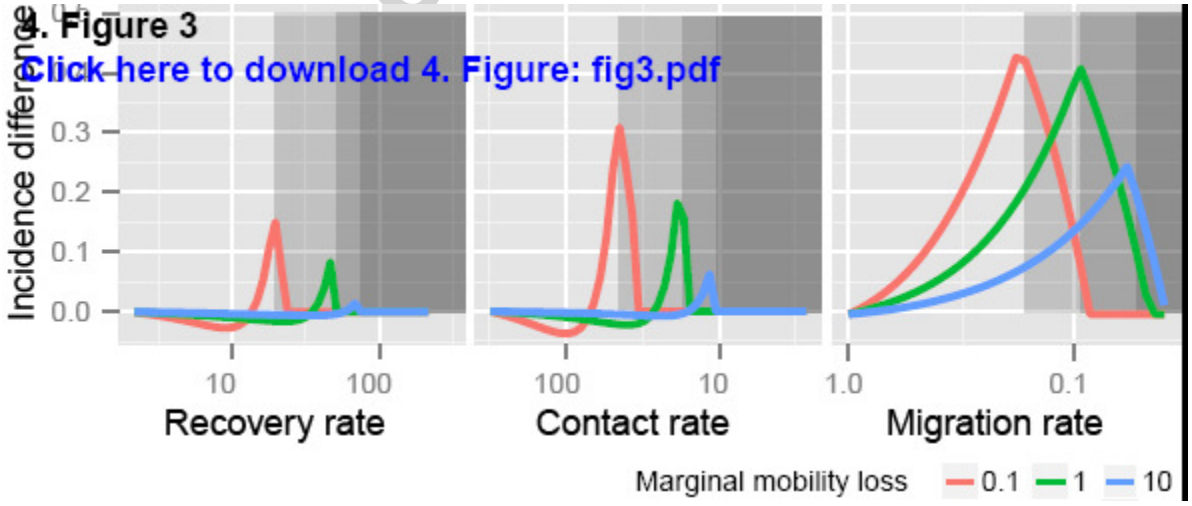

4. Figure 4

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