8

Virulence on the Edge: A Source–Sink Perspective

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8.1 Introduction

A recognition of spatial processes can be found even in the earliest glimmerings of intellectual understanding of the parasitic origin of infectious disease. As described in Ewald (1994a, p. 184), the Renaissance thinker Girolamo Fracastoro hypothesized that disease-specific germs could multiply within a person's body and be transmitted either directly over short distances, or over long distances (e.g., via contaminated objects). In recent years, a number of authors have emphasized how many epidemiological phenomena cannot be understood without explicitly considering infectious processes in a spatial context (e.g., Holmes 1997). There are several general issues that arise automatically when spatial aspects of the dynamics of infectious disease are considered. For instance, if infections are localized, spatial separation increases the degrees of freedom of a host–parasite system, permitting a rich array of dynamical behaviors to arise even in a spatially homogeneous world (e.g., Hassell *et al.* 1994). Moreover, spatial heterogeneity is the norm rather than the exception in ecological systems (Williamson 1981). Dispersal often couples habitats that differ strongly in local population parameters (e.g., carrying capacity), or involve anisotropic spatial flows. This leads to the potential for asymmetries among habitats in the degree of the impact of spatial coupling on local ecological and evolutionary dynamics.

In population ecology, an example of such asymmetries that has received considerable attention in recent years is "source–sink" dynamics. In these, in some habitats ("sinks") a species may persist despite a demographic deficit (with local births less than local deaths), because of immigration from "source" habitats (Box 8.1; see also Holt 1985; Pulliam 1996; Dias 1996). Sink populations may readily arise at the edges of species' ranges, or where habitats that differ greatly in productivity are juxtaposed. Given that genetic variation is present, natural selection might be expected to improve the ability of a species to utilize the sink habitat. Other chapters in this volume point out the potential for a rapid evolution of virulence in host–pathogen systems. However, recent theoretical studies suggest that there can be substantial constraints on adaptive evolution to conditions in sink habitats, leading to a kind of evolutionary conservatism in spatially heterogeneous environments (Bradshaw 1991; Brown and Pavolvic 1992; Kawecki 1995; Holt 1996; Holt and Gomulkiewicz 1997; Kirkpatrick and Barton 1997; Gomulkiewicz *et al.* 2000). Management practices that tend to foster such conservatism (for the

Box 8.1 Source and sink habitats in population biology

All naturalists know that species tend to be variable in abundance through space, being common in some places, rarer in others, and totally absent in yet others. Spatial variation in abundance can arise in part from chance, but most often reflects real spatial variation in habitat quality (including the abundance of other species such as competitors and predators). Such variation persists over time and can be quantified by ecologists (for example, variation in soil nutrient supply can underlie variation in plant seed production). Movement of individuals reshuffles abundances among different habitats and can obscure the influence of local demographic rates (births and deaths) on local abundances. This is particularly the case when there are sources and sinks, which have been the focus of much recent attention in population biology (Pulliam 1988; Holt 1993; Dias 1996).

A "sink" in common parlance is a "place where things are swallowed up or lost" (*Oxford English Dictionary*). As the coin of biological success is to leave successful offspring in future generations, a sink habitat is one in which residents on average do not quite replace themselves, because local deaths exceed local births. What is "lost" in a sink is the ability of individuals to have descendants into the indefinite future in that local environment. If a population is to persist at equilibrium in a sink, local losses must therefore be replenished by immigration from elsewhere and, in particular, from source habitats, where local births exceed local deaths.

Two general mechanisms can readily lead to a source–sink structure in population dynamics: passive dispersal or diffusion in heterogeneous landscapes (Holt 1985), and interference competition (e.g., territoriality) in high-quality habitats (Pulliam 1988). In general, movement that has a random component or is positively density-dependent (i.e., greater movement rates at higher densities) tends to move individuals down abundance gradients, increasing population size in low-quality or marginal habitats. In some situations ("true sinks"), births do not match deaths at any density, and therefore extinction is inevitable in the absence of immigration. A convincing example of a true habitat sink is provided by Keddy (1981), who found that interior dune populations of the seaside annual plant *Cakile edentula* would have become extinct in the absence of the wind-deposited seeds produced on the seaward edges of the dunes; at all densities, local seed production did not permit replacement of annual losses. In other situations, populations can persist without immigration, but only at a low carrying capacity; immigration from habitats with higher carrying capacity tends to push population size above these low numbers, and because of density-dependence local deaths then exceed local births at the higher equilibrium abundance induced by immigration. Watkinson and Sutherland (1995) refer to such habitats as "pseudosinks," because immigration is not absolutely required for population persistence. Thomas *et al.* (1996) and Boughton (1999) describe a complex spatial system for Edith's checkerspot butterfly, *Euphydryas editha*, in the Sierra Nevada of California, USA, including pseudosinks. In the pseudosinks, sufficient host plants are present to permit population persistence, but immigration from source populations inflates

continued

Box 8.1 *continued*

the local abundance of butterflies above carrying capacity. This leads to intense competition for host plants, such that individuals do not tend to replace themselves. (In addition to the pseudosinks, the system also contains true sinks, in which host plants are too rare or ephemeral to support a butterfly population in the absence of immigration.)

Ascertaining whether or not a given habitat is a sink is also important in evolutionary analyses as exemplified by the models discussed in the main text. More general theoretical studies (e.g., Gomulkiewicz *et al.* 1999, Holt 1996, Holt and Gaines 1992, Holt and Gomulkiewicz 1997, Kawecki 1995) further highlight how demographic constraints can hamper or even prevent natural selection from improving adaptation to sink environments. This is a phenomenon of general importance in evolutionary biology, for instance in understanding evolutionary dynamics at the edges of species' ranges, or understanding switches between host species (which can be viewed as distinct "habitats") by herbivores or pathogens.

pathogen) or weaken it (for the host) may help mitigate the long-term potential for highly virulent infectious diseases to evolve.

There is a rich and growing theoretical and empirical literature on the evolution of virulence (e.g., Anderson and May 1982; Bull 1994; Lenski and May 1994; Frank 1996c; Lipsitch *et al.* 1995a; Van Baalen and Sabelis 1995a), which focuses largely on how virulence reflects the balance of selective forces operating at different levels (within-host competition, and between-host transmission; e.g., Mosquera and Adler 1998; Koella and Doebeli 1999). The study of the interplay between gene flow and selection as determinants of local adaptation is, of course, a classic problem in evolutionary genetics (e.g., Antonovics 1976; Endler 1977; Nagylaki 1979). Yet few studies focus explicitly on the potential implications of source–sink dynamics for our understanding of the evolution of virulence and resistance (for an analysis of comparable issues in predator–prey coevolution along a gradient, see Hochberg and Van Baalen 1998). In a recent review Kaltz and Shykoff (1998) suggest that local adaptation by parasites to their hosts is often not observed, and they suggest this might arise from asymmetric gene flow in heterogeneous environments. This suggestion has particular force in systems with sources and sinks, which automatically contain asymmetric flows of individuals among habitats.

The organization of this chapter is as follows. First, as the motivation for theoretical studies we sketch several hypothetical examples that illustrate how, in principle, host–pathogen interactions of practical interest in human, animal, and plant epidemiology could match qualitatively the ecological assumptions of asymmetrical spatial flows that generate source–sink systems. We then present several models of evolution in which a source habitat is linked to a sink habitat, either for a host or pathogen, and discuss the initial stages of adaptation for a host–pathogen interaction in a sink habitat. The models are deliberately quite simple, but their

qualitative conclusions illuminate a much broader range of source–sink systems. Finally, we point out some potential conclusions of our results for applied evolutionary epidemiology.

8.2 Sources and Sinks: Pervasive in Host–Pathogen Systems?

Source–sink dynamics may be common in many important applied epidemiological situations. The three situations described next are hypothetical, but we believe quite plausible.

1. An organic farmer is attempting to grow corn (an annual plant) in an environmentally responsible manner, and so uses no pesticides or fungicides. The crop is generated from retention of some seeds from the previous year's production, supplemented by purchases from a commercial seed company. A fungal blight is present in the field and is reducing crop yield. Ideally, the farmer would like to develop a local strain that could be resistant to the blight. This goal implicitly involves the evolution of resistance in the host to a resident blight; the pathogen could either be a specialist on corn and so dynamically responsive to the corn crop itself, or a generalist that inflicts many local species, and so less tightly coupled to the corn. The farmer would like to know how many seeds she should retain, so as to balance the long-term goal of fostering local adaptation by her corn population to the blight, against the shorter-term economic goal of maximizing seed yield. What should a population biologist tell her?
2. A group of ranchers husband cattle on ranches, where the cattle usually range at low densities. The livestock carry a pathogen, which is usually benign as measured by its effect on mortality and morbidity. However, in recent years the practice has arisen to ship the cattle from different ranches to a common feedlot, to be fattened before being sent off for slaughter. Should these ranchers be concerned at all about the emergence of a more serious disease from the historically benign pathogenic infection, arising because of the admixture of different herds?
3. Doctors managing a large nursery ward are concerned with the potential for outbreaks of serious neonatal diarrheal diseases. These doctors are aware that in human epidemiology many bacterial species that are usually maintained in human populations in a relatively benign form can develop virulent forms in hospitals or other institutional settings (Ewald 1994a). For instance, *Escherichia coli* can lead to diarrheal diseases in hospital nurseries, despite being an innocuous component of the gut microflora in most people. Ewald (1994a) has argued that this localized evolution of virulence in institutional settings reflects the evolution of specific virulent strains of the bacterium in hospital wards. Presumably, attendants, parents, and visitors to wards all carry the benign community strain, out of which the virulent strain has evolved. What general conditions characterize the evolution of locally adapted bacterial strains in these situations? Should the doctors minimize visits by parents to their babies, or focus on other management procedures in the hospital environment?

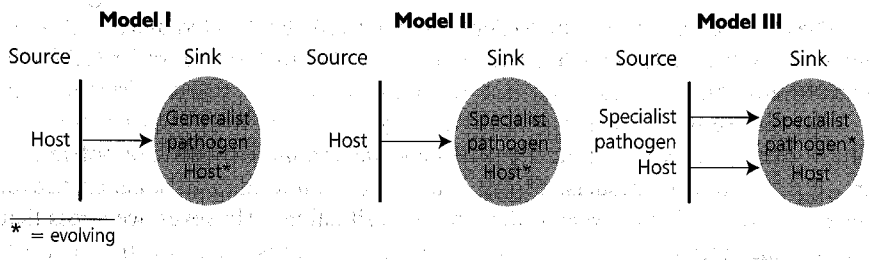

Figure 8.1 Three evolutionary models of source–sink populations discussed in this chapter. In Models I and II, the host in the sink adapts, respectively, to a generalist or to a specialist pathogen. In Model III, the pathogen in the sink adapts to its host.

In the first of these situations, the practical issue is to develop management practices that foster the evolution of reduced susceptibility to infection in the host. In the second and third situations, the focus is on how to prevent evolution toward greater virulence in a local population of the pathogen. What unifies these three situations is that they all involve spatial dynamics (in the broad sense of mixing together individuals drawn from distinct populations); depending upon the quantitative details, these scenarios could involve a source–sink structure for either the host or pathogen. Recent theoretical studies on adaptive evolution in sink environments (e.g., Kawecki 1995; Holt 1996; Gomulkiewicz *et al.* 2000) suggest management practices that could reduce the likelihood of the evolution of a virulent, locally adapted strain of pathogen, or enhance the evolution of resistance in the host.

8.3 A Limiting Case: Two Coupled Patches

Imagine that a host–pathogen interaction exists in a landscape with two distinct habitat patches. Spatial flows of individuals and heterogeneity in local demographic properties are assumed to generate a strong asymmetry, such that ecological and evolutionary dynamics in one habitat are strongly influenced by coupling with the other habitat, but without a marked reciprocal effect. We consider, in turn, three models that correspond to the three situations schematically depicted in Figure 8.1. In the first model, the source contains the host alone (effectively, in a refuge from the parasite), whereas the sink has both the host and pathogen. The pathogen is a generalist, so its dynamics are decoupled from the focal host species. Only the host disperses from the source into sinks. In the second model, we also assume the host flows from source to sink, but now the pathogen is a specialist with a dynamical response, such that the realized level of infection depends upon local host dynamics. For these two models, we examine the evolution of resistance of the host to infection. In the third model, we assume that both habitats contain the host and pathogen. However, there is cross-habitat infection, with infected individuals in the source infecting healthy individuals in the sink. For this model, we examine evolution of virulence of the pathogen in the sink habitat.

These models are not meant to duplicate faithfully the detailed dynamics of the hypothetical examples sketched above, but instead to illustrate more broadly how source–sink dynamics can lead to constraints on the evolution of virulence and resistance. We believe the simple models explored below capture some essential features of the above hypothetical situations, and are limiting cases of potentially much more complex models. Models I and II pertain to the first situation above, whereas model III is relevant to the other two situations. However, we stress that specific management suggestions for the evolution of resistance require detailed, empirically validated demographic models for the specific systems in which the evolution is occurring. The models below are strategic tools to help highlight broader issues, rather than tactical models directly useful in the development of policy decisions.

Simplifying assumptions

We make a number of simplifying assumptions at the outset. With respect to genetics, we assume haploid or clonal variation, and that the source population is fixed and is not itself evolving (relaxing these genetic assumptions does not fundamentally alter our basic conclusions; Gomulkiewicz *et al.* 2000). With respect to basic ecology, we assume that the host exhibits continuous generations, and that any direct density-dependence in the sink is dominated by the effects of the pathogen. Further, to simplify the many potential ramifications of virulence, we make a number of assumptions about basic epidemiology: once a host is successfully infected so that it itself is infectious, it cannot be super- or multiply-infected; and infected hosts do not recover, do not give birth, and remain infectious until removed from the population. In future work, it will be important to relax these simplifications.

Evolution of the pathogen can, of course, influence virulence, for instance if a higher transmission rate from infected hosts leads to a higher death rate (Frank 1996c). At first glance, because we assume infected hosts do not recover, it might seem that host evolution has no impact on virulence evolution. We suggest that a more subtle view may be appropriate. With no potential for host recovery, host evolution in response to the pathogen is related to the likelihood of successful infection in the first place and to the production of infected host individuals who themselves are infectious. The transmission parameter β at the heart of a standard epidemiological model defines the rate at which susceptible hosts themselves become infective. As a result of the deleterious effects of infection upon fitness, it is reasonable to assume that selection on the host tends toward a lower β value, all else being equal. This could happen either through effective avoidance of initial infection, so the host individual is not penetrated by the pathogen at all, or because of rapid host defenses that (when successful) reduce the pathogen titer quickly to trivial levels within the host body. By contrast, hosts whose defenses fail may continue to carry a high pathogen load, and so be infectious to other hosts (viz., be counted in the infectious class). Selection through host defenses could increase the frequency with which some hosts recover so rapidly that they, for all practical purposes, remain uninfected. If virulence is measured by assessing the average

fitness across all hosts carrying the pathogen, including those whose successful defenses are reducing the pathogen titer toward extinction, selection on hosts can clearly influence the mean realized virulence experienced in the host population.

We first consider the evolution of a focal host species, immigrating into a habitat where it faces a genetically fixed pathogen. Let S be the density of the immigrant (= ancestral) host type in the sink habitat, S_{mut} the density of a novel type, and I the density of infected hosts. We consider in turn two distinct kinds of pathogen dynamics, and for each derive conditions for the initial increase of host alleles favored in the sink. We then turn to a situation in which infections of hosts in one habitat arise because of pathogens maintained in a source habitat, and examine evolution in the pathogen.

Model I: Host evolution in a sink with generalist pathogen

Here, we assume that the pathogen is maintained by alternative hosts, and that the density of infected hosts is, to a reasonable approximation, fixed at I. In our corn example, the pathogen might be a fungal blight sustained by grass species in pasturelands surrounding the field. In this case, we are not concerned with pathogen persistence. Let b be the intrinsic birth rate of the host, and d its death rate in the absence of the pathogen, so that $r = b - d$ is the focal host species' intrinsic growth rate. We assume that healthy hosts immigrate at a constant rate H, and that infection from the resident infected alternative hosts is described by a mass action law, parameterized by β, a transmission rate. The evolution of virulence is governed by evolution in β.

The dynamics of the immigrant susceptible host in the sink habitat are described by

$$\frac{dS}{dt} = rS - \beta SI + H \,. \tag{8.1}$$

When r is sufficiently greater than 0, the habitat is not a sink at all. In this case, the focal host species should increase in abundance when rare, and eventually Equation (8.1) no longer characterizes its dynamics adequately (e.g., direct density-dependence should become more important). We assume here that this is not the case, but instead that the habitat is a demographic sink.

There are two basic ecological situations that can lead to a sink for the host. First, one might have $r < 0$, that is, the habitat is an *intrinsic* sink, regardless of the presence of the pathogen. Second, one could have $0 < r < \beta I$. In this case, it is the presence of the pathogen itself, at sufficient abundance, that creates the sink habitat for the host; the sink condition is *induced* by the infectious disease agent. As we show, the potential for adaptive evolution of the resistance by hosts to infection is profoundly different in intrinsic than in induced sinks.

We now consider the fate of a novel allele arising in the sink, which is *not* part of the immigrant stream. Assume that the novel mutation experiences a lower infection rate, $\beta_{\text{mut}} < \beta$. Moreover, assume that $r_{\text{mut}} = r$, so there is no cost associated with this lowered rate of infection. Clearly, the novel type has a higher

relative fitness than the immigrant type in the sink environment. But will it be retained by evolution?

The dynamics of the novel type are described by

$$\frac{dS_{\text{mut}}}{dt} = r_{\text{mut}} S_{\text{mut}} - \beta_{\text{mut}} S_{\text{mut}} I \,. \tag{8.2}$$

In an intrinsic sink, we have $r_{\text{mut}} = r < 0$. It is immediately clear that, regardless of the magnitude of β_{mut}, S_{mut} tends toward 0. Thus, if the local habitat is a sink for the host even in the absence of the natural enemy, natural selection cannot retain alleles that increase host resistance (reduced rate of infection) to the pathogen, even if these alleles are cost-free. This implies that the likelihood of local adaptation by hosts to pathogens via the accumulation of locally favored mutations is greatly reduced in intrinsic sink habitats.

Alternatively, the sink may be induced by the pathogenic infection itself, such that $0 < r < \beta I$. A novel allele in the host can increase in abundance (and thus frequency) provided $r > \beta_{\text{mut}} I$. Hence, an allele with a sufficiently low susceptibility can successfully invade and convert the induced sink into a source. The minimum magnitude of the mutational effect (measured by the quantity $\Delta\beta = \beta - \beta_{\text{mut}}$) required for a decrease in transmission to be deterministically retained by evolution is $\Delta\beta = \beta - r/I$, where β is the transmission rate experienced by immigrant hosts. One can imagine that there is a distribution of mutational effects on β, centered on the transmission rate of the immigrant type. Mutants that arise with a higher β than the immigrant are, of course, selectively disfavored and should rapidly disappear. Mutants that have a very small effect upon transmission are not retained in the local host population, even though they have a higher relative fitness than immigrant hosts. If there is a cost to reduced susceptibility, so that $r_{\text{mut}} < r$, the threshold mutational effect required for a mutant with lowered susceptibility to be selected will exceed $\Delta\beta$.

We can therefore draw the following conclusions:

- Local adaptation of the host to the pathogen is less likely if productivity in the sink (r) is low, or if pressure from the pathogen (I) is high. This means, for example, that if $r_{\text{mut}} < r$ due to a cost associated with higher resistance in the mutant host, an even larger decrease in β is required, compared to the resident type, than without such a cost.
- At larger I, or smaller r, evolution occurs only if mutants with a sufficiently large effect arise.
- In intrinsic host sinks, evolution in the hosts toward reduced transmission rates is not expected at all.

What is the role of host immigration in this sink model? First, immigration from the source defines an ancestral condition, against which the effect of each new mutation is measured. Second, in this particular model, the rate of immigration does not directly influence conditions for the retention of novel, favorable alleles.

(Recall that the model assumes hosts do not directly compete; with direct density-dependence, high immigration rates can depress local fitnesses by increasing local population size, and thereby hamper local adaptation; Holt and Gomulkiewicz 1997.) A final effect not directly addressed in the above model (which focuses on the fate of single mutations) is that of immigration on genetic variation in sink populations (Gomulkiewicz *et al.* 2000). Higher rates of immigration can increase local population size of the host in the sink habitat, making it more likely that favorable mutants will arise. A larger immigration rate also provides a larger sample drawn from the variation available in the source. For these genetic reasons, larger rates of immigration might indirectly facilitate local adaptation to the sink habitat, by increasing the total amount of variation available for selection in the sink. Combining these distinct effects, the greatest scope for local adaptation to a sink habitat may be provided by intermediate rates of immigration from source habitats (Gomulkiewicz *et al.* 2000).

Model II: Host evolution in a sink with specialist pathogen

In model I, for simplicity we assumed that the abundance of infected hosts was fixed by alternative host species. We now assume that the pathogen is a specialist, maintained solely by the focal host, so that the magnitude of infection is a dependent dynamical variable of the interaction. A canonical model for basic host–pathogen dynamics (Anderson and May 1981) is

$$\frac{dS}{dt} = rS - \beta SI + H \,, \tag{8.3a}$$

$$\frac{dI}{dt} = \beta SI - \mu I \,. \tag{8.3b}$$

This is the usual SI model with an additional term for immigration by healthy hosts.

The parameter μ equals the sum of intrinsic host deaths d plus additional deaths due to the infection α, so $\mu = d + \alpha$. At equilibrium, $S^* = \mu/\beta$, and $I^* = r/\beta + H/\mu$. If $r < 0$, then we must have $H > |r|d/\beta$ for the pathogen to persist. In other words, a specialist pathogen must be sufficiently transmissible to persist in an environment that is an intrinsic sink for its host. Given that the pathogen persists, at equilibrium the habitat is always a sink (intrinsic or induced) for the host; the abundance of infected individuals rises until the negative growth rate of the host population just matches the rate of input from outside.

As before, the initial dynamics of a rare, novel mutation in the host are described by

$$\frac{dS_{\text{mut}}}{dt} = r_{\text{mut}} S_{\text{mut}} - \beta_{\text{mut}} S_{\text{mut}} I \,. \tag{8.4}$$

Here, I is the abundance of infected hosts, exerting a force of infection on the invading host type, but determined indirectly by the dynamics of the resident host. As before, consider cost-free mutations lowering disease transmission such that

$r_{mut} = r$, but $\beta_{mut} < \beta$. If the habitat is an intrinsic sink for the host ($r_{mut} < 0$), then S_{mut} tends to 0. Hence, as in model I, evolution does not promote local adaptation by the host to the pathogen, even if the pathogen is dynamically dependent upon that host. If, by contrast, the habitat is an induced sink for the host ($r_{mut} > 0$), then $dS_{mut}/dt > 0$ if

$$\beta_{mut} < \beta / \left(1 + \frac{H\beta}{r\mu}\right). \tag{8.5}$$

Host immigration H and local production r have similar ecological effects on the incidence of infection in the local population, as shown by the expression for equilibrium incidence, $I^* = r/\beta + H/\mu$. However, Equation (8.5) shows that these two parameters have diametrically *opposing effects* on local adaptation to the pathogen. Increasing the host intrinsic growth rate r increases the range of mutational effects on β that can be captured by selection within the local host population; by contrast, increasing the immigration rate H makes local adaptation more difficult.

This model leads to several interesting predictions regarding local adaptation by hosts to parasites in sink habitats. Local adaptation of hosts toward lower transmission rates for an infection is more likely for:

- Habitats with high host productivity (and is conversely particularly unlikely in intrinsic sinks);
- Habitats in which the pathogen initially has a low rate of transmission (low β);
- Habitats in which infected individuals are short-lived [high μ, which can arise from either high intrinsic death rates (high d) or a highly virulent pathogen (high α)];
- Unproductive source habitats (low H).

Host immigration indirectly increases pathogen abundance, and thus increases the magnitude of the mutational effect required to retain a novel host mutant with lower β. These predictions hold even if mutations that affect the rate of infection are cost-free for the host. Including such costs (i.e., assuming $r_{mut} < r$) makes local adaptation by the host to the pathogen more difficult. [Comparable results arise in predator–prey coevolution along gradients (Hochberg and Van Baalen 1998).]

Model III: Pathogen evolution in a sink

In models I and II, the host evolves, but the pathogen does not. We now look at a counterpart model in which the host–pathogen interaction occurs in both habitats, and evolution of pathogen transmission occurs in the pathogen population given unidirectional movement of the pathogen (or infected hosts) from a source to a sink habitat. This model schematically matches the feedlot and neonatal ward situations discussed earlier. The source habitat in these models is comparable to the notion of disease reservoirs in epidemiology (Anderson and May 1991). In the hypothetical example of the cattle feedlots sketched above, for instance, the source or reservoir could be a benign infection maintained in low-density, free-ranging cattle herds. In the sink, the dynamics of the infection itself are described

by

$$\frac{dI}{dt} = \beta_{\text{source}} I_{\text{source}} S + \beta I S - \mu I \,. \tag{8.6}$$

Here the term $\beta_{\text{source}} I_{\text{source}} S$ denotes the force of infection on healthy, susceptible hosts in the sink caused by infected individuals in the *source* (e.g., long-distance dispersal of infective propagules; alternatively, infected individuals could immigrate from the source at a fixed rate, and die or emigrate at a constant rate, in which case I_{source} denotes the equilibrium abundance of such individuals). For simplicity, we assume I_{source} is constant and that $S = K$, a constant (e.g., K could be host-carrying capacity, which is reasonable if the infection is initially very rare). By definition, the habitat is an intrinsic sink for the pathogen if $\beta K < \mu$, or $\beta < \mu/K$. We assume that the habitat is initially a sink for the pathogen (otherwise, the assumption that $S = K$ would be unreasonable). Biologically, three factors are likely to make a host population an intrinsic sink for an immigrating pathogen strain:

- The host is scarce (low K);
- Transmission rates are low (low β);
- Infected hosts have high death rates, either because hosts have intrinsically high death rates (high d), or the pathogen is highly virulent (high α).

As a result of external inputs, a pathogen can persist in a local host population that is intrinsically a sink with respect to local pathogen dynamics.

Imagine that a novel pathogen strain arises with a different rate of transmission and death rate (e.g., because of a correlation between virulence and transmissibility) than the immigrant type. When rare, this strain has dynamics described by

$$\frac{dI_{\text{mut}}}{dt} = \beta_{\text{mut}} I_{\text{mut}} K - \mu_{\text{mut}} I_{\text{mut}} \,. \tag{8.7}$$

The novel strain can increase provided $\beta_{\text{mut}} > \mu_{\text{mut}}/K$. Unlike the host models I and II presented above, in which there was no evolution on host resistance to transmission in an intrinsic sink, a sufficient increase in transmission in the parasite is always selected if it has no pronounced effects on virulence. If $\mu = \mu_{\text{mut}}$ (so no virulence costs are associated with increased transmission), a novel mutation will be successful only if it increases the transmission rate from β to β_{mut} by at least an amount $\mu/K - \beta$. All else being equal, novel strains in the parasite that provide a small increase in transmission are more likely to be favored if the host population is abundant than if it is scarce. Small increases in the transmission rate can be favored if infected hosts have low μ. If the host is an intrinsic sink for the pathogen, then either K is low, or μ is high. Evolution of the pathogen in a host habitat that is a sink for the pathogen thus occurs only if mutants that have a large effect upon transmission arise.

Now, consider a host–pathogen interaction in which there is a trade-off between transmission and virulence, such that increasing transmission translates into

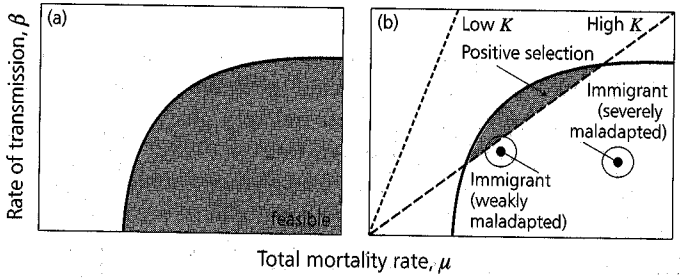

Figure 8.2 (a) A fitness set for a pathogen. Increased transmission to healthy hosts incurs the cost of higher mortality of infected hosts. (b) Evolutionary potential in a pathogen sink. For any pathogen allele to be favored, it must increase when rare (i.e., $\beta K > \mu$, where K is the abundance of the host). The dashed lines show the minimal configurations of β and μ that permit pathogen persistence at low host K and high host K. Given the available variation (which lies within the fitness set), no feasible pathogen genotype can persist (without immigration) in the low host K environment, so evolution there is impossible. In the high host K environment, some feasible genotypes permit persistence. If most mutants have a small effect, we can represent the immigrant genotype and available mutational variation as a dot at the center of a small cloud of available variation. If immigrants are severely maladapted, most mutants are likewise maladapted, and evolution of the pathogen does not occur. By contrast, if immigrants are only weakly maladapted, it is likely that mutants of modest effect will arise with positive growth, and hence will be retained by evolution.

greater host mortality. The shaded zone in Figure 8.2a represents all feasible phenotypes for the pathogen. In Figure 8.2b, the straight lines denote, for two different values of host K, combinations of β and μ that permit demographic persistence of a rare allele; for each case, pathogens with values of β and μ falling below the line are expected to go extinct. Immigrant types have a particular value of β and $\mu = d + \alpha$ (denoted by large dots in Figure 8.2b for two different possible cases corresponding to weakly and strongly maladapted immigrants). Mutants with a small effect may be more likely to arise than mutants that have a large effect (the circles around the dots indicate zones of likely mutational input in this phenotype space). At low K, given the array of possible pathogen phenotypes in the sink, no pathogen strain can increase when rare. In this circumstance, no evolutionary change in pathogen transmission (or virulence) would occur in the sink habitat. At higher K, it is feasible for some pathogen strains to invade, if the immigrant strains are not too badly maladapted to the host in the sink habitat.

This simple model suggests that if a pathogen is sustained by immigration into a given host population, which demographically is a sink for the pathogen, then local adaptation in rates of transmission and virulence are more likely if:

- The host population is abundant;
- The immigrant parasite strain is not too badly maladapted to the local host in the first place.

The effect of host abundance on the retention of parasite alleles leading to higher transmission suggests that pathogen adaptation is more likely in habitats that are favorable for hosts. Across a host species' geographical range, if host Ks are low near the range margin, these sites are unlikely places for local adaptation of the pathogen (see also Hochberg and Van Baalen 1998). If host abundances increase toward the range interior, pathogen adaptation should become increasingly feasible. (We caution that making precise geographical predictions depends upon knowing the detailed spatial texture of abundances, relative flux rates among habitats, and so forth, across the range.) Finally, if the host population in the sink is dynamically responsive to parasitism, a fuller analysis shows that increasing pathogen immigration from a source tends to depress the abundance of available, susceptible hosts in the sink, a demographic effect that reduces pathogen fitness. This suggests that increased pathogen immigration from a source can indirectly hamper local adaptation in the parasite in a sink, as measured in an adaptive balance between transmission and virulence. As this effect operates by a reduction in the availability of healthy hosts, it is unlikely to be of practical utility in managing the evolution of virulence.

Concretely, a more virulent pathogen strain is most likely to invade a sink habitat when:

- Mutations occur that confer a substantial difference between the immigrant and mutant pathogen strains. If most mutations tend to be small in effect, pathogens are not likely to be become locally adapted to hosts in sink habitats.
- Host density in the sink, K, is high. (With increasing K, the slope of a dashed line in Figure 8.2b decreases, increasing the feasible invasion space for more virulent pathogens.)
- The pathogen in the immigrant stream is low in virulence to begin with. (Again, invasion requires that the dynamic properties of the mutant be in the hatched parameter space of Figure 8.2a.)

The final message, therefore, is that evolution of virulence in habitats receiving inputs of pathogens depends on the initial transmissibility and virulence of pathogen streams from not-too-distant habitats. If a given pathogen is not approximately adapted to the sink habitat in the first place, so that for the pathogen the host in the sink habitat is a severe intrinsic sink, local adaptation is not likely to occur. The particular trajectory of evolution in a given focal habitat and, indeed, whether pathogen evolution is likely at all, depends on the intrinsic quality of local host populations and on the initial virulence of the immigrant pathogen strain.

8.4 On to Praxis

What practical advice do these theoretical ruminations suggest? Let us return to the three hypothetical situations sketched in the introduction, given that the simple, abstract models described above surely miss crucial details of concrete real-world situations. In particular, the assumptions made in the models about basic host population dynamics (e.g., continuous clonal growth, and no age or stage structure)

would have to be modified to match the complexities of the actual host species dynamics. However, these strategic models do help to highlight some general issues that practitioners should think about in managing the evolution of virulence and resistance.

Consider first the crop yield problem, in which the organic farmer wishes to develop a variety of an annual crop adapted to a blight resident in her field. One simple "rule-of-thumb" that the host evolution models (I and II) suggest is that local adaptation to a pathogen should not occur in a host that inhabits an intrinsic sink. What makes a habitat an intrinsic sink for an annual plant is simply the number of expected successful offspring an average individual leaves. The farmer can influence the "sink" quality of her crop by the magnitude of seed retention. In years of bad harvest it might be tempting to sell all or most of an entire meager crop, and to purchase seeds from a seed company for the following year. This is good economic sense, but removes any possibility of local adaptation to particular strains of the blight, because it makes the local habitat an intrinsic sink for the crop plant. Local adaptation obviously requires retention of locally recruited plants.

The model also suggests that if the blight is sufficiently serious for the crop not to be self-sustaining, any action taken to make it more self-sustaining (e.g., changes in cultivation practices that reduce the impact of the blight by lowering β, or increasing local fecundity, r) indirectly may facilitate adaptive evolution to the blight, by making it more feasible for mutants that have a smallish effect on fitness to invade the host population. One interesting issue, which goes beyond the particular model discussed above, is the magnitude of foreign (nonlocal) seed that should be introduced, and its genetic character. If the seed source is itself genetically variable, introduced seeds can provide a valuable source of novel genetic variation. However, if instead the seed source is genetically homogeneous (a far more likely scenario in this era of hybrid seeds marketed by giant agrobusiness firms), little evolutionary traction is provided by supplementation from external host sources, and external seeds may vitiate local adaptation by competition with resident, better-adapted plants (Gomulkiewicz *et al.* 2000).

The problem faced by our hypothetical cattle ranchers and neonatal pediatricians, by contrast, is to prevent the evolution of novel, virulent infectious diseases. The ranchers have a difficult problem. By pooling their livestock together in feedlots they in effect increase the size of the potential host populations, and because interindividual distances are shorter, pathogen transmission is likely to be easier. Conditions here seem ripe for the evolution of a more virulent form of the benign pathogen brought in from the range, along with the cattle. The only model parameter open for manipulation appears to be d, the removal rate of infected hosts. The intrinsic "death" rate of an animal in the feedlot is likely to be determined by the amount of time required for sufficient fattening before being sent off for slaughter; this is governed by market requirements and other factors, largely out of the ranchers' control. The one remaining parameter is α, the additional rate of death or removal an animal incurs upon infection. The ranchers already have an obvious incentive to remove infected animals whenever encountered, namely to

reduce the rate of infection of still healthy individuals. In addition to the direct ecological benefit of quick removal of infected hosts, our theoretical results help highlight an additional evolutionary benefit of this practice – it may make it harder for the immigrant pathogen to evolve a more virulent strain in the first place. Thus an even higher premium is now placed upon earlier detection, and removal, of infected animals. It would behoove the ranchers to invest in diagnostic procedures to facilitate this task.

There is a similar problem in the hospital neonatal ward – the enhanced risk of infection posed by parental visits to their babies and by other hospital procedures. With respect to the evolution of self-sustaining hospital strains, parental visits provide a source of variation for pathogen evolution. By contrast, hospital management practices can determine the selective fate of novel pathogen strains. Minimizing contact among infants (including contacts via indirect channels such as hospital personnel who come into contact with numerous infants) reduces transmission rates. The economies of scale that lead to the creation of large homogeneous wards for a given class of patients, such as suites for neonates, automatically creates a long-term evolutionary risk. Likewise, managing care so as to reduce the length of hospital stays in effect increases μ, the depletion rate of infected infants. Managed care plans in the USA today, for crass economic reasons, often reduce patient stays to the barest minimum. Though bad for any individual patient, unwittingly this practice may eventually benefit patients as a class, by reducing the chances of evolution of virulent pathogen strains adapted to the hospital environment. Both reducing transmission rates among patients (e.g., reducing β by creating multiple small wards with few patients, or attempting to reduce assiduously routes of contact among patients) and decreasing hospital stays (e.g., increasing the parameter μ) in effect turn hospital wards into sink habitats for invasive pathogens, and make the evolution of locally adapted, possibly more virulent strains, a more difficult evolutionary hurdle for the pathogen.

Concern is growing about emerging diseases for which the evolutionary origins are in species other than humans and domesticated species (Ewald 1994a). A simple message of the above models is that the demographic context of the initial stages of contact with novel hosts may be crucial in predicting emergence. If the demographic context is that the novel hosts are sinks for pathogens invading from another species, then adaptation by the pathogen to the host requires mutants of large effect; if such genes are rare, the emergence of the disease as a serious problem may be unlikely. The epidemiological goal of preventing a self-sustaining infectious disease in a novel host thus has the useful side-effect of precluding adaptive transformation in the disease agent.

8.5 Discussion

Many of these suggestions about management are commonsensical, and involve practices that are useful in reducing disease incidence even without considering host–pathogen evolution. In general, the emergent infectious diseases of greatest public health concern may not be those that are initially the most devastating to

their individual hosts, and acquired mainly by recurring infection from alternative reservoir hosts, but instead any novel disease that can, with relatively little modification, become self-sustaining in the focal host species of interest.

If managing the evolution of virulence in pathogens is to become seriously integrated into public policy in agriculture, husbandry, and medical practice, it must be recognized that the direction of evolution in host–pathogen systems can be profoundly influenced by the direction and magnitude of spatial flows in heterogeneous environments, and that such flows often involve sources and sinks. Sophisticated management of the evolution of virulence can exploit the evolutionary impact of asymmetric spatial flows. As John Donne once famously remarked "No man is an island"; doubtless, our pathogens would agree.

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