Diversity and the maintenance of sex by parasites

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The Red Queen hypothesis predicts that parasite-mediated selection will maintain sexual individuals in the face of competition from asexual lineages. The prediction is that sexual individuals will be difficult targets for coevolving parasites if they give rise to more genetically diverse offspring than asexual lineages. However, increasing host genetic diversity is known to suppress parasite spread, which could provide a short-term advantage to clonal lineages and lead to the extinction of sex. We test these ideas using a stochastic individual-based model. We find that if parasites are readily transmissible, then sex is most likely to be maintained when host diversity is high, in agreement with the Red Queen hypothesis. If transmission rates are lower, however, we find that sexual populations are most likely to persist for intermediate levels of diversity. Our findings thus highlight the importance of genetic diversity and its impact on epidemiological dynamics for the maintenance of sex by parasites.

Introduction

Understanding why organisms reproduce sexually is one of the most fundamental challenges in evolutionary biology. Given that asexual lineages do not produce males and thus have higher *per capita* rates of reproduction than sexual populations, asexuals should rapidly replace sexuals, if all else is equal (Hamilton, 1980; Bell, 1982). The predominance of sex among eukaryotes indicates that there must be ecological or genetic factors that offset the reproductive advantage of asexuals (Williams, 1975; Maynard Smith, 1978).

A prominent theory for the maintenance of sexual reproduction is the Red Queen hypothesis (RQH) (Hamilton, 1980; Bell, 1982). The RQH predicts that sex is advantageous in the presence of coevolving antagonists, as recombination and segregation generate offspring with novel gene combinations that on average have a higher fitness than clonal lineages (although this advantage may be periodic, see Vergara et al. 2014). Conditions are most likely to favour sex when parasites induce negative frequency-dependent selection, as sex facilitates the production of rare genotypes that tend to be more resistant to contemporaneous parasites (Hamilton, 1980; Hamilton *et al.*, 1990). Yet, coevolving parasites favour the maintenance of host genetic diversity, not sex *per se* (King *et al.*, 2011). This leads to the expectation that any advantage sex gains from genetically variable progeny may be reduced upon the invasion of multiple clonal lineages (Lively & Howard, 1994; Lively, 2010a). However, the extent to which contrasting levels of genetic diversity in sexual and asexual populations affects the maintenance of sex is not yet clear.

A key assumption of most theoretical models of the RQH is that the size of the host and parasite populations remain constant, so that dynamics are dependent on the frequency, but not the density, of each genotype (table 2; although see e.g. May and Anderson 1983; Lively 2010b; Ashby and Gupta 2014). Thus, changes in host diversity do not negatively affect parasites. However, more realistic models that incorporate density-dependent processes (i.e. ecological feedbacks) predict that host genetic diversity reduces the overall prevalence of

disease, as parasites are less likely to come into contact with compatible hosts (Lively, 2010c; King & Lively, 2012). Conversely, reducing host genetic diversity should increase disease prevalence, as parasites are less likely to encounter resistant hosts. The underlying idea, known as the monoculture effect, is well-documented in agricultural studies and is supported by direct empirical tests of the phenomenon showing that lower host diversity facilitates disease spread (Altermatt & Ebert, 2008; Ganz & Ebert, 2010). In the context of the RQH, high levels of diversity in sexual populations may reduce parasite prevalence and tip the balance in favour of asexual reproduction in the short-term. This temporary advantage may be sufficient for sex to be driven extinct before parasites adapt to the dominant clone. Hence, we predict that intermediate levels of diversity may be optimal for the maintenance of sex.

Here, we use a stochastic individual-based model to explore the relationship between genetic diversity and the maintenance of sex. We find that sexual populations perform poorly compared to invading asexual lineages when diversity is low and are much more likely to persist when diversity is greater, provided parasites are readily transmissible. However, a turning point occurs when transmission is poor, such that parasite prevalence is substantially reduced at higher levels of genetic diversity. As a consequence, the net benefit of asexual reproduction is temporarily restored and sex is often lost from the population.

Models

Qualitative prediction

Lively (2010c) showed that the probability of an epidemic varies inversely with the genetic diversity of the host population. We briefly reformulate this result in terms of the standard susceptible-infectious (SI) epidemiological model consisting of G host genotypes, each with a unique (matching) pathogen:

$$\frac{dS_i}{dt} = b(S_i + I_i) - \beta_i S_i I_i - \mu S_i \quad (1)$$

$$\frac{dI_i}{dt} = \beta_i S_i I_i - (\alpha + \mu) I_i \quad (2)$$

where S_i and I_i are the proportions of the population that are susceptible or infectious and belong to genotype i, α and μ are the disease-associated and natural mortality rates, β_i is the transmission rate for genotype i and b is the *per capita* birth rate. The average number of secondary infections in a completely susceptible population of genotype i is given by:

$$R_{0i} = \frac{\beta_i}{\alpha + \mu} \quad (3)$$

To explore the effects of host genetic diversity on disease spread, we set $\beta_i = 0$ for all $i > 1$, so that only one host genotype experiences infection. We also keep the population size constant $\sum S_i + I_i = 1$ using $b = \alpha \sum I_i + \mu$ and set the initial abundance of susceptible hosts to $S_i = 1/G$ for all genotypes. For an epidemic to occur equation (2) must be positive, which requires $S_i > 1/R_{0i}$. Hence, the disease does not spread when $G > R_{0i}$ and no epidemic occurs. Moreover, increasing the number of host genotypes up to this threshold reduces the size of the epidemic (figure 1). This simple model demonstrates that greater host genetic diversity reduces the prevalence of disease and can drive infectious agents extinct, which has important implications for the maintenance of sex.

The RQH posits that sexual populations can offset the cost of males by producing genetically diverse offspring that are better than asexual individuals at avoiding contemporaneous parasites. However, this simple model shows that increasing genetic diversity suppresses parasite prevalence, which will inevitably reduce the advantages of sex. In other words, asexual lineages benefit from an overall reduction in parasite prevalence caused by high diversity in the sexual population, but do not have to pay the cost of producing males. Very high parasite prevalence should also select against sex, as the probability of avoiding infection is low. For example, if resistance is only beneficial for a short time (e.g. due to low diversity or rapid adaptation by parasites), then sex is likely to remain costly. We therefore predict that sex should peak when parasite prevalence is at intermediate levels (figure 2).

Further, high diversity should select against sex if there is a sufficient reduction in parasite prevalence. We test these predictions using a stochastic individual-based model (IBM).

Simulation design

We simulate the invasion of asexual hosts into sexual populations in the presence of coevolving parasites (see table 1 for a summary of the model variables and parameters). All hosts are diploid with haplotypes that each consist of n biallelic loci. Parasites are haploid with n biallelic loci and can only infect hosts that possess a matching haplotype (i.e. matching alleles specificity, see e.g. Ashby and Gupta 2014). Hosts are classed as either susceptible (S_{ij}^k) or infectious ($I_{ij,m}^k$), where i and j correspond to host haplotypes, k to host type (asexual: $k = a$; sexual: $k = s$) and m to the parasite haplotype with which hosts are infected. The total population size is $N = N_a + N_s$, where $N_k = \sum_{ij}(S_{ij}^k + \sum_m I_{ij,m}^k)$ is the number of hosts of type k. Offspring with haplotypes i and j are produced at a rate of b_{ij}^k. For simplicity, we assume that the sexual birth rate is limited by the number of females, such that:

$$b_{ij}^s = c_b r F_0 \left(M_i F_j + M_j F_i\right)(1 - h_b N) \tag{4}$$

where M_i and F_i are the proportion of male and female gametes in the population that belong to haplotype i (similarly for haplotype j), F_0 is the total number of sexual females in the population ($b_{ij}^s = 0$ if no males are present), h_b modifies the strength of density-dependence and the parameters c_b and r control the maximum birth rate for sexuals. The parameter c_b corresponds to additional costs (e.g. inability to find a mate, $c_b < 1$) or benefits (e.g. shared parental care, $c_b > 1$) of sex with respect to fecundity. On average, there is a twofold cost of sex when $c_b = 1$ (due to the presence of males). Recombination occurs independently between each pair of adjacent loci at a rate of $\rho_0 = 1 - (1 - \rho)^{(1/n)}$, where ρ is the overall rate of recombination. This keeps the underlying rate of recombination constant for all values of n.

The birth rate for asexuals is given by:

$$b_{ij}^{a} = rA_{ij}(1 - h_b N) \tag{5}$$

where $A_{ij} = S_{ij}^{a} + I_{ij,i}^{a} + I_{ij,j}^{a}$ is the number of asexuals with haplotypes i and j. The *per capita* birth rate of sexuals compared to asexuals is therefore:

$$\frac{\sum_{ij} b_{ij}^{s}/N_S}{\sum_{ij} b_{ij}^{A}/N_A} = \frac{c_b F_0}{N_S} \tag{6}$$

which recovers the twofold cost of sex when $c_b = 1$ and the male-female sex ratio is equal. Each asexual genotype immigrates at a rate of $\zeta \,/\, g$, where ζ is the overall immigration rate and g is the number of potential host genotypes (i.e. each asexual genotype enters the population with a fixed probability per unit time).

Hosts experience a force of infection of $\lambda_i + \lambda_j$, where

$$\lambda_i = \frac{1}{2}\left(\beta(1-\varepsilon)\sum\nolimits_{k,p} I_{ip,i}^{k} + \frac{\beta\varepsilon}{n}\sum\nolimits_{k,p,q} \eta_{ip} I_{pq,p}^{k} + \kappa\right) \tag{7}$$

is the force of infection from parasite haplotype i (similarly for λ_j). The terms correspond to transmission arising from: (i) hosts infected by matched parasites; (ii) mutation by parasites that differ at a single locus ($\eta_{ip} = 1$ if haplotypes i and p differ at exactly one locus; otherwise $\eta_{ip} = 0$); and (iii) the immigration of parasites (each parasite genotype enters the population with a fixed probability per unit time). The parameters β, ε and κ are transmission, mutation and immigration rates, respectively. We assume that there are no effects of dominance, so that on average heterozygotes and homozygotes have equal fitness. Dominance shifts the overall benefits of sex by altering the fitness of heterozygotes relative to homozygotes, which is most likely to be important when sexual and asexual populations are equally diverse (Agrawal & Otto, 2006; Agrawal, 2009a).

Sexual individuals experience a *per capita* natural mortality rate of $\mu_s = \mu(1 + h_\mu N)$, where μ modifies the overall natural mortality rate and h_μ dictates the strength of density-dependent mortality. The *per capita* natural mortality rate for asexuals is $\mu_a = c_\mu \mu_s$, where c_μ corresponds to additional costs (e.g. risk of contracting sexually transmitted parasites, $c_\mu < 1$) or benefits (e.g. mutation accumulation, $c_\mu > 1$) of sex with respect to survival. Infection leads to an additional mortality at a rate of α per unit time.

The underlying dynamics of our model can be represented by the following set of ordinary differential equations:

$$\frac{dS_{ij}^k}{dt} = b_{ij}^k - \left(\mu_k + \lambda_i + \lambda_j\right) S_{ij}^k \tag{8}$$

$$\frac{dI_{ij,m}^k}{dt} = \lambda_m \left(\delta_{im} + \delta_{jm}\right) S_{ij}^k - (\mu_k + \alpha) I_{ij,m}^k \tag{9}$$

where $\delta_{ip} = 1$ if $i = p$ and is otherwise zero. We use the event-driven algorithm proposed by Gillespie (1977) to convert this deterministic mean-field model into a stochastic individual-based model (IBM; source code available online as a supplementary file). This allows us to model finite rather than infinite populations so that extinctions of host and parasite genotypes can occur. Each simulation is initiated with a sexual population composed of random genotypes, with 1% infected by randomly chosen parasites and no asexuals present. We allow a burn-in period of 2,000 time units, where only parasites are allowed to immigrate (stochastically, at a rate of κ). Following the burn-in period, asexuals may also immigrate (stochastically, at a rate of ζ). All immigration events are independent, which allows the number of clonal lineages or parasite types that are present to fluctuate over time. Thus, clonal diversity is able to increase if previous lineages have not been driven extinct by the time a new lineage attempts to invade. When new sexual offspring are born, one male and one female are randomly chosen from the sexual population to be parents. Following recombination, one gamete is inherited from each parent and the sex of the offspring is chosen randomly with equal probability. We run each simulation for 5,000 time units

following the burn-in period (preliminary analysis of the model indicated that this was more than sufficient to detect strong effects of diversity on the maintenance of sex). For each simulation, we record if the sexual population persists, if it is driven extinct by asexuals or if no hosts survive. We also record the mean number of unique haplotypes during the second half of the burn-in period as a measure of the diversity of the sexual population prior to invasion. We conduct 250 repeats for each parameter combination and data is excluded from further analysis if the sexual population dies out during the burn-in period.

Simulation results

We focus on how sexual diversity (controlled by the number of loci per haplotype, n), the transmission rate (β) and the cost of sex (modified through the birth rate multiplier, c_b) influence the ability of sexual populations to persist when invaded by asexual lineages. For the sake of brevity, we fix the remaining parameters as follows: $c_\mu = 1$, $h_b = 1/500$, $h_\mu = 0$, $r = 1/2$, $\alpha = 1$, $\varepsilon = 0$, $\zeta = 1/200$, $\kappa = 1/500$, $\mu = 1/20$, $\rho = 1/20$. However, the supplementary figures show that our results are robust to the following changes: the inclusion of density-dependent mortality (figure S1); lower costs of sex due to effects on the relative mortality rates (figure S2); lower (figure S3) and higher (figure S4) recombination rates; the inclusion of parasite mutations (figure S5); higher parasite immigration rates (figure S6); larger population sizes (figure S7); an alternative formulation of the density-dependent birth rate (figure S8; equations S1-S2); and frequency-dependent transmission of parasites (figure S9; equation S3).

The diversity of the sexual population (measured as the mean number of haplotypes prior to invasion) increased with the number of loci involved in specificity, n, (figure 3a) and host extinction was common during the burn-in period when diversity was low (63% of simulations for $n \leq 4$, but no extinctions occurred for $n > 4$; figure 3b). Crucially, there was a marked difference in the success of sexual and asexual populations as the number of loci (and hence sexual diversity) varied. For low diversity ($n \leq 4$), the sexual population either

died out during the burn-in period or was almost always invaded and replaced by clonal lineages, even when the cost of sex was less than twofold (figures 4-5). For greater diversity ($n > 4$), however, the outcome was heavily dependent on both the transmission rate and the cost of sex. When the transmission rate was high ($\beta = 1/10$), the sexual population persisted in nearly every simulation, and lower costs of sex (i.e. greater c_b) increased the maintenance of sex for intermediate levels of diversity (figure 5). The picture was much more complex for lower transmission rates ($\beta = 1/20$). The sexual population tended to perform poorly as diversity increased and was most likely to persist for moderate levels of diversity. This relationship shifted towards the qualitative pattern described for high transmission rates when costs of sex were lower (figure 5).

These findings can be understood by examining the relationship between disease prevalence and the maintenance of sex (figure 6). Sex was most likely to be maintained when disease was neither too rare nor too common, in agreement with our prediction (figure 2). The prevalence of infection was primarily determined by two parameters: the number of loci per haplotype (n) and the transmission rate (β). For small numbers of loci (low diversity), the prevalence of infection was relatively high and sexual individuals were either driven extinct due to disease or were unable to avoid infection sufficiently more often than asexuals to offset the cost of sex (figure 2: region B). For large numbers of loci (high diversity) and small transmission rates, the average level of infection in the sexual population was sufficiently low that asexuals were unlikely to be infected soon after invading (figure 2: region A). Although asexuals would have eventually experienced an epidemic, extinction would have been less likely due to the low transmission rate of the parasite. This increased the chances that the number of asexual lineages would accumulate through time, further eroding any advantages of sexual reproduction. Hence, the peak in the maintenance of sex (figure 5) occurred for intermediate numbers of loci when transmission rates were small: the sexual population was sufficiently diverse as to avoid infection more often than asexuals, but not too diverse as to suppress parasite prevalence to very low levels (figure 2: region C). This trade-off did not

occur for higher transmission rates, as asexuals were more likely to be infected soon after their initial emergence and would have experienced more severe epidemics. Both factors increased the likelihood of being driven extinct before the immigration of another asexual linage, thereby allowing sex to be maintained when diversity was high (figure 5).

Discussion

We have demonstrated that more diverse, sexual populations can avoid being outcompeted by faster growing, but less diverse clonal populations in the presence of parasites (figure 5). If, however, disease prevalence is sufficiently diminished due to high host diversity (figure 1) then the advantages of sex may be lost in the short-term, allowing clonal lineages to invade and replace sexuals. Sex may therefore peak for intermediate levels of diversity (figure 5), as disease is neither too rare nor too common (figures 2, 6). In general, we should expect sexual populations to be more diverse than asexual ones, due to the processes of recombination and segregation that facilitate the production of diverse offspring. Yet, our findings suggest that while producing diverse offspring in the presence of parasites can be beneficial, greater diversity *per se* is not necessarily advantageous for sexual populations.

At first glance, our findings appear to contrast with those of Lively (2010b), who found that ecological feedbacks could prevent a single asexual lineage from replacing an established sexual population. Lively (2010b) argued that low disease prevalence could initially allow a clonal lineage to spread, leading to a reduction in sex and thus host diversity. The establishment of a single dominant genotype should then allow parasites to cause an epidemic, restoring the benefits of sex. Such behaviour was in fact common in our simulations, as shown by fluctuations in the frequency of sex due to temporary dominance of asexuals (figure 4). The key difference in the present study, however, is that sexual populations are much less likely to recover once they have been driven to low levels, even if parasites begin to infect a large number of asexuals. This is because our simulations featured the effects of drift, which were absent in Lively's deterministic model. Further, our model

allows the number of asexual genotypes to accumulate over time due to successive invasions, but Lively (2010b) focused on a single immigration event. Sex would have eventually been replaced in Lively's deterministic model if multiple immigration events were permitted.

Our model differs from most other theoretical explorations of the RQH (table 2) in a number of important ways. For example, we incorporate ecological feedbacks (variable host and parasite population sizes, see e.g. Lively 2010b) and stochasticity (extinction of rare genotypes), and we model diploid rather than haploid hosts with overlapping rather than discrete generations. These factors are known to have a considerable impact on ecological and coevolutionary dynamics (Kouyos *et al.*, 2007; Agrawal, 2009a; Ashby *et al.*, 2014a), and hence the maintenance of sex (Ashby and Gupta 2014). Two additional aspects of the present study are particularly important for understanding our results in the context of existing theory. First, we have specifically focused on differences in the diversity of sexual and asexual hosts, but most studies assume that all genotypes are present for both populations (table 2). A small number of studies have considered contrasting levels of diversity, but this approach remains the exception rather than the rule (table 2). Studies with contrasting levels of diversity have usually held relative diversity constant (e.g. invasion of a single clone; table 2); here, we have varied the dimensionality of genetic space and have shown that the relative diversity of sexual and asexual populations is crucial for the maintenance of sex.

Contrasting levels of diversity are more relevant to understanding the maintenance of sex, as it is unlikely that a large number of clonal lineages will simultaneously invade a sexual population, especially if parthenogenesis arises due to mutation and if immigration rates are not excessive (Lively & Howard, 1994). This would be a more realistic scenario for the many species in which clonal lineages 'spin-off' from a sexual progenitor (Vrijenhoek, 1998; Simon *et al.*, 2003) and thus only capture a fraction of the sexual genotypic space (Jokela *et al.*, 1997). (Note: we did not allow asexuals to arise via mutations from sexuals, as this allowed us to keep the influx of asexuals constant as we varied the dimensionality of the system). We should therefore expect the diversity of invading asexual populations to be much

lower than that of resident sexual populations. If all genotypes are present for both populations, then the advantages of sex only arise if rare (fitter) genotypes are produced at a much faster rate than by asexuals. Studies with equally diverse populations tend to report conditions for the maintenance of sex (diploids) or recombination (haploids) that are quite limited, usually relying on strong selection and rapid coevolutionary cycling (Hamilton, 1980; May & Anderson, 1983; Peters & Lively, 1999; Otto & Nuismer, 2004; Agrawal & Otto, 2006; Gandon & Otto, 2007; Kouyos *et al.*, 2007, 2009; Ashby & Gupta, 2014). These factors ensure that rare genotypes are optimal for only a short period of time and that hosts that lack recombination mechanisms are unable to respond to selection quickly enough, despite all genotypes being present in the population. However, this approach neglects a major advantage of recombination and segregation: rare genotypes may be lost due to extinction, but can readily reappear through these processes (Hamilton, 1980). Even if recombination is infrequent in sexual populations, higher standing diversity may be sufficient to prevent exclusion by a small number of asexual lineages (Lively & Howard, 1994; Doebeli, 1996; Lively, 2010a). Our results highlight the importance of standing genetic diversity for the maintenance of sex.

The second major difference between the present study and most existing theory is that we vary the number of loci involved in host-parasite specificity and hence the relative diversity of the sexual and asexual populations. The vast majority of studies have modelled specificity based on interactions at a fixed number of loci and it is unclear how greater diversity would affect many results (table 2). As an exception, Otto and Nuismer (2004) found that increasing the number of loci reduced selection for recombination, in stark contrast to our observations. It is difficult to fully reconcile the two sets of results, as we have taken a fundamentally different modelling approach. Specifically, Otto and Nuismer (2004) used a modifier allele approach to determine selection for recombination in haploid hosts, rather than competing diploid sexual and asexual populations, and did not include ecological feedbacks, stochasticity or contrasting levels of diversity in sexual and asexual populations. If all host

and parasite genotypes are always present and selection leads to changes in frequency (but not density), then greater diversity decreases the strength of selection at each locus, making recombination less advantageous. In our model, the sexual population becomes more diverse (in an absolute sense and relative to asexuals) as the number of loci increases, widening the gap between the two populations. In addition, the presence of ecological feedbacks means that genotypes fluctuate in both frequency and density, so the risk of extinction per genotype increases with the number of loci. Although our model differs in a number of key areas, some common themes still exist with Otto and Nuismer (2004). Their study, along with previous theory (Hamilton, 1980; Peters & Lively, 2007), demonstrates that population-level or long-term advantages to recombination do not necessarily lead to its persistence. These findings resonate with our own in that high diversity is good for reducing the overall prevalence of infection in the sexual population, but can provide asexual lineages with a short-term advantage that leads to the extinction of sex.

Theoreticians often work with limited diversity in their models as this reduces the complexity of the system, but our results show that the number of loci involved in specificity is crucial for the maintenance of sex. The genetic underpinnings of host-parasite interactions are increasingly being uncovered in natural systems, many of which appear to be governed by multiple loci (Jones & Dangl, 2006; Scanlan *et al.*, 2011; Penman *et al.*, 2013; Barribeau *et al.*, 2014). When discussing multiple loci and the evolution of sex, it is important to distinguish between loci that are under selection due to interspecific interactions (RQH) and loci that may negatively affect fitness due to the presence of deleterious mutations. We did not incorporate deleterious mutations in our model, but this will provide an additional advantage for sex as it purges unfit genotypes from the population (Maynard Smith, 1978; Howard & Lively, 1994, 1998; West *et al.*, 1999). While we have shown that increasing the number of loci that govern specificity can select against sex, more loci (that are unrelated to specificity) tend to favour sex in the context of deleterious mutations (Iles *et al.*, 2003).

Real host-parasite systems are inevitably far more complex than our model, but we expect the general pattern of our results to hold under a wide range of conditions. For example, we did not explore the effects of parasitic castration on the maintenance of sex, but this will tend to impose an extra cost on the sexual population due to a reduction in the availability of fertile mates (Ashby & Gupta, 2014). Ashby and Gupta (2014) showed that parasitic castration can also be crucial for the persistence of coevolutionary cycling, but focused on a deterministic system with all host and parasite genotypes present. Here, coevolutionary cycling persisted due to stochasticity, which meant that currently unfit host and parasite genotypes could be driven extinct before being reintroduced through recombination, mutation or immigration. As cycling was maintained in our model without castration, its inclusion would not alter the coevolutionary dynamics of our model to the extent observed by Ashby and Gupta (2014), but it would effectively increase the cost of sex by lowering the average birth rate. We also assumed that the populations mixed homogeneously, but spatial structure in natural populations should tend to increase the advantages of sex as parents and offspring are likely to be challenged by similar parasites (Keeling & Rand, 1995; Agrawal, 2006, 2009b). Still, a greater advantage for sex should not be taken for granted, as the effects of spatial structure on coevolutionary dynamics are often complex (e.g. Gomez *et al.*, 2015) and can strongly influence epidemiological feedbacks (Best *et al.*, 2011; Ashby *et al.*, 2014b). Another complexity of real systems relates to the precise nature of host-parasite specificity, including dominance. It has recently been argued that dominance tends to select against sex (Agrawal & Otto, 2006; Agrawal, 2009a). However, this is only likely to be true when sexual and asexual populations are equally diverse, as the benefits of sex depend solely on the overproduction of heterozygotes (Agrawal & Otto, 2006; Agrawal, 2009a). Dominance effects are likely to be much less important when the two populations have contrasting levels of diversity, as the benefits of sex arise through the production of a greater number of genotypes rather than through differential production of the same genotypes. We also assumed that interactions between host and parasite genotypes were highly specific, which is consistent for many

systems where host-parasite coevolution has been evaluated (e.g. Lively 1989; Luijckx et al. 2013).

Although many models of the Red Queen assume that asexual competitors are saturated for the genotypic space available to sexuals (table 2), here we argue that a difference in genetic diversity is not only realistic, but also important to the maintenance of sex by parasites (see also Lively 2010a). Theory predicts that parasite-mediated selection against common host genotypes should maintain diversity (Haldane, 1949) and thus sex in host populations (Hamilton, 1980; Bell, 1982). However, a high level of genetic diversity should drastically reduce parasite transmission and prevalence (Lively, 2010c; King & Lively, 2012), giving an advantage to asexuals paying a lower reproductive cost. Our model supports these hypotheses as ends of a spectrum and finds that an intermediate level of genetic diversity maintains sex.

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Tables

Table 1

Model variables and parameters for stochastic simulations

Sub/superscript k	Host type: sexual ($k = s$) or asexual ($k = a$)
Subscript i or j	Host haplotype i or j
Subscripts ij	Host genotype composed of haplotypes i and j
Subscript m	Host infected by parasite haplotype m
b_{ij}^{k}	Birth rate
c_b	Birth rate multiplier for sexuals
c_μ	Death rate multiplier for asexuals
g, n	Number of host genotypes, loci per haplotype
h_b, h_μ	Coefficient for density-dependent birth, death rates
M_i, F_i	Proportion of gametes following recombination that are of haplotype i (males, females)
$N, N_s, N_a, F_0, S_{ij}^{k}, I_{ij,m}^{k}$	Number of hosts (all, sexual, asexual, female, susceptible, infected)
r	Maximum *per capita* birth rate
α	Disease-associated mortality rate
β	Transmission rate
ε, κ	Parasite mutation, immigration rates
ζ	Asexual immigration rate
λ_i	Force of infection
μ	Coefficient for natural mortality rate
μ_k	*Per capita* natural mortality rate
ρ, ρ_0	Rate of recombination (overall, per locus)

Table 2

Summary of modeling assumptions in theoretical studies

Reference	Ecological feedbacks	Drift	Host ploidy	Generations	Loci	Asexual diversity*
Present study	Yes	Yes	Diploid	Overlapping	Variable	Variable
Agrawal (2006)	No	No	Diploid	Discrete	Variable	Equal
Agrawal and Otto (2006)	No	No	Diploid	Discrete	Fixed	Equal
Agrawal (2009)	No	No	Diploid	Discrete	Fixed	Equal
Ashby and Gupta (2014)	Yes	No	Diploid	Overlapping	Fixed	Equal
Engelstädter and Bonhoeffer (2009)	No	No	Haploid	Discrete	Fixed	Equal
Doebeli (1996)	Yes	No	Haploid	Discrete	Quantitative	Variable
Gandon and Otto (2007)	No	No	Haploid	Discrete	Fixed	Equal
Green and Mason (2013)	No	Yes	Diploid	Discrete	Variable	Single clone
Hamilton (1980)	No	No	Diploid, haploid	Discrete	Variable	Equal
Hamilton et al. (1990)	No	Yes	Haploid	Discrete	Variable	Equal
Hodgson and Otto (2012)	No	No	Haploid	Discrete	Fixed	Equal
Howard and Lively (1994)	No	Yes	Haploid	Discrete	Fixed	Single clone
Howard and Lively (1998)	No	Yes	Haploid	Discrete	Fixed	Single clone
Keeling and Rand (1995)	Yes	Yes	Haploid	Both	Fixed	Single clone
Kouyos et al. (2007)	No	Yes	Haploid	Both	Fixed	Equal
Kouyos et al. (2009)	No	No	Haploid	Both	Fixed	Equal
Ladle et al. (1993)	No	Yes	Haploid	Discrete	Fixed	Equal
Lively (2009)	No	No	Diploid, haploid	Discrete	Fixed	Single clone
Lively (2010b)	Yes	No	Haploid	Discrete	Fixed	Single clone
Lively and Howard (1994)	No	Yes	Haploid	Discrete	Variable	Variable
May and Anderson (1983)	Yes	No	Diploid, haploid	Overlapping	Fixed	Equal
Mostowy et al. (2010)	No	No	Haploid	Discrete	Fixed	Equal
Mostowy and Engelstädter (2012)	No	No	Diploid, haploid	Discrete	Fixed	Equal
Otto and Nuismer (2004)	No	No	Haploid	Discrete	Variable	Equal

Parker (1994)	No	No	Haploid	Discrete	Fixed	Equal
Peters and Lively (1999)	No	No	Haploid	Discrete	Fixed	Equal
Peters and Lively (2007)	No	No	Haploid	Discrete	Fixed	Equal
Salathé et al. (2008)	No	No	Haploid	Discrete	Fixed	Equal
Salathé et al. (2009)	No	No	Haploid	Discrete	Fixed	Equal
Sasaki et al. (2002)	No	No	Haploid	Discrete	Variable	Variable

*Relative to the sexual population

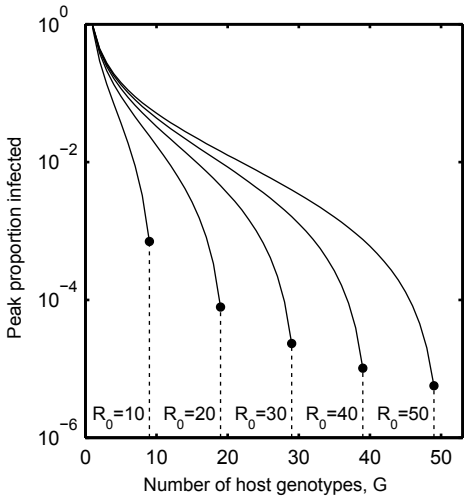

Figure 1 - Epidemic size in the deterministic model (equations 1-2) as a function of the number of host genotypes (G). Each curve represents the peak proportion infected for a given basic reproductive ratio (R_0). Circles and dotted lines show the highest value of G for which an epidemic occurs ($G=R_0-1$).

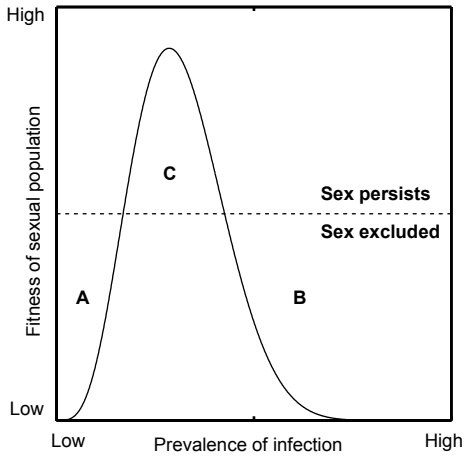

Figure 2 – Qualitative prediction for the relationship between the prevalence of infection and selection for sex. In region A, infection is rare (e.g. high genetic diversity or low transmission rates), so the advantages of sexual reproduction do not outweigh the twofold cost of males and asexuals will prevail. In region B, infection is very common (e.g. genetic diversity is poor or parasites rapidly overcome resistance), so sexual offspring are unlikely to avoid disease; again, asexuals prevail. In region C, infection is neither too rare nor too common; greater resistance to parasites offsets the costs of producing males, so sex persists.

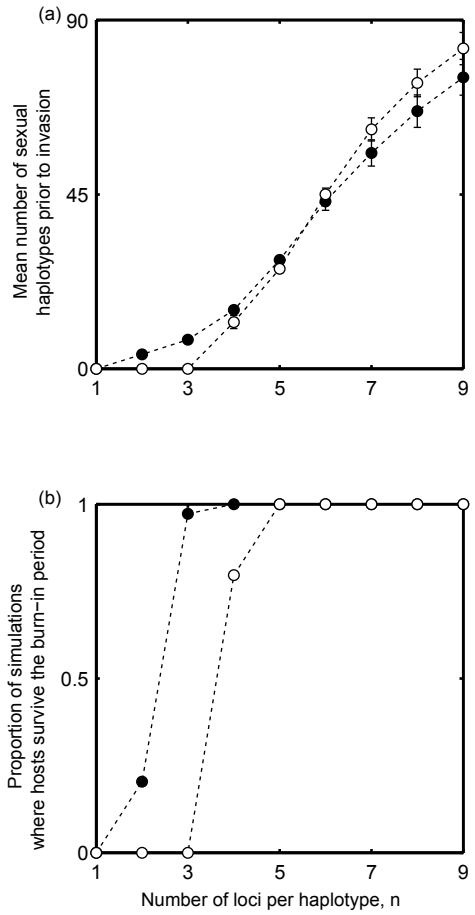

Figure 3 – Effects of the number of loci per haplotype (n) on (a) the mean number of sexual haplotypes prior to invasion (i.e. sexual diversity); and (b) the proportion of simulations where hosts survive the burn-in period. Error bars correspond to 1 standard deviation. Shading corresponds to low (β=1/20; black) and high (β=1/10; white) transmission rates. Parameters: c_b=1.1, c_μ=1, h_b=1/500, h_μ=0, r=1/2, α=1, ε=0, ζ=1/200, κ=1/500, μ=1/20, ρ=1/20.

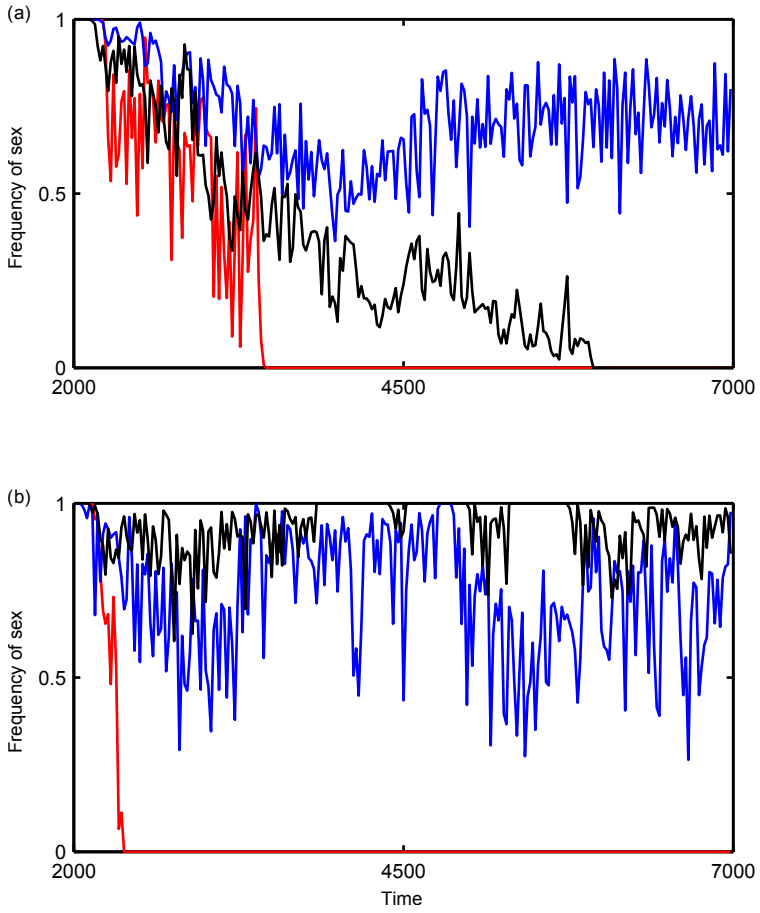

Figure 4 – Example simulation dynamics for 3 (red), 5 (blue) and 7 (black) loci per haplotype (n), showing the frequency of sex for (a) low (β=1/20) and (b) high (β=1/10) transmission rates. (a) Sexual populations that have intermediate levels of diversity are favoured when parasites have a low transmission rate. (b) High diversity is favoured when parasites are more readily transmissible. Remaining parameters as specified in figure 3.

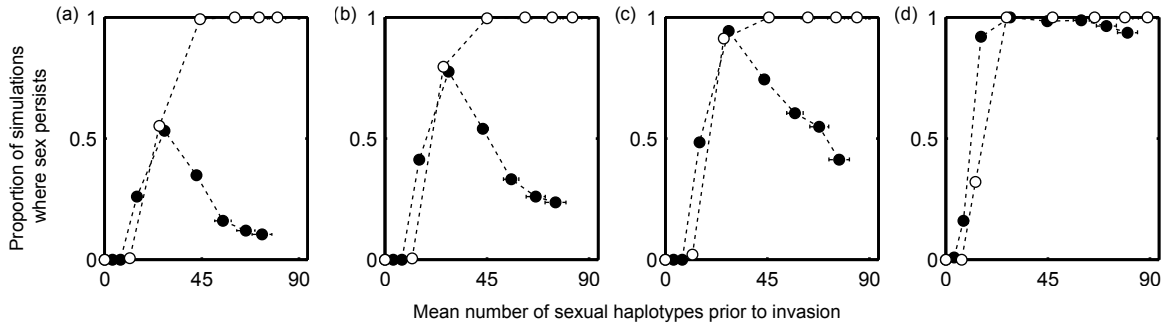

Figure 5 - Proportion of simulations where hosts persisted and the sexual population was still present for low (β=1/20; black) and high (β=1/10; white) transmission rates. The panels correspond to different values for the birth rate multiplier, c_b, which reduces the cost of being sexual (e.g. lower infant mortality rate due to shared parental care or a lower deleterious mutation load): (a) c_b=1 (no change), (b) c_b=1.1, (c) c_b=1.2, (d) c_b=1.5. Error bars correspond to 1 standard deviation. Remaining parameters as specified in figure 3.

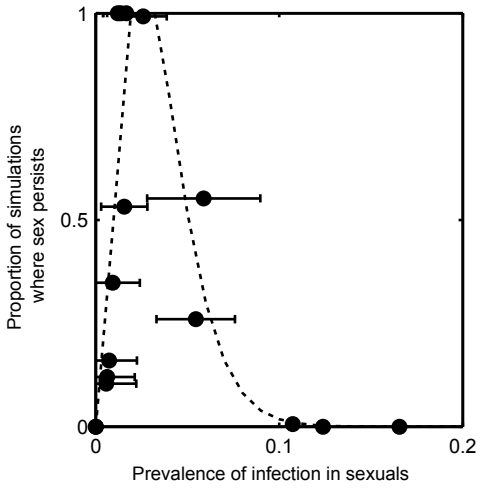

Figure 6 - Relationship between the prevalence of infection in the sexual population (mean ± SD) to the proportion of simulations where hosts persisted and the sexual population was still present. Each data point corresponds to a set of simulations with equal parameters (transmission rate and number of loci per haplotype). The dotted curve is given by the equation $a_0(p\text{^}a_1)(1\text{-}p)\text{^}a_2$, with a_0=71,527, a_1=2.37, a_2=92.4 and p equal to the prevalence of infection (R^2=0.84). Sex is most beneficial for intermediate levels of disease. Parameters as specified in figure 3, with c_b=1.

Diversity and the maintenance of sex by parasites: supplementary material

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In the main text, we focus on how sexual diversity (controlled by the number of loci per haplotype, n), the transmission rate (β) and the cost of sex (modified through the birth rate multiplier, c_b) influence the ability of sexual populations to persist when invaded by asexual lineages. For the sake of brevity, the following parameters are held constant: $c_\mu = 1$, $h_b = 1/500$, $h_\mu = 0$, $r = 1/2$, $\alpha = 1$, $\epsilon = 0$, $\zeta = 1/200$, $\kappa = 1/500$, $\mu = 1/20$, $\rho = 1/20$. Here, we show that our results are robust to the following changes: the inclusion of density-dependent mortality (figure S1); lower costs of sex due to effects on the relative mortality rates (figure S2); lower (figure S3) and higher (figure S4) recombination rates; the inclusion of parasite mutations (figure S5); higher parasite immigration rates (figure S6); larger population sizes (figure S7); an alternative formulation of the density-dependent birth rate (figure S8); and frequency-dependent transmission of parasites (figure S9). In figure S8, the sexual birth rate is given by:

$$b_{ij}^s = \frac{c_b r F_0 \left(M_i F_j + M_j F_i\right)}{1 + h_b N} \tag{S1}$$

and the asexual birth rate is given by:

$$b_{ij}^a = \frac{r A_{ij}}{1 + h_b N} \tag{S2}$$

For figure S9, the force of infection from parasite haplotype i is equal to:

$$\lambda_i = \frac{1}{2}\left(\frac{\beta}{N}(1-\epsilon)\sum_{k,p} I_{ip,i}^k + \frac{\beta\epsilon}{nN}\sum_{k,p,q}\eta_{ip} I_{pq,p}^k + \kappa\right) \tag{S3}$$

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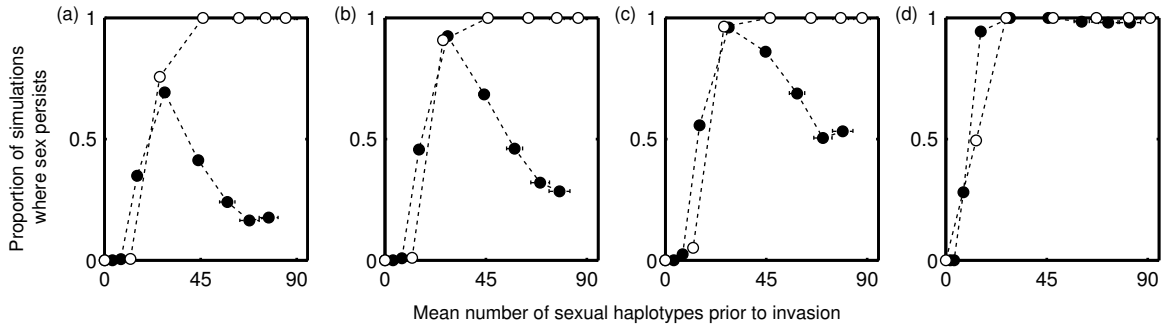

Figure S1: Effects of density-dependent mortality ($h_\mu = 1/500$, $h_b = 0$ and $\mu = 1/40$). Proportion of simulations where hosts persisted and sexual (resident) hosts were still present after 7,000 time units for low ($\beta = 1/20$; black) and high $\beta = 1/10$; white) transmission rates. The panels correspond to different values for the birth rate multiplier, c_b, which reduces the cost of being sexual (e.g. lower infant mortality rate due to shared parental care or a lower deleterious mutation load): (a) $c_b = 1$ (no change), (b) $c_b = 1.1$, (c) $c_b = 1.2$, (d) $c_b = 1.5$. Error bars correspond to 1 standard deviation. Remaining parameters as specified in figure 3 in the main text.

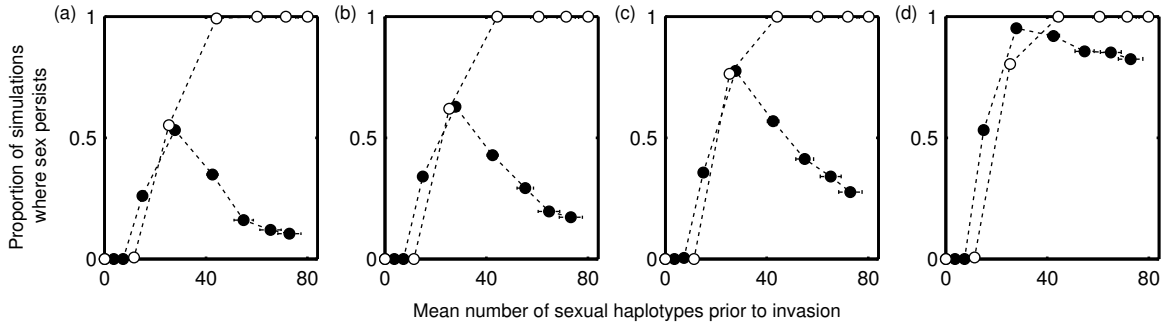

Figure S2: Effects of the mortality rate multiplier. Proportion of simulations where hosts persisted and sexual (resident) hosts were still present after 7,000 time units for low ($\beta = 1/20$; black) and high $\beta = 1/10$; white) transmission rates. The panels correspond to different values for the mortality rate multiplier, c_μ, which reduces the cost of being sexual (e.g. lower infant mortality rate due to shared parental care or a lower deleterious mutation load): (a) $c_\mu = 1$ (no change), (b) $c_\mu = 1.1$, (c) $c_\mu = 1.2$, (d) $c_\mu = 1.5$. Error bars correspond to 1 standard deviation. Remaining parameters as specified in figure 3 in the main text, with $c_b = 1$.

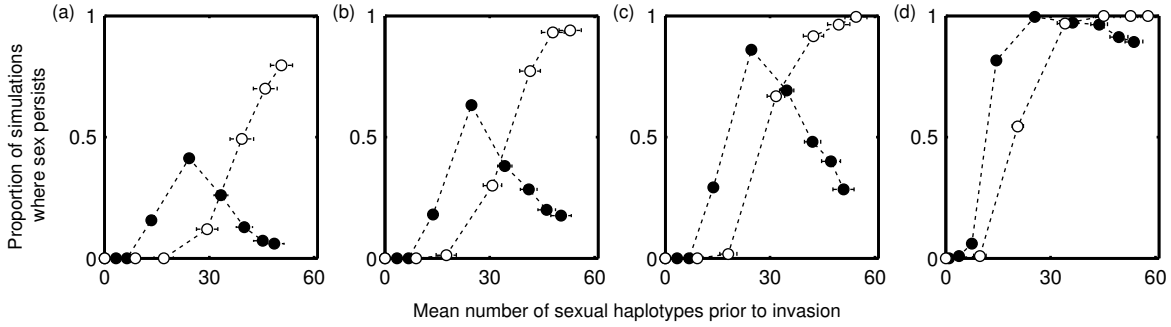

Figure S3: Effects of a lower recombination rate ($\rho = 1/50$). Proportion of simulations where hosts persisted and sexual (resident) hosts were still present after 7,000 time units for low ($\beta = 1/20$; black) and high $\beta = 1/10$; white) transmission rates. The panels correspond to different values for the birth rate multiplier, c_b, which reduces the cost of being sexual (e.g. lower infant mortality rate due to shared parental care or a lower deleterious mutation load): (a) $c_b = 1$ (no change), (b) $c_b = 1.1$, (c) $c_b = 1.2$, (d) $c_b = 1.5$. Error bars correspond to 1 standard deviation. Remaining parameters as specified in figure 3 in the main text.

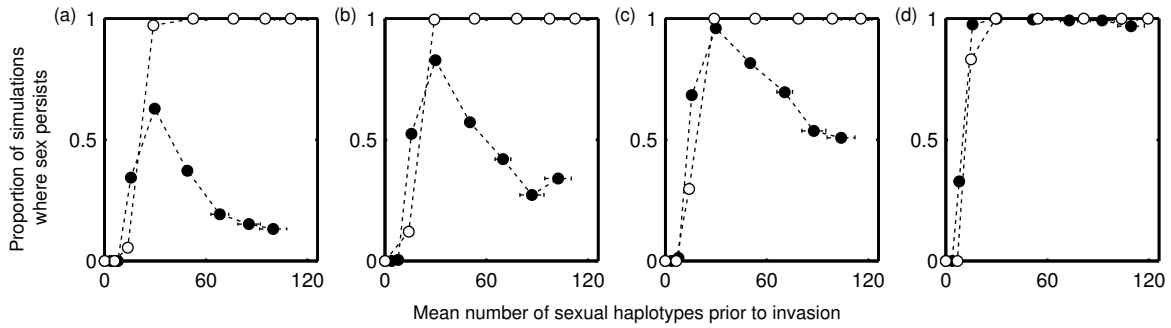

Figure S4: Effects of a higher recombination rate ($\rho = 1/10$). Proportion of simulations where hosts persisted and sexual (resident) hosts were still present after 7,000 time units for low ($\beta = 1/20$; black) and high $\beta = 1/10$; white) transmission rates. The panels correspond to different values for the birth rate multiplier, c_b, which reduces the cost of being sexual (e.g. lower infant mortality rate due to shared parental care or a lower deleterious mutation load): (a) $c_b = 1$ (no change), (b) $c_b = 1.1$, (c) $c_b = 1.2$, (d) $c_b = 1.5$. Error bars correspond to 1 standard deviation. Remaining parameters as specified in figure 3 in the main text.

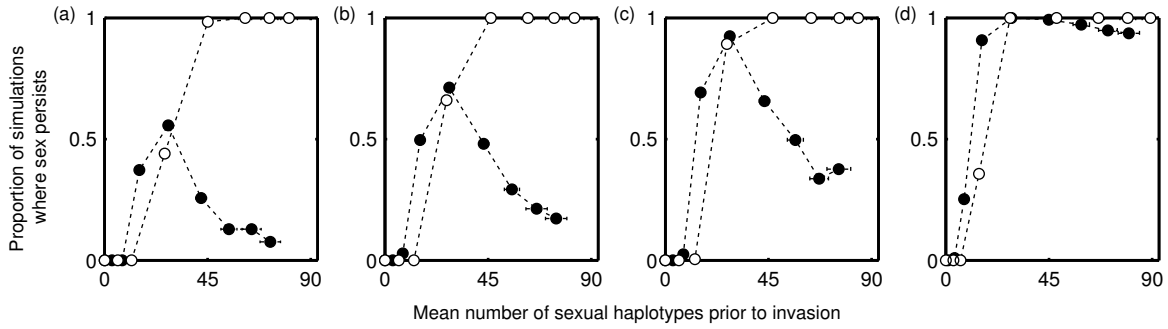

Figure S5: Effects of parasite mutations ($\epsilon = 1/20$). Proportion of simulations where hosts persisted and sexual (resident) hosts were still present after 7,000 time units for low ($\beta = 1/20$; black) and high $\beta = 1/10$; white) transmission rates. The panels correspond to different values for the birth rate multiplier, c_b, which reduces the cost of being sexual (e.g. lower infant mortality rate due to shared parental care or a lower deleterious mutation load): (a) $c_b = 1$ (no change), (b) $c_b = 1.1$, (c) $c_b = 1.2$, (d) $c_b = 1.5$. Error bars correspond to 1 standard deviation. Remaining parameters as specified in figure 3 in the main text.

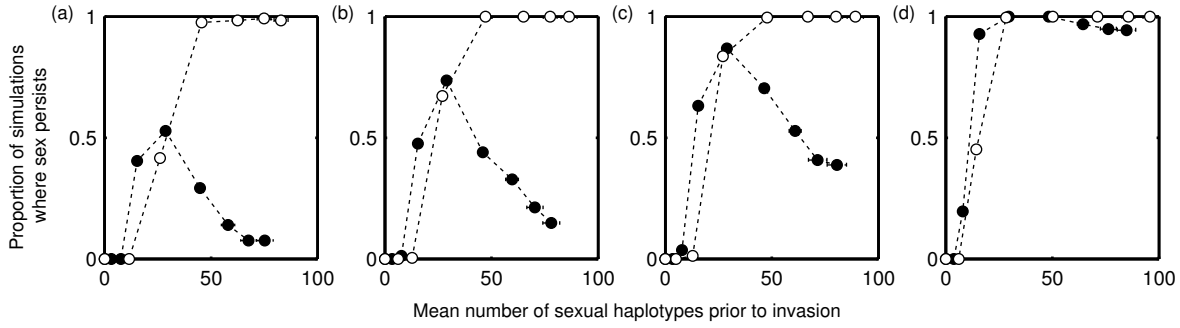

Figure S6: Effects of a higher parasite immigration rate ($\kappa = 1/100$). Proportion of simulations where hosts persisted and sexual (resident) hosts were still present after 7,000 time units for low ($\beta = 1/20$; black) and high $\beta = 1/10$; white) transmission rates. The panels correspond to different values for the birth rate multiplier, c_b, which reduces the cost of being sexual (e.g. lower infant mortality rate due to shared parental care or a lower deleterious mutation load): (a) $c_b = 1$ (no change), (b) $c_b = 1.1$, (c) $c_b = 1.2$, (d) $c_b = 1.5$. Error bars correspond to 1 standard deviation. Remaining parameters as specified in figure 3 in the main text.

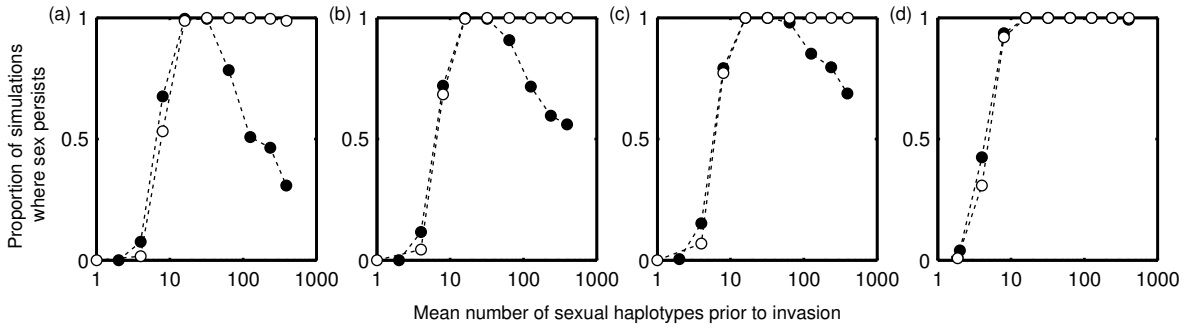

Figure S7: Effects of greater population sizes due to a higher carrying capacity ($h_b = 1/5000$; transmission rates adjusted accordingly). Proportion of simulations where hosts persisted and sexual (resident) hosts were still present after 7,000 time units for low ($\beta = 1/200$; black) and high $\beta = 1/100$; white) transmission rates. The panels correspond to different values for the birth rate multiplier, c_b, which reduces the cost of being sexual (e.g. lower infant mortality rate due to shared parental care or a lower deleterious mutation load): (a) $c_b = 1$ (no change), (b) $c_b = 1.1$, (c) $c_b = 1.2$, (d) $c_b = 1.5$. Error bars correspond to 1 standard deviation. Remaining parameters as specified in figure 3 in the main text.

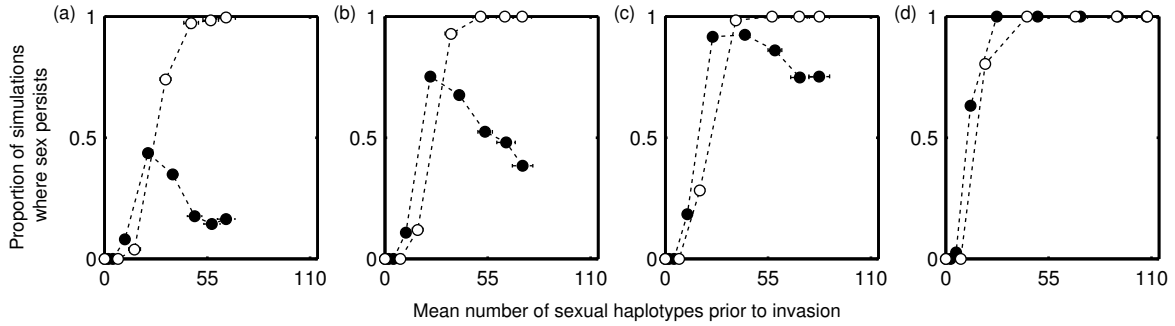

Figure S8: Effects of using an alternative formulation for the density-dependent birth rate (equations S1 and S2; $h_b = 1/100$). Proportion of simulations where hosts persisted and sexual (resident) hosts were still present after 7,000 time units for low ($\beta = 1/20$; black) and high $\beta = 1/10$; white) transmission rates. The panels correspond to different values for the birth rate multiplier, c_b, which reduces the cost of being sexual (e.g. lower infant mortality rate due to shared parental care or a lower deleterious mutation load): (a) $c_b = 1$ (no change), (b) $c_b = 1.1$, (c) $c_b = 1.2$, (d) $c_b = 1.5$. Error bars correspond to 1 standard deviation. Remaining parameters as specified in figure 3 in the main text.

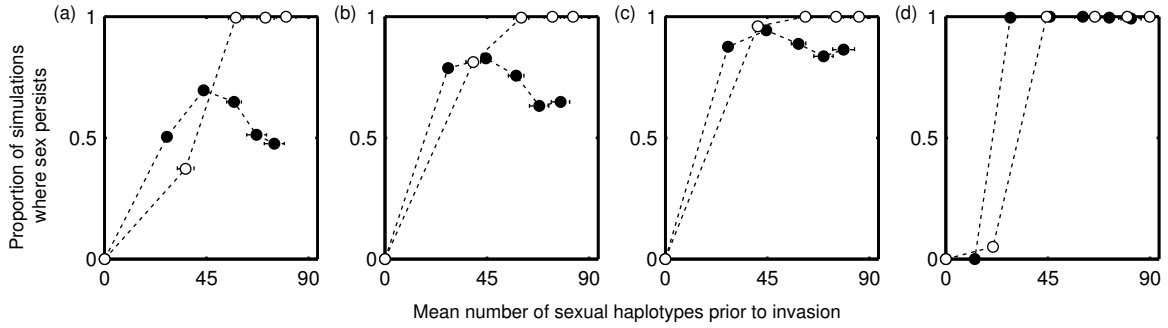

Figure S9: Effects of frequency-dependent transmission (equation S3; transmission rates adjusted accordingly). Proportion of simulations where hosts persisted and sexual (resident) hosts were still present after 7,000 time units for low ($\beta = 25$; black) and high $\beta = 50$; white) transmission rates. The panels correspond to different values for the birth rate multiplier, c_b, which reduces the cost of being sexual (e.g. lower infant mortality rate due to shared parental care or a lower deleterious mutation load): (a) $c_b = 1$ (no change), (b) $c_b = 1.1$, (c) $c_b = 1.2$, (d) $c_b = 1.5$. Error bars correspond to 1 standard deviation. Remaining parameters as specified in figure 3 in the main text.