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Local host competition in the evolution of virulence

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Abstract

The evolution of parasite life histories should usually have correlated effects on host survivorship and/or reproductive success. For example, parasites that reproduce more rapidly might be expected to cause greater reductions in host fitness. Important theoretical advances have recently been made on virulence evolution, but the results are not always consistent. Here I compare two models [*Q. Rev. Biol.* **71** (1996) 37; *Q. Rev. Biol.* **75** (2000) 261] on the evolution of virulence that get qualitatively different results with respect to the effects of coinfection. I also construct a third model that attempts to connect these two formulations. The results suggest that parasite growth rates should increase as local host competition increases, unless relatedness is at equilibrium. In addition, the qualitative effect of adding coinfections on parasite growth rates depends critically on how the number of coinfections affects transmission success.

Introduction

There has been an explosion of interest in modelling the evolution of within-host growth rates by parasites. Of particular interest in this field is the effect of coinfection, i.e. the simultaneous infection of hosts by two or more parasite strains that coexist (May & Nowak, 1995). Two similar approaches have been taken: epidemiological and game theoretic. The classic result from these models has been that coinfection selects for increases in the within-host growth rates by parasites, which may then lead to higher virulence (Hamilton, 1972; Bremermann & Pickering, 1983; Frank, 1992, 1996; Bonhoeffer & Nowak, 1994; van Baalen & Sabelis, 1995; May & Nowak, 1995; Taylor & Frank, 1996; Gandon, 1998). Recently, however, some models have found that increasing the number of coinfections can decrease the within-host growth rates by the individual parasite strains within a coinfected host (Chao *et al.*, 2000; Brown *et al.*, 2002; Schjorring & Koella, 2003; Lively, 2005).

Some of the differences in results may have to do with the assumptions regarding how parasites interact within the host (Chao *et al.*, 2000; West & Buckling, 2003; Gardner *et al.*, 2004). If, for example, the parasites interact directly through toxin production ('spite' models), greater relatedness among coinfections might lead to greater virulence, as the interference competition that results from toxin production can decrease as relatedness increases (Gardner *et al.*, 2004; Massey *et al.*, 2004; Vigneux *et al.*, 2008). Similarly, virulence might also be expected to increase with increasing relatedness among coinfections, if cooperating parasites produce costly public goods (e.g. siderophores) that can also be used by noncooperating cheaters ('public goods' models) (Chao *et al.*, 2000; Brown *et al.*, 2002; West & Buckling, 2003). However, the results can differ, even for models that assume only exploitative competition among parasites ('tragedy of the commons' models). For example, Frank (1996) found that increasing the number of unrelated coinfections (thereby decreasing relatedness, R) resulted in selection to increase the within-host reproductive rates of the parasites. By contrast, Chao *et al.* (2000) found the opposite result: increasing the number of unrelated coinfections resulted in selection to decrease the within-host reproductive rates of the parasites. Thus, although both models assumed only exploitation competition (tragedy of the commons), they found qualitatively different results. Here, I construct a third model that attempts to bridge the difference between the two findings.

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Models

Frank's model

In 1996, Frank reviewed models for the evolution of parasite virulence (Frank, 1996). As part of his review, he suggested that one could generally write the fitness equation for a mutant parasite strain as

$$W = zf(\bar{z}), \tag{1}$$

where z depends on the growth rate of the mutant strain and gives the number of propagules that would be produced during within-host growth, assuming all of the propagules survive to transmission; $\bar{z}$ is the mean of this number over all coinfecting parasites in the focal host containing the mutant strain and $f(\bar{z})$ is a function that captures the negative effect of the group on successful transmission of the mutant strain, and thus represents the 'tragedy of the commons'. Specifically, Frank (1996) wrote $f(\bar{z})$ as equal to $(1 - \alpha\bar{z})/\bar{z}$; hence, the fitness of the rare mutant in a coinfected host is

$$W = \frac{z(1 - \alpha\bar{z})}{\bar{z}}, \tag{2}$$

where α is a constant that scales the effect of $\bar{z}$ on transmission to the next host. Virulence can be thought of as being positively correlated with the product of α and $\bar{z}$.

The evolutionarily stable strategy (ESS) for z (z^*) can be found using Taylor & Frank's (1996) model for analysing kin selection. Specifically, the candidate ESS is the solution for z when:

$$\left|\frac{\partial W}{\partial z} + R\frac{\partial W}{\partial \bar{z}}\right|_{z=\bar{z}=z^*} = 0, \tag{3}$$

where R gives the relatedness among coinfections. Following Day & Taylor (1998), the solution is evolutionarily stable (an ESS) if

$$\left|\frac{\partial^2 W}{\partial z^2} + 2R\frac{\partial^2 W}{\partial z\,\partial \bar{z}} + R^2\frac{\partial^2 W}{\partial \bar{z}^2}\right|_{z=\bar{z}=z^*} < 0, \tag{4}$$

and continuously stable (a CSS) if

$$\left|\frac{\partial^2 W}{\partial z^2} + (1+R)\frac{\partial^2 W}{\partial z\,\partial \bar{z}} + R\frac{\partial^2 W}{\partial \bar{z}^2}\right|_{z=\bar{z}=z^*} < 0. \tag{5}$$

Using this method, it is easy to show that z^* is both evolutionarily and continuously stable at

$$z^* = \frac{1 - R}{\alpha}, \tag{6}$$

where R is the relatedness among coinfecting strains (Frank, 1996). The solution requires that R is not equal to one. W at the ESS is equal to R.

Note that the number of coinfections, K, is not in the model. However, if K is the number of unrelated parasites that infect a host, then $R = d\bar{z}/dz = 1/K$, and

$$z^* = \frac{K - 1}{\alpha K}. \tag{7}$$

Thus, increasing the number of coinfections increases the within-host growth rate of the coinfecting parasites. This then gives the classic result that coinfection selects for increased rates of within-host growth, which has been independently derived several times (e.g. van Baalen & Sabelis, 1995; May & Nowak, 1995).

Chao *et al.*'s model

Chao *et al.* (2000) also published a review of virulence models. Their main point was to consider public good-type interactions among coinfecting parasites (see also Brown *et al.*, 2002; West & Buckling, 2003), but they also constructed a model that was similar to Frank's model in that it assumed exploitation competition (tragedy of the commons model). Specifically, in the Chao *et al.* model, fitness was written as:

$$W = z(1 - \alpha K\bar{z}), \tag{8}$$

where the term in parenthesis reflects the tragedy of the commons.

There are two main differences between the models by Frank and Chao *et al.*: (1) Chao *et al.* explicitly consider the number of coinfections, K, in their model, but (2) they did not include a standardization of fitness by the mean strategy in the population. Hence, fitness in the Chao *et al.* model seems to be absolute rather than relative. Under these assumptions, the best strategy is to maximize the total number of transmission stages, which is the solution that maximizes the product of $zf(\bar{z})$. Using Taylor & Frank's (1996) method for finding the ESS in a kin selection model, it can be shown that

$$z^* = \frac{1}{\alpha K(1 + R)}, \tag{9}$$

which is both evolutionarily and continuously stable. (W at the ESS is equal to one.) For $R = 1/K$, the result becomes

$$z^* = \frac{1}{\alpha(K + 1)}. \tag{10}$$

Thus, in contrast to Frank's (1996) result, z^* decreases with increases in the number of coinfections. I obtained the same result as Chao *et al.* (2000) under the assumption of no local competition for hosts (Lively, 2005) (see also p. 41 in West & Buckling, 2003).

Chao *et al.* (2000) recognized the difference between their result and the result obtained by Frank, and they

attributed it to the fact that their model considered the impact of the total number of infections, $K\bar{z}$, on the successful production of transmission stages, whereas Frank only included the effect of the mean ($\bar{z}$) strategy on the successful production of transmission stages. Whether or not this is true can be determined by replacing $\bar{z}$ in Frank's model with $K\bar{z}$, and again solving for the ESS, giving (assuming $R < 1$):

$$W = \frac{z}{\bar{z}}(1 - \alpha K\bar{z}). \tag{11}$$

For this formulation, the ESS is at

$$z^* = \frac{(1 - R)}{\alpha K}. \tag{12}$$

The result does not converge exactly on the result by Chao *et al.* (eqn 9). Nonetheless, z^* decreases with an increase in the number of coinfections, which is consistent with the overall conclusion by Chao *et al.* This result raises an obvious question: does $f(\bar{z})$ in eqn 1 depend on the number of infections? Or does it depend only on the mean growth strategy taken over all the infections in the host?

Local host competition

In order to extend the models by Frank (1996) and Chao *et al.* (2000), I now consider local competition for hosts in a haploid, asexual parasite population. The model is conceptually similar to some previous models, in that parasite dispersal can be local (Frank, 1998; Boots & Sasaki, 1999; O'Keefe & Antonovics, 2002; Boots & Mealor, 2007); but, in the present model, the mobile hosts are dispersing away from their natal patches (e.g. the arthropod hosts of soil-dwelling, entomopathogenic nematodes), and hence are not locally depleted by infection, thereby leading to different conclusions. The relative fitness of an individual with a mutant allele, A, in a population of resident strains having the wild-type allele, a, can be written as

$$W_A = \frac{\left(a + \frac{1-a}{H}\right) z_A (1 - \alpha K^x \bar{z})}{\left(a + \frac{1-a}{H}\right) K\bar{z}(1 - \alpha K^x \bar{z}) + \frac{1-a}{H}(H-1) K z_a (1 - \alpha K^x z_a)} K + \frac{\frac{1-a}{H} z_A (1 - \alpha K^x \bar{z})}{\frac{1-a}{H} K\bar{z}(1 - \alpha K^x \bar{z}) + \left(a + \frac{1a}{H}(H-1)\right) K z_a (1 - \alpha K^x z_a)} \times K(H-1) \tag{13}$$

where H is the total number of infected hosts in the local population; z_A is the mutant's strategy and z_a is the resident's strategy (note: H can be more generally treated as the number of patches in a structured population). K^x measures the negative impact, if any, of increasing the number of coinfections on total reproductive output for the parasite, where x controls the shape of the relationship ($x = 0$ in Frank's model; and $x = 1$ in the model by Chao *et al.*). The variable a gives the scale of competition (Frank, 1998; West *et al.*, 2001; West & Buckling, 2003). So, for example, if 100% of the propagules produced in a host are transferred together to a single new host (the 'private host'), and there is no competition from propagules produced in other hosts, then $a = 1$; if, instead, the propagules are mixed evenly with all the propagules produced by all the hosts in the local host population, then $a = 0$. The first term on the right-hand side of eqn 13 gives the proportion of K infections gained in the 'private host'. The second term on the right-hand side of equation gives the proportion of the $K(H - 1)$ infections gained in all other hosts, assuming that $(1 - a)$ of the mutant's propagules become randomly mixed with $(1 - a)$ of the propagules produced in the other hosts. Note that the numerator in the second term is similar to that for Chao *et al.* (2000), except that it is now multiplied by $(1 - a)/(H)$, which gives the fraction of propagules per host that compete in the randomly mixed population of propagules. The denominator of the second term contains the sum of two terms: the term on the left-hand side of the denominator $[K\bar{z}(1 - \alpha K^x \bar{z})]$ gives the total production of transmission stages produced in the focal host (the host containing the lineage with the mutant allele), whereas the term on the right-hand side of the denominator $Kz_a(1 - \alpha K^x z_a)$ gives the number of transmission stages produced in all other $(H - 1)$ susceptible hosts in the population. Fitness is thus estimated as the proportion of transmission stages in the population that are generated by the mutant stain with allele A. The specific assumptions regarding the biology of the host–parasite interaction are similar to that given in Lively (2005).

The solution for the equilibrium using Taylor & Frank's (1996) method turns out to be:

$$z^* = \frac{K^{-x}}{\alpha}\left(\frac{H(1 - a^2R) - R(1 - a^2)}{H(1 + R - 2a^2R) - 2R(1 - a^2)}\right), \tag{14}$$

which is both an ESS and a CSS, as the conditions of eqns 4 and 5 are met respectively. If the host population is infinitely large, the ESS simplifies to become:

$$z^* = \frac{K^{-x}}{\alpha}\left(\frac{1 - a^2R}{1 + R(1 - 2a^2)}\right) \tag{15}$$

If, in addition to an infinite host population, there is also random dispersal among hosts ($a = 0$), the ESS simplifies to

$$z^* = \frac{1}{\alpha K^x(1 + R)}, \tag{16}$$

which for $x = 1$ is the same result obtained by Chao *et al.* (2000) and Lively (2005).

On the other hand, if the local host population is small, or if the scale of competition (a) is high, then a more aggressive parasite growth is favoured by selection. For example, for either H or a equal to 1, then eqn 14 simplifies to become:

$$z^* = \frac{1}{\alpha K^x}. \tag{17}$$

Note that the term for relatedness (R) has dropped out of the result in eqn 17, and that more aggressive parasite reproduction is expected than for the case where there is no local host competition (assuming $R > 0$ in eqn 16). Thus, in the absence of between-host competition, there is no selection on parasites to reduce their growth rate in proportion to their relatedness. This result is similar to that obtained by Taylor & Bulmer (1980); they showed that selection favours a Fisherian sex ratio, independent of the number of foundresses, if there is only one patch. The result is also similar to Wade's (1985) finding that between-group competition is required to select for altruism (see also equation 11 in Gardner & West, 2006).

The results above are presented in an 'open' form, in which a and R are allowed to vary independently (see Gardner & West, 2006). Although there are advantages in using the open form, there are also advantages in using the 'closed' form in which R is defined in terms of other variables in the model, including the scale of competition, a (Taylor, 1992; Gardner & West, 2006). Taylor (1992) was the first to give recursion equations for the change in relatedness over time in viscous populations. The equilibrium value for R is then easily obtained (Gardner & West, 2006). Assuming an infinite host population, and following Taylor (1992), the equilibrium relatedness is

$$R = \frac{1}{K - a^2(K-1)}. \tag{18}$$

Substituting this value for R into eqn 15, we get:

$$z^* = \frac{K^{1-x}}{\alpha(1+K)}. \tag{19}$$

Note that the scale of competition, a, has dropped out of the solution for z^*. This finding suggests that population viscosity would not affect the evolution of parasite virulence, at least in large host populations. Similar results have been found in closed models for the evolution of indiscriminate, whole-group altruism, in which the scale of competition did not affect the conditions for the spread of an altruistic trait (Taylor, 1992; Wilson *et al.*, 1992; Gardner & West, 2006). The reason is that, while population viscosity increases relatedness at equilibrium, it also increases local competition, and the two effects exactly cancel each other out (see Gardner & West, 2006).

By contrast, the variable x (which determines how the number of coinfections affects the tragedy of the commons) has a large qualitative effect on the ESS. Based on a numerical analysis of eqn 19, two coinfections would each be expected to reproduce at a faster rate than a single infection (giving Frank's result) if x is less than 0.4. Otherwise ($x > 0.4$), the effect of adding a coinfection would be to reduce the rate of reproduction for each of the individual strains (giving Chao *et al.*'s result).

The above results (eqns 18 and 19) assume that relatedness, R, is at equilibrium. An alternative view is that the relatedness of the rare mutant bearing the A allele is simply $1/K$ at the locus controlling the growth rate. Substituting $1/K$ for R in eqn 14, we get:

$$z^* = \frac{K^{-x}}{\alpha}\left(\frac{HK - a^2(H-1) - 1}{H(1+K) - 2a^2(H-1) - 2}\right), \tag{20}$$

which for an infinite host population simplifies to:

$$z^* = \frac{K^{-x}}{\alpha}\left(\frac{K - a^2}{K + 1 - 2a^2}\right). \tag{21}$$

Note that the scale of competition does not drop out of the solution. Hence, whether or not the scale of competition, a, affects the ESS depends on how relatedness, R, is modelled. If instead the host population is finite, and there is random parasite dispersal ($a = 0$), eqn 20 simplifies to become:

$$z^* = \frac{K^{-x}}{\alpha}\left(\frac{HK - 1}{H(K+1) - 2}\right) \tag{22}$$

Taken together, these results suggest that the parasite's growth rate at equilibrium, z^*, increases as local host competition increases (i.e. z^* increases as either H becomes smaller or a becomes larger).

In Fig. 1, z^* in eqn 21 is plotted against the scale of competition (a) for different values for K (the number of infections per host) and x (the exponent controlling the negative effect of the number of infections on parasite productivity). As above, the overall pattern for z^* depends strongly on x. For $x = 0$, the parasite is expected to reproduce more rapidly as the number of coinfections increases (Fig. 1a), which is consistent with Frank's model under the same assumption. For $x = 1$, each coinfection is expected to reproduce more slowly as the number of coinfections increases (Fig. 1c), which is consistent with the results of Chao *et al.* (2000) and Lively (2005). In either case, z^* increases as the scale of competition increases, but the effect is modest for values of K greater than about 10 (Fig. 1a–c). This latter result

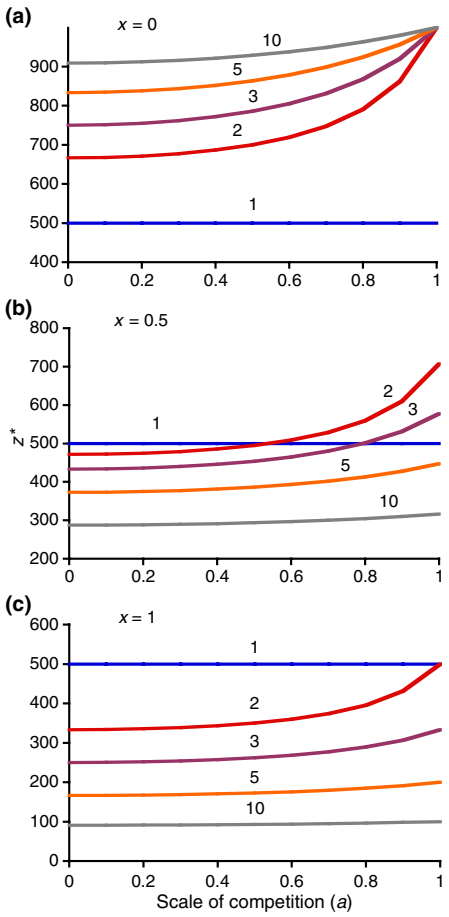

Fig. 1 The evolutionarily stable strategy (ESS), z^*, plotted as a function of the scale of competition, a. (a) $x = 0$, meaning that the negative effect of parasite reproduction on transmission does not depend on the number of coinfections (as in Frank, 1996). (b) $x = 0.5$, meaning that the negative effect of parasite reproduction on transmission depends on the square root of the number of coinfections. (c) $x = 1.0$, meaning that the negative effect of parasite reproduction on transmission does depends on the number of coinfections (as in Chao *et al.*, 2000; Lively, 2005). The numbers above the lines give the number of infections (K) in the host, where $K = 1$ represents the baseline situation for one infection per host. Note that increasing x from 0 to 0.5 reverses the effect of adding coinfections on the ESS. Moreover, note that increasing the number of coinfections reduces the relative effect of the scale of competition, a. This later result may explain the results from an experimental evolution study on parasitic nematodes in which no effect of the scale of competition was observed, given a large number of coinfections (Bashey *et al.*, 2007). The results presented here are for $\alpha = 0.001$, $H = 1000$ and $R = 1/K$.

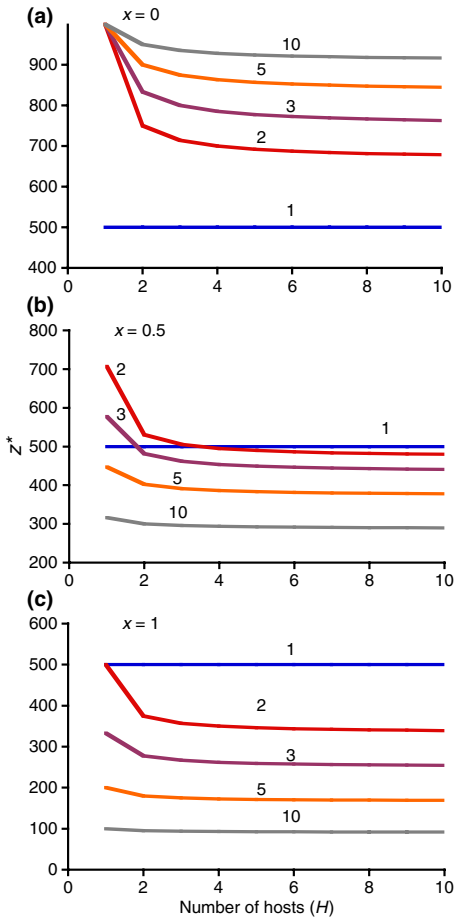

Fig. 2 The evolutionarily stable strategy (ESS), z^*, plotted as a function of the number of hosts, H, in the local host population. (H can be more generally interpreted as the number of patches in a structured population). (a) $x = 0$. (b) $x = 0.5$. (c) $x = 1.0$. As in Fig. 1, the numbers above the lines give the number of infections (K). The results presented here are for $\alpha = 0.001$, $a = 0$ and $R = 1/K$.

may explain the outcome of an experimental evolution study, which found no effect of varying the scale of competition, but used a large number of coinfections (Bashey *et al.*, 2007). More generally, the condition for coinfection to increase z^* in an infinite host population is:

$$\frac{2(K-a^2)}{K^x(K+1-2a)} > 1. \qquad (23)$$

The results are conceptually similar for a finite host population. In Fig. 2, z^* is plotted as a function of the number of hosts (or patches) in the population, assuming random dispersal of parasites ($a = 0$) (eqn 22). The results show that parasite growth rates are selected to decrease as the number of hosts in the population increases (but the magnitude of the effect is small for host number (H) greater than about 4). Thus, decreasing the host population has the same effect on the parasite's ESS as increasing the scale of competition.

Discussion

In the present study, two kin selection models were compared for the evolution of parasite life history.

Frank's (1996) model shows that increasing the number of unrelated coinfection selects for more within-host reproduction by the parasite. By contrast, the model by Chao *et al.* (2000) found exactly the opposite result. The reason for this difference is not immediately obvious. The results of the present study suggest that the difference could be due to how the two models treat the effect of adding coinfections on the tragedy of the commons. Under, Frank's (1996) assumption ($x = 0$ in the present model), the number of coinfections has no effect on the tragedy of the commons, which relies only on the mean reproductive strategy of the coinfections. In this case, more aggressive growth is favoured by each of the coinfecting strains as the number of coinfections increases (Fig. 1a). Alternatively, under the assumption of Chao *et al.*'s (2000) model ($x = 1$), the effect of each coinfection increases the tragedy of the commons in a linear way. This reverses the effect of adding coinfections, such that less aggressive parasite growth is favoured by selection as the number of coinfections increases (Fig. 1c). If we examine the effect of x over the continuum from zero to one, we find that the rank order for the effect of K on z^* changes at an intermediate value of x (Fig. 1c). These results suggest that measuring the effects of adding coinfections on the tragedy of the commons, $f(\bar{z})$, would repay the effort.

The results of the present study also suggest that, if relatedness is at equilibrium (see Taylor, 1992), the scale of competition, a, does not affect the ESS. In this case, the increase in local competition associated with an increase in the scale of competition (a) exactly cancels out the effect of increasing relatedness. This result mirrors previous 'closed' models on the evolution of whole-group altruism, wherein the scale of competition was found not to influence the spread of altruistic behaviours when relatedness was at equilibrium (Taylor, 1992; Gardner & West, 2006).

On the other hand, mutations at a locus controlling parasite growth rate might be expected to perturb the equilibrium relatedness (at least at that one locus). If the model is 'closed' by assuming that the mutant is unrelated to all other coinfections, then $R = 1/K$. Under this assumption, both the scale of competition and the size of the local host population affect the ESS. When parasite propagules are dispersed at random ($a = 0$), the ESS converges on the result of Chao *et al.* (2000) as the size of the susceptible host population increases. Conversely, when the host population is very small or the scale of competition is high selection favours parasite genotypes that grow more rapidly. The magnitude of this effect, however, diminishes with increases in the number of coinfections (Figs 1 and 2).

Why would greater virulence be selected in small host populations than in large host populations or when the scale of competition is high? I think the result stems from the way the relative fitness was portrayed in eqn 13. As host population size increases, the contribution of transmission stages from the focal host to the total pool of competitors becomes very small. Hence, there is selection to simply maximize the number of successful transmission stages as a strategy to compete primarily with the propagules produced in other hosts. However, if the host population size is very small (or the scale of competition is high), then there would be a selective advantage to growing faster, effectively reducing the total number of successful transmission stages, as a way of increasing fitness relative to the other infections in the same host (the focal host). Thus, more aggressive reproduction might be expected when within-host competition is more important than between-host competition, as might be expected in emerging infectious diseases. (These results depend on the assumption that hosts are widely dispersed; different results would be expected if infection depletes the local host population; Boots & Sasaki, 1999; O'Keefe & Antonovics, 2002; Boots & Mealor, 2007). On the whole, the present results are consistent with other models on a variety of social interactions that consider the effects of local competition, including sex ratio evolution (Taylor & Bulmer, 1980), the evolution of cooperation (Frank, 1998; West *et al.*, 2001, 2007; West & Buckling, 2003; Griffin *et al.*, 2004) and the evolution of spite (Gardner & West, 2004).

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