

Cooperation, virulence and siderophore production in bacterial parasites

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Kin selection theory predicts that the damage to a host resulting from parasite infection (parasite virulence) will be negatively correlated to the relatedness between parasites within the host. This occurs because a lower relatedness leads to greater competition for host resources, which favours rapid growth to achieve greater relative success within the host, and that higher parasite growth rate leads to higher virulence. We show that a biological feature of bacterial infections can lead to the opposite prediction: a positive correlation between relatedness and virulence. This occurs because a high relatedness can favour greater (cooperative) production of molecules that scavenge iron (siderophores), which results in higher growth rates and virulence. More generally, the same underlying idea can predict a positive relationship between relatedness and virulence in any case where parasites can cooperate to increase their growth rate; other examples include immune suppression and the production of biofilms to aid colonization.

Keywords: biofilm; coevolution; competition; iron; kin selection; symbiosis

1. INTRODUCTION

Recent years have seen an increasing interest in developing evolutionary theory to predict parasite virulence, the damage to a host resulting from parasite infection (Bull 1994; Ebert & Herre 1996; Frank 1996, 1998; Ebert 1998; Gandon *et al.* 2002). A large fraction of the theoretical work in this area has been based on kin selection (Hamilton 1964; Frank 1998), focusing on the consequences of variation in the genetic relatedness between the parasites infecting a host—higher numbers of unrelated parasite lineages infecting a host lead to a lower relatedness. The basic prediction arising from this body of theory is that a lower relatedness favours higher virulence (Hamilton 1972; Bremermann & Pickering 1983; Nowak & May 1994; Frank 1992, 1996). This occurs because it leads to greater competition for host resources, which favours rapid growth to achieve greater relative success within the host, and that higher parasite growth rate leads to higher virulence.

Despite the enormous amount of theoretical work in this area, there are few empirical data that support the prediction that virulence should be negatively correlated with within-host relatedness of parasites (Chao *et al.* 2000; Read & Taylor 2001; Griffin & West 2002; Read *et al.* 2002; for an exception see Herre 1993, 1995). One possible explanation for this discrepancy is the difficulty of appropriately measuring genetic relatedness and virulence in natural populations (Herre 1993; Pickering *et al.* 2000). However, another possibility is that the details of particular host–parasite interactions can break the assumptions of standard kin-selection virulence models, and lead to different predictions (Frank 1996; Turner & Chao 1999; Chao *et al.* 2000; Brown *et al.* 2002; Read *et al.* 2002). We describe and model a specific example, siderophore-

mediated iron acquisition by bacteria, where the underlying biology can lead to a positive correlation between relatedness and virulence, which is the opposite of the usual prediction.

Many parasites of medical and veterinary importance are bacteria. A major factor limiting the *in vivo* growth of parasitic bacteria is iron availability (Guerinot 1994; Ratledge & Dover 2000). Under aerobic conditions, iron exists in the largely insoluble ferric form (Fe(III)) and, many host species actively withhold iron from infecting bacteria using proteins with a high iron affinity (Payne 1993). In response, bacteria have evolved numerous mechanisms to scavenge iron from their hosts. One mechanism common to many species of parasitic bacteria (and many other microbes) is the production and uptake of siderophores: iron-binding agents released into the environment in response to iron deficiency (Guerinot 1994; Ratledge & Dover 2000). To date, more than 500 siderophores produced by bacteria, yeasts and fungi have been identified (Ratledge & Dover 2000). The relationship between siderophore production and bacterial growth rates has led to the belief that siderophore production contributes to bacterial virulence. This view is supported by the reduced virulence of mutants deficient in siderophore production. Examples include *Yersinia pestis*, the causative agent of bubonic plague (Bearden *et al.* 1997), *Pseudomonas aeruginosa*, an opportunistic pathogen of patients suffering from cystic fibrosis (Meyer *et al.* 1996) and *Vibrio vulnificus*, a cholera-related pathogen associated with septicemia arising from eating infected shellfish (Litwin *et al.* 1996).

A crucial feature of siderophores is that they potentially benefit all bacteria within the locality. Assuming siderophore production is metabolically costly, there is a clear potential for the evolution of selfish bacteria that do not produce siderophores but are capable of their uptake once iron has been bound. Such selfish bacteria exist and are able to spread in populations of siderophore producers

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(De Vos *et al.* 2001). Consequently, the evolutionary stable level of siderophore production can be influenced by kin selection, and is a classic ‘tragedy of the commons’ problem. We show that high relatedness between bacteria parasites within a host can select for higher levels of siderophore production, a form of cooperation that allows the parasites to better exploit the host, and leads to a higher virulence. The model that we develop is very general, and we suggest other parasite systems to which it could apply.

2. SIDEROPHORE PRODUCTION

(a) *Simplest scenario*

In this section, we provide a simple model for siderophore production and virulence in bacteria. Our model is of a form commonly used to examine a behaviour that is costly to the individual performing it, but provides a benefit to the group in which it is a member (Frank 1998). In the following sections we extend this model to incorporate two complicating factors that can influence the evolution of parasite growth rates (and hence virulence): parasite induced host mortality (§ 2b), and within-host competition for resources (§ 2c).

We consider the fitness of a focal bacteria lineage (clone or genotype) that is allocating a proportion y of its resources to the production of siderophores. This focal lineage is assumed to be infecting a host in which (i) the average relatedness between the bacteria is r (e.g. $r = 1$ if the host is only infected by the focal lineage, or $r = 1/n$ if n equally abundant lineages are infecting the host), (ii) the average allocation of resources to siderophore production by all the bacteria lineages infecting the host is z , and (iii) the survival of the host and resources available to the parasites are not influenced by the growth rate of the parasite (this assumption is relaxed in § 2b). Our aim is to find the unbeatable value of y (denoted y^* ; Hamilton 1967), the rate of siderophore production that cannot be outcompeted by any other strategy.

We assume that the fitness of the focal lineage is directly proportional to the rate at which it grows within a host. Siderophore production will influence growth rate in two ways.

- (i) Siderophore production by the focal lineage will decrease its growth rate because it means fewer resources can be put directly into growth or reproduction. We allow for this by assuming that growth rate is a positive function of G , which is a function of y . Our predictions are obtained without specifying a relationship for G , except that there is a negative relationship between G and y . However, when a specific relationship is required for illustrative purposes (figures 1–4), we use $G = (1 - y)$.
- (ii) Siderophore production can increase growth rate because it increases iron availability when growth is iron limited. We allow for this by assuming that growth rate is a positive function of I , which is a function of z , the average rate of siderophore production in the host. Our predictions are obtained without specifying a relationship for I , except that there is a positive relationship between I and z . However, when a specific relationship is required for illustrative purposes (figures 1–4), we use $I = z^b$ ($b < 1$).

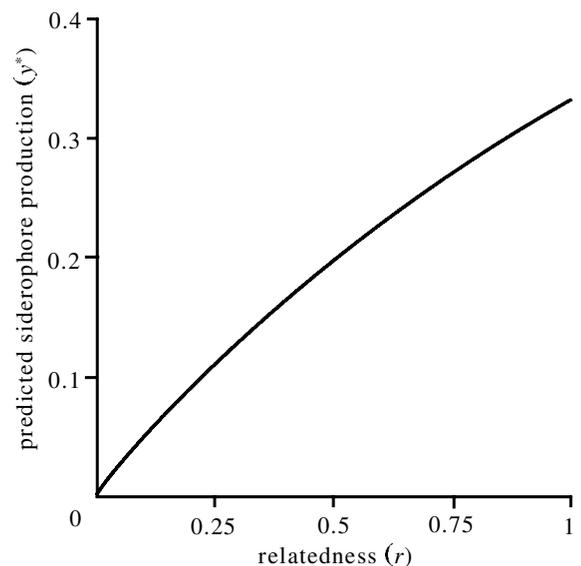


Figure 1. The unbeatable rate of siderophore production (y^*) plotted against the relatedness between the bacteria infecting a host (r). Results were obtained numerically with the multiplicative model (§ 2a; equation (A 3)), assuming $G = 1 - y$ and $I = z^{0.5}$. A greater relatedness between the bacteria infecting a host favours a higher rate of siderophore production.

These assumptions illustrate the trade-off that is fundamental to our model of siderophore production. Increasing siderophore production is beneficial to the lineage because it leads to a greater supply of iron (through the contribution of y to z), but costly because it decreases the resources available for growth (i.e. increases I , and decreases G). Crucially, the benefit of siderophore production is shared with other bacterial lineages, and so the importance of this benefit will depend upon the relatedness between the lineages infecting the host—higher relatedness increases the kin-selected benefit of siderophore production.

The functions G and I could be combined to give an equation for the overall fitness (growth rate) of a bacteria lineage (W) either multiplicatively ($W = GI$) or additively ($W = G + I$). The relation of these equations to Hamilton’s rule (Hamilton 1963, 1964) and related theory (e.g. Frank 1998; Brown 1999; West *et al.* 2002a) are discussed in § 3 and Appendix A. For both the multiplicative and additive case, we show in Appendix A that the following results are obtained.

(i) *Result 1*

The unbeatable rate of siderophore production (y^*) is positively correlated with the relatedness of bacteria lineages in a host (r) (figure 1). As relatedness increases, the benefits of increased iron scavenging will be shared with closer relatives, increasing the kin-selected benefit of siderophore production (i.e. higher cooperation is favoured).

We assume that the virulence of the bacteria parasites is proportional to their growth rate (W). In this case, virulence is proportional to the unbeatable rate of siderophore production (y^*), and so:

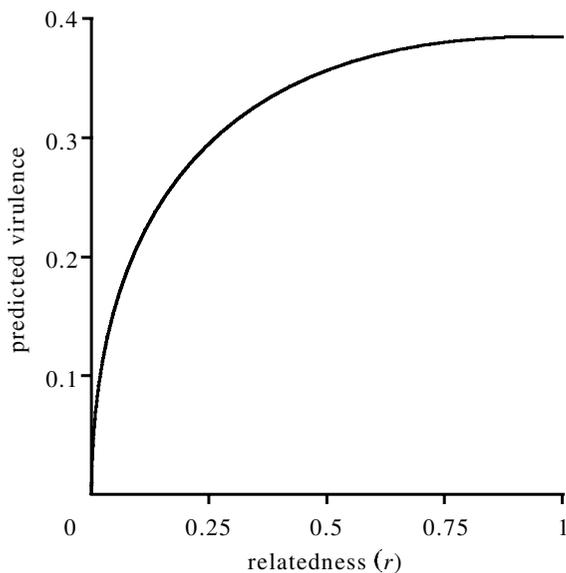


Figure 2. The predicted virulence (damage to the host) plotted against the relatedness between the bacteria infecting a host (r). Virulence is assumed to be proportional to the mean growth rate of the bacteria in a host, and is plotted here as GI (see § 2a, multiplicative model). Results were obtained numerically with the multiplicative model, assuming $G = 1 - y$ and $I = z^{0.5}$. A greater relatedness between the bacteria infecting a host leads to a higher virulence.

(ii) *Result 2*

The virulence of a bacterial infection will be positively correlated to the relatedness of bacteria lineages in a host (r) (figure 2). As relatedness increases, greater cooperation between the bacteria infecting a host is selected for—this allows the bacteria to produce more siderophores and grow more in the host, which leads to a higher virulence.

(b) *Host mortality*

The model described above illustrates the basic points of how higher relatedness might lead to higher levels of siderophore production (a form of cooperation between bacterial parasites), and hence higher parasite virulence. However, this model assumed that the amount of host resources available to the parasites was independent of bacterial parasite growth rate or virulence. Although this may be the situation for some parasites, in other cases increased parasite growth rate or virulence can lead to a reduced resource availability, for example due to a higher host mortality rate (Frank 1996).

We allow for this by assuming that parasite fitness is proportional to the host survival rate (S) (Frank 1996). S is a function of the growth rate of bacteria, and hence a function of z , the average rate of siderophore production in the host. Our predictions are obtained without specifying a relationship for S , except that there is a negative relationship between S and z . However, when a specific relationship is required for illustrative purposes, we assume that $S = 1 - cF$, where c is a constant and F is the mean growth rate of the bacteria in the host (Frank 1996), given by $F = G(z) + I(z)$ or $F = G(z)I(z)$ in the additive and multiplicative case, respectively.

This alters the trade-offs involved because it leads to the added complication that increasing siderophore production (and parasite growth) can be costly because it

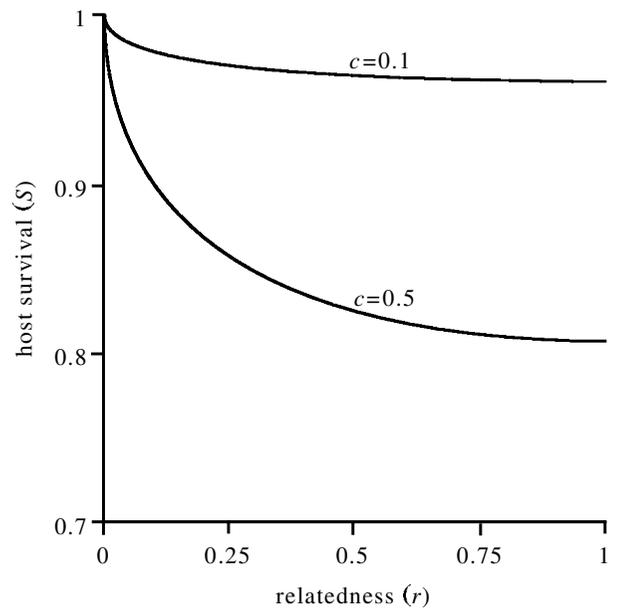


Figure 3. The predicted host survival (S ; negatively related to virulence) plotted against the relatedness between the bacteria infecting a host (r). Results were obtained numerically with the multiplicative model (§ 2b), assuming $G = 1 - y$, $I = z^{0.5}$ and $S = 1 - cF$. A greater relatedness between the bacteria infecting a host leads to a higher rate of host mortality.

decreases the host survival rate S (i.e. increases parasite-induced mortality). Crucially, this cost is shared with all of the bacteria infecting the host, and so its importance will depend upon the relatedness between the lineages infecting the host (higher relatedness increases the kin-selected cost of mortality resulting from increased siderophore production and growth).

The effect of host survival is incorporated multiplicatively into our model (as is usually done with models of parasite virulence; see Frank 1996, 1998), giving $W = GIS$ or $W = (G + I)S$. In either case, we show in Appendix A that results 1 and 2 still hold. Consequently, the inclusion of host mortality does not alter our prediction that there will be a positive relationship between relatedness and parasite virulence. Figure 3 shows some specific examples of how host survival (negatively correlated to parasite virulence) is predicted to vary with relatedness in this model. Interestingly, analyses of specific examples suggest that the unbeatable rate of siderophore production (y') is largely invariant to the effect on host mortality. Although parasite-induced host mortality leads to quantitatively lower levels of siderophore production, as it can favour lower growth rates, this effect is usually negligible. This suggests that in contrast to other scenarios, medical intervention to prevent death might have little direct effect on the evolution of virulence (although there could be indirect effects of drug intervention via its influence on relatedness r) (van Baalen & Sabelis 1995; Frank 1996).

(c) *Within-host competition*

The above models assumed that the growth and transmission rate of a lineage is independent of the rate at which other lineages are growing in a host (i.e. only absol-

ute growth rate is important; global competition or hard selection). Although this can make sense in some cases, different lineages may often compete for limited host resources or opportunities for transmission (this point is discussed in detail by Frank 1996). This is commonly allowed for by assuming that the transmission rate of the focal lineage depends upon its growth rate *relative* to the other lineages in the host (Frank 1996; local competition within hosts, or soft selection; this distinction is similar to that between superinfection and coinfection; May & Nowak 1995; Frank 1996). For example, the multiplicative version of our simplest model would become $W = G(y)I(z)/G(z)I(z)$. In Appendix A we show that when we extend our model in this way to make transmission depend upon relative growth rate, then for all situations (multiplicative or additive, with or without parasite-induced host mortality).

(i) *Result 3*

If transmission depends upon relative growth rate then siderophore production is never favoured ($y^* = 0$). The reason for this is that siderophores provide a greater benefit to the other lineages in a host, who gain the benefit of increased iron scavenging, but do not pay the cost of siderophore production. Hence, siderophore production would reduce the relative growth rate of the focal lineage, and not be favoured. The fact that siderophore production does occur, suggests that this extreme form of competition does not occur, and that absolute growth rate must be important to some extent.

It is of course possible to imagine scenarios in which the transmission rate of a lineage depends not upon the extremes of either absolute or relative growth rate, but somewhere between these two extremes. We extended our model to allow for this possibility by making transmission rate depend upon relative growth rate with a probability a , and absolute growth rate with a probability $(1 - a)$. The parameter a can vary from 0 to 1.0: when $a = 0$ growth and transmission of a lineage are independent of the rate at which other lineages are growing in the host (global competition); as a increases the growth and transmission of a lineage becomes more dependent upon its growth relative to the other lineages in the host (competition becomes more local); in the extreme, when $a = 1$ the growth and transmission of a lineage depends only upon its growth relative to the other lineages in the host (local competition). In Appendix A we show that with intermediate forms of competition ($a < 1$) results 1 and 2 still hold.

(ii) *Result 4*

As the transmission rate of a lineage depends more upon relative growth rates within hosts (higher a ; more local competition), a lower level of siderophore production is favoured (lower y^* ; figure 4), and a lower predicted parasite virulence. Result 3 represents the extreme case of when $a = 1$, and siderophore production is not favoured ($y^* = 0$).

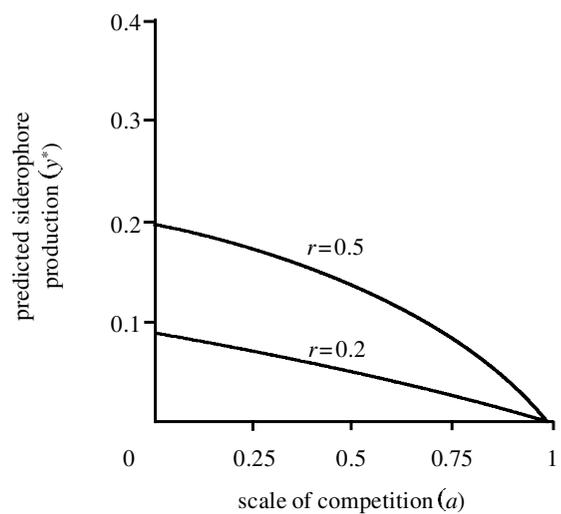


Figure 4. The unbeatable rate of siderophore production (y^*) plotted against the extent to which transmission is determined by relative growth rate within a host (a). Results were obtained numerically with the multiplicative model (§ 2c), assuming $G = 1 - y$, $I = z^{0.5}$ and $S = 1 - 0.1F$. Different lines represent different relatedness between the bacteria infecting a host. As transmission becomes more dependent upon relative growth rate, a lower rate of siderophore production (and therefore virulence) is favoured.

3. DISCUSSION

(a) *Siderophore production and cooperation in bacteria*

We predict a positive correlation between the within-host relatedness of bacterial parasites (r), and the rate of siderophore production (y^* ; figure 1). The reason for this is that as relatedness increases, the benefits of increased iron scavenging will be shared with closer relatives, increasing the kin-selected benefit of siderophore production. Our model predicts variation across populations or species dependent upon the average relatedness, as well as facultative variation in cases where bacteria can assess within-host relatedness (i.e. clone recognition). There are few reports of siderophore cheats in natural populations (but see De Vos *et al.* 2001), which is consistent with the apparent clonality (high relatedness; Tibayrenc 1996) of most bacterial infections. Of course, both lack of within-host genetic variation and siderophore cheats may reflect sampling deficiencies and insensitivity of measures. Indeed, the significant contribution of recombination to the genetic diversity of many species of parasitic bacteria (Feil & Spratt 2001) demonstrates that mixed genotype infections do occur.

Analogous predictions could be applied to a range of traits in bacteria and other organisms. For example, (i) siderophore production in free-living bacteria: in this case we would predict greater siderophore production when there is a higher relatedness over the spatial scale at which siderophores disperse (although this could be reduced by competition between relatives; West *et al.* 2002a,b). (ii) Any trait that increases the fitness of all parasites within a host: Brown (1999) has discussed this in the context of host-manipulating parasites, giving a range of examples (e.g. parasite manipulation of host behaviour to increase susceptibility to predation, concomitant immunity and

immune suppression; see also Chao *et al.* 2000), and made the same prediction based upon some special cases of the multiplicative model without host mortality (i.e. $W = GI$). (iii) Any trait in any organism that has a cost, but provides a general benefit locally or within groups (Frank 1998; Brown 1999, 2001; Brown *et al.* 2002; see table 1 of Pepper 2000): examples within bacteria include social predation, and aggregations of cells into spore-producing fruiting bodies (Strassmann *et al.* 2000; Velicer *et al.* 2000; Crespi 2001).

(b) Cooperation and parasite virulence

We predict a positive correlation between the within-host relatedness of bacterial parasites, and the damage that they do to their host (parasite virulence) (figures 2 and 3). This prediction is in the opposite direction to that commonly given by kin selection models of parasite virulence (Frank (1996) but see Chao *et al.* (2000) for an exception that is discussed below). It arises because a higher relatedness can lead to a greater production of siderophores (as described above), which results in the acquisition of more resources from the host and higher parasite growth rates. Importantly, our prediction remains when there is parasite-induced host mortality (§ 2b) or some within-host competition for resources (§ 2c). Similar ideas could apply to any parasite species in which different lineages can cooperate to increase their within-host growth rates, and hence acquisition of host resources, for example, anything that is released to help devour the host (e.g. Shiga toxins; O'Loughlin & Robins-Browne 2001), to avoid host immune response (immune suppression) or antibiotics (such as the forming of biofilms), or help colonization (Brown 1999, 2001; Turner & Chao 1999; Chao *et al.* 2000; Crespi 2001; Miller & Bassler 2001; Brown *et al.* 2002; Drenkard & Ausubel 2002). As well as explaining variation in virulence, our results predict how virulence will evolve in response to intervention programmes. For example, control programmes that reduced parasite transmission could lead to an increase in relatedness r , and hence an increase in virulence.

Chao *et al.* (2000) have previously suggested some situations in which a positive relationship between relatedness and virulence could be produced. Their arguments seem to rely on the same mechanism that we have modelled here, namely cooperation between parasites increasing the utilization of host resources. Specifically, they (i) developed verbal arguments based upon a lower relatedness favouring lower levels of a behaviour that benefits all the parasites in the host (protein synthesis by a virus), but which involves a cost to the individual (decreased resources for replication) (Turner & Chao 1999); and (ii) examined the invasion conditions for a fitness equation that was based on one of Frank's virulence models (Frank 1996), and is analogous to our multiplicative model with host mortality (i.e. $W = GIS$). Consequently, in some respects we have formalized and extended their arguments. However, Chao *et al.* (2000) argue that their prediction is in the opposite direction to classical kin selection models of virulence because classical models assume hard selection with absolute growth rate determining fitness, whilst they examine the consequences of soft selection, where fitness is determined by relative growth. We find this soft or hard selection distinction less

useful because (i) contrary to the claim of Chao *et al.* (2000), many classical kin selection models that produce a negative relationship between relatedness and virulence assume soft selection over competition for resources within hosts (e.g. eqns 3 and 4 of Frank 1996); (ii) soft selection within hosts can actually lead to a steeper negative relationship between relatedness and virulence (pp. 42–43 of Frank 1996); (iii) the evolution of cooperation appears to be the crucial factor producing a positive relationship between relatedness and virulence (which can be conceptualized with kin or group selection approaches; Frank 1998); and (iv) as discussed in § 2c, soft selection over competition for resources within a host can actually remove the positive relationship between relatedness and virulence that arises due to possible cooperation (figure 4). More generally, the consequences of the scale of competition (hard or soft, or global or local) for all forms of social behaviour have recently been reviewed by Frank (1998) and West *et al.* (2002b).

We have made a number of simplifying assumptions with our models, and there are a number of ways in which they could be extended. In particular, we have assumed a static model, with no feedback between siderophore production and population dynamics. Although this provides an approximation, specific models could be developed to see how they interplay. For example, (i) a specific population structure with migration and infection could be assumed, and then a fitness measure explicitly derived (Frank 1998; Pen & Weissing 2000); and (ii) theory could be developed based upon classical epidemiological models (Anderson & May 1982; Frank 1996). The development of such models could be particularly useful for cases where the aim is to predict how the virulence of a specific parasite will respond to a given intervention programme (Gandon *et al.* 2002). Another possibility is to allow for effects of group size and quorum sensing, which may be important with some cooperative traits (Brown 1999, 2001; Brown & Johnstone 2001). Finally, the scale of cooperation and competition could be given much more attention. We have assumed the simplest possible scenario with no within-host population structure, and more complex scenarios should be examined. In particular, siderophore production and uptake could take place on a very local scale, leading to a high relatedness even when multiple lineages infect a host (see West *et al.* (2000) for an analogous case with sex ratio evolution in intestinal parasites); whereas host mortality and the relevant relatedness would be determined by all the lineages infecting a host.

(c) Kin selection: parasite virulence versus the sex ratio

It has often been noted that kin selection theory predicts that parasite virulence and the proportion of offspring that are male (termed the sex ratio) should evolve in an analogous way in response to aspects of population structure/demography that influence r (Frank 1992, 1998; Herre 1993; Read *et al.* 1995; Pickering *et al.* 2000; West *et al.* 2000, 2001b). However, whilst empirical data often provides a striking fit to sex ratio theory (Werren 1980; Charnov 1982; Herre 1985), even with microparasites (Read *et al.* 1995; West *et al.* 2000), this has not been the case with parasite virulence. Our results suggest a clear

difference between sex ratios and parasite virulence that can explain this (aside from the fact that sex ratios can usually be measured more easily). Kin selection models for the sex ratio rely on a fundamental trade-off—an offspring must be either male or female, and the form of competition between males does not influence the total number of mates that are available to them (i.e. the biological details often do not matter; Nee *et al.* 2002). By contrast, we have shown how biological details can fundamentally alter the underlying trade-offs of parasite virulence models, hence altering theoretical predictions quantitatively and even qualitatively.

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APPENDIX A

(a) *Model I: simplest scenario*

All of our results are derived using the 'direct fitness' formulation of inclusive fitness of Taylor & Frank (1996; Frank 1998). The fitness of a focal bacteria lineage is given by $W(y, z)$, which is a function of the resources that the bacteria lineage puts into growth ($G(y)$), and the overall iron-scavenging rate ($I(z)$). y is the rate at which the focal lineage produces siderophores, and z is the average rate of siderophore production by all the parasite lineages in the host. $G(y)$ is a negative function of y , and $I(z)$ is a positive function of z . Following Taylor & Frank (1996), the unbeatable rate of siderophore production (y^*) is found by solving $(dW)/(dy)|_{z=y^*} = 0$, with the derivative of W being obtained with the chain rule, and the phenotypic derivatives replaced with the corresponding relatedness coefficient (r).

If $G(y)$ and $I(z)$ interact additively in their fitness effects, then $W = G + I$, and the equilibrium condition is given by

$$G' + rI' = 0. \quad (\text{A } 1)$$

The relationship between r and y^* can be found with implicit differentiation. Writing $H(y^*, r, G, I)$ for the left-hand side of equation (A 2), we obtain

$$\frac{dy^*}{dr} = -\frac{\partial H/\partial r}{\partial H/\partial y^*}. \quad (\text{A } 2)$$

In order for y^* to be convergence stable (in a population close to y^* , selection favours mutants that are closer to y^*), the denominator of the right-hand side of equation (A 2) must be negative (Taylor 1996). Hence, assuming convergence stability, the sign of dy^*/dr must equal the sign of $\partial H/\partial r$ (Pen 2000). This gives I' , which is positive, and so y^* is positively correlated with r .

If $G(y)$ and $I(z)$ interact multiplicatively in their fitness effects, then $W = GI$, and the equilibrium condition is given by

$$G'I + rGI' = 0. \quad (\text{A } 3)$$

Implicitly differentiating as above the sign of dy^*/dr is then given by GI' , which is positive, and so y^* is positively correlated with r .

Note that (i) as is usually the case (Frank 1998; Pen &

Weissing 2000), the equilibrium solutions represent a form of Hamilton's rule ($rb - c > 0$; Hamilton 1963, 1964). For example, equation (A 1) gives $c = -G'$ and $b = I'$, and equation (A 3) gives $c = -G'I$ and $b = GI'$. (ii) Analogous versions of the multiplicative model ($W = GI$) have been analysed previously, generally and with a specific case in the context of nitrogen fixing by *Rhizobia* bacteria (West *et al.* 2002a), and for a variety of specific cases in the context of host manipulation by parasites (Brown 1999, 2001). (iii) The use of the direct fitness approach, and equations such as $W = GI$, to examine problems in social evolution more generally is discussed in detail by Frank (1998, ch. 7).

(b) *Model II: host mortality*

Model I is extended by assuming that the host survival rate is $S(z)$. $S(z)$ is assumed to be negatively correlated with the parasite growth rate, and therefore z .

If $G(y)$ and $I(z)$ interact additively in their fitness effects, then $W = (G + I)S$, and the equilibrium condition is given by $G'S + r(S'(G + I) + I'S) = 0$. Implicitly differentiating as above, to give the sign of dy^*/dr , we obtain $S'(G + I) + I'S$, which is positive, and so y^* is positively correlated with r .

If $G(y)$ and $I(z)$ interact multiplicatively in their fitness effects, then $W = GIS$, and the equilibrium condition is given by $G'IS + rG(IS' + I'S) = 0$. Implicitly differentiating as above, to give the sign of dy^*/dr , we obtain $G(IS' + I'S)$, which is positive, and so y^* is positively correlated with r .

(c) *Model III: scale of competition*

Assume that the fitness of a bacterial lineage is given by its growth rate relative to the other strains in the host (following Frank 1996). In this case the fitness equation for the additive case with no parasite-induced host mortality becomes $W = (G(y) + I(z))/(G(z) + I(z))$, and

$$\frac{dW}{dy} = (1 - r)\frac{G'}{G + I}. \quad (\text{A } 4)$$

G' is negative, and so $dW/dy \leq 0$. Consequently, $y^* = 0$, and siderophore production will never be favoured. The same result ($dW/dy \leq 0$; $y^* = 0$) can be shown to hold for multiplicative interactions ($W = G(y)I(z)/G(z)I(z) = G(y)/G(z)$), and also for when there is parasite-induced host mortality (additive: $W = (G(y) + I(z))/G(z) + I(z)S(z)$; multiplicative: $W = (G(y)I(z))/(G(z)I(z))S(z) = (G(y)/G(z))S(z)$).

Assume now that the fitness of a bacterial lineage can be given by anything along the continuum from its absolute growth rate to its growth rate relative to other strains. We do this by incorporating a parameter a , which is the extent to which transmission depends upon relative growth rate ($0 \leq a \leq 1$). In this case, the fitness equation for the additive case with parasite-induced mortality becomes

$$W = (G(y) + I(z))S(z) \left(\frac{a}{G(z) + I(z)} + \frac{1 - a}{G(\bar{z}) + I(\bar{z})} \right),$$

where \bar{z} is the mean rate of siderophore production in the population. This gives the equilibrium condition

$$G'S + r(S'(G + I) + SI' - Sa(G' + I')) = 0. \quad (\text{A } 5)$$

Implicitly differentiating as above, to give the sign of dy'/dr , it can be shown that y' is positively correlated with r . The sign of dy'/da is given by $-rS(G' + I')$ —this could be negative or positive, but for the specific equations we used (i.e. $G = 1 - y$, and $I = z^b$ with $b < 1$) the slope is always negative, and so y' is negatively correlated with a . Qualitatively similar results are obtained with the multiplicative model. Readers familiar with Frank's use of a to scale whether competition is local or global (Frank 1998, p. 114; see also West *et al.* 2001a, 2002a,b) should note that a difference here is that in this case transmission always depend upon an amount of resources that is determined locally (the $S(z)$ term), and that similar results are obtained if the equation is written in a form more similar to eqn (7.1) of Frank (1998).

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