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THE EVOLUTIONARY IMPLICATIONS OF CONFLICT BETWEEN PARASITES WITH DIFFERENT TRANSMISSION MODES

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Understanding the processes that shape the evolution of parasites is a key challenge for evolutionary biology. It is well understood that different parasites may often infect the same host and that this may have important implications to the evolutionary behavior. Here we examine the evolutionary implications of the conflict that arises when two parasite species, one vertically transmitted and the other horizontally transmitted, infect the same host. We show that the presence of a vertically transmitted parasite (VTP) often leads to the evolution of higher virulence in horizontally transmitted parasites (HTPs), particularly if the VTPs are feminizing. The high virulence in some HTPs may therefore result from coinfection with cryptic VTPs. The impact of an HTP on a VTP evolution depends crucially on the nature of the life-history trade-offs. Fast virulent HTPs select for intermediate feminization and virulence in VTPs. Coevolutionary models show similar insights, but emphasize the importance of host life span to the outcome, with higher virulence in both types of parasite in short-lived hosts. Overall, our models emphasize the interplay of host and parasite characteristics in the evolutionary outcome and point the way for further empirical study.

KEY WORDS: **Evolution, feminization, life span, parasites, protection, vertical transmission, virulence.**

Host parasite theory often considers the impact of a single parasite on the dynamics of a single host. However, in natural systems hosts are often challenged by multiple parasites (Woolhouse et al. 2000; Haine et al. 2005; Woolhouse and Gowtage-Sequeria 2005) and this is of course likely to have important implications to the evolutionary dynamics of both parasites and hosts. For example, superinfection, where an invading strain displaces a resident strain in an individual host, often selects for more virulent and competitive parasites (Levin and Pimental 1981; Bremermann and Pickering 1983; Nowak and May 1994). If parasites coinfect the same individual, both within host and population level interactions become important, there are a range of outcomes resulting from multiple infections (Nowak and May 1994; van Baalen and Sabelis 1995; Brown et al. 2002) and in certain circumstances lead to the evolution of greater virulence and the possibility of parasite coexistence (Mosquera and Adler 1998). When parasites that share the same host have different transmission modes and in particular when there is vertically transmission from parent to offspring, conflicts arise. VTPs and horizontally transmitted parasites (HTPs) are both selected to minimize the additional mortality that infection causes. Reduced virulence benefits vertically transmitted parasites (VTPs) by extending the period of host reproduction from infected individuals and equally benefits HTPs by lengthening the infectious period. However, while

the birth rate of the infected host is vital for the persistence and spread of a VTP, the fitness of HTPs is not directly affected by a change in host birth rate. Indeed, HTPs will be selected to castrate hosts if this leads to increased transmission (Jaenike 1996; O'Keefe and Antonovics 2002). Here, we examine, theoretically, the evolutionary implications of the resulting conflict over host reproduction between parasites with different transmission modes.

Vertically transmitted parasites are particularly common in invertebrates (Werren 1997; Hogg et al. 2002; Kelly et al. 2003; Stouthamer et al. 2009) but are found across many taxa (Mims 1981). However, purely VTPs that cause virulence to their host will not persist without some other mechanism that compensates for this virulence (Fine 1975; Lipsitch et al. 1995). An important mechanism, by which a virulent VTP may persist, is the manipulation of the host's reproductive output through altering the sex ratio of the host by either increasing the total number of females born, converting males to females (feminization) or by male killing (Werren 1997; Kageyama et al. 2002; Cordaux et al. 2004; Zeh and Zeh 2006). Hurst (1993) showed, using theory that a sex-ratio distorting purely VTP can be maintained in a population even when there is selection against infected hosts by increasing the number of females born in each cohort. There is also evidence that some VTPs may protect the host against other natural enemies (Oliver et al. 2003; Haine et al. 2005). Recently, theory (Lively et al. 2005; Faeth et al. 2007; Jones et al. 2007) has shown that a purely VTP that causes some virulence to the host is able to persist by protecting the host from a virulent HTP. Furthermore, the greater the virulence of the HTP the easier for the vertical host to persist (Jones et al. 2007). Parasites that transmit vertically may also persist if they transmit to some extent horizontally (Busenburg et al. 1983; Regniere 1984) and in nature many pathogens may indeed possess both means of transmission (Burden et al. 2002; Hackett et al. 2005; Zhou et al. 2005). The evolutionary dynamics of parasites that possess both vertical and horizontal transmission modes have been examined in detail by Lipsitch et al. (1996). A key result is that as parasite numbers increase, they select for greater vertical transmission, due to both the higher potential for generation-to-generation infection and reduced encounters with susceptible individuals (Lipsitch et al. 1996). However, the evolutionary dynamics of purely HTPs and purely VTPs that coinfect the same hosts have not been considered in detail.

Here, our aim is to understand the evolutionary behavior of parasite pathogenicity arising from conflict between two different parasite species that can both infect the same host. We consider a purely VTP, maintained in populations through the manipulation of host reproduction, and assume that it coinfects with an HTP. We start with evolutionary models that examine how in turn the presence of a VTP selects on a horizontally transmitted one and vice versa. Next, we present a fully coevolutionary model that examines the coevolutionarily stable states of both types of parasite in hosts with different characteristics.

The Model

We model the densities of the susceptible host population, X, the population infected with the VTP alone, V, the population infected with the HTP alone, Yx, and the population infected by both the VTP and HTP, Yv and assume that the HTP is directly transmitted. The dynamics are represented by the following system of equations, where all three types of infection (VTP, HTP and both VTP and HTP) coexist

$$\frac{dX}{dt} = (a - qH)(X + (1-\kappa)Y_x) + (1-p)(af - qH)(V + (1-\kappa)Y_v) - (\beta Y + b)X, \quad (1)$$

$$\frac{dV}{dt} = p\,(af - qH)\,(V + (1-\kappa)\,Y_v) - \beta VY - (\alpha_v + b)\,V, \quad (2)$$

$$\frac{dY_v}{dt} = \beta VY - (\alpha_y + \alpha_v + b)Y_v, \quad (3)$$

$$\frac{dY_x}{dt} = \beta XY - (\alpha_y + b)Y_x, \quad (4)$$

where $H = X + V + Y_X + Y_V$ and $Y = Y_X + Y_V$.

Hosts are born at rate a, and have a natural death rate b, with density dependence from the total host population acting on the birth rate via the crowding parameter, q. The birth rate of hosts infected with the VTP can be increased due to the feminization of hosts by a factor, f. A proportion, P, (where $0 \leq P < 1$) of the offspring are born infected with the vertical parasite (therefore $(1 - P)$ are born into the susceptible class), this is a measure of the efficiency of transmission of the VTP. Those infected with the HTP potentially reproduce at a reduced rate due to the level of castration, κ, by the HTP (where $0 \leq \kappa \leq 1$). Susceptible and vertically infected hosts are equally susceptible to horizontal infection, at rate βY. The parameters α_V and α_Y are the additional death rates due to infection from the VTP and HTP, respectively, and assuming a process of coinfection an individual infected with both the HTP and VTP experiences the sum of the mortality rates. A coinfected individual is one infected by both the VTP and HTP and not individuals infected with multiple HTPs or VTPs. For simplicity, we assume that a host infected by one parasite is equally vulnerable to succumb to the additional virulence of a second, and hence the virulence is additive. There are however different possibilities of the effect on overall virulence of multiple infections (Brown et al. 2002).

Results and Analysis

EVOLUTION OF HORIZONTALLY TRANSMITTED PARASITES

For the HTP, we assume a trade-off between transmission rate and virulence (Bremermann and Pickering 1983; Anderson and May 1991; van Baalen and Sabelis 1995; Restif and Koella 2003). This is based on the assumption that the parasites growth rate has a positive relationship on both the transmission and virulence of the HTP on the host (Ebert 1998; Mackinnon and Read 1999a,b; de Roode et al. 2008). Since in many host–parasite interactions transmission is likely to saturate more quickly with parasite growth rates than virulence (Ebert 1998; Mackinnon and Read 1999a,b), we assume that the costs to transmission in terms of virulence are accelerating, leading to an evolutionarily stable transmission and virulence rate (a continuously stable strategy, CSS) (Eshel and Motro 1981). We restrict our analysis to a part of the parameter space where all three parasites coexist and denote this stable equilibrium as $(X_r, V_r, Y_{Xr}, Y_{Vr})$. The techniques of adaptive dynamics (Geritz et al. 1998) are then used to examine the invasion of rare mutants. The invasion exponent, I_m, of a given mutant with parameters (β_m, α_{Ym}), attempting to invade a resident strain with parameters (β_r, α_{Yr}) at equilibrium can be determined by considering the determinant of the resident-mutant Jacobian matrix at the resident equilibrium (see Miller et al. 2005). Assuming there is a trade-off between virulence and transmission such that $\beta_i = g(\alpha_{Yi})$ the invasion exponent (or fitness) can be expressed as follows:

$$I_m = g(\alpha_{Ym})\,(V_r\,(\alpha_{Ym} + b) + X_r\,(\alpha_{Ym} + \alpha_V + b)) - (\alpha_{Ym} + \alpha_V + b)\,(\alpha_{Ym} + b)\,. \quad (5)$$

When $I_m > 0$ the mutant can invade the resident strain.

We examine how VTPs with different characteristics select on the life-history strategy for HTP. In particular, the important life-history characteristics of the VTP are the rates of feminization, f, vertical efficiency, P, and virulence α_v. The derivative of the invasion exponent with respect to the evolving (mutant) parameter can be used to determine the location of the CSS (it occurs when the derivative, fitness gradient, is zero). Pairwise-invasibility plots (PIPs) and simulations of the evolutionary process were additionally used to confirm the properties of the parasite CSS.

The presence of a VTP always selects the HTP for higher transmission and virulence (Fig. 1A and B), an effect that saturates as feminization increases to its maximum (Fig. 1A). This is a consequence of the overall intrinsic growth rate of the host being increased by feminization resulting in more susceptible individuals. As a consequence of their higher prevalence in the host population, VTPs with higher vertical efficiencies, P, will also select for higher HTP transmission and virulence. However, it is VTPs with intermediate rates of virulence that lead to the evolution of the highest transmission and virulence in the HTP (Fig. 1B). This reflects the fact that the greatest number of susceptibles in the system also occurs when the VTP has intermediate virulence. It has been demonstrated previously that larger susceptible densities can select for more virulent pathogens (Andre and Hochberg 2005).

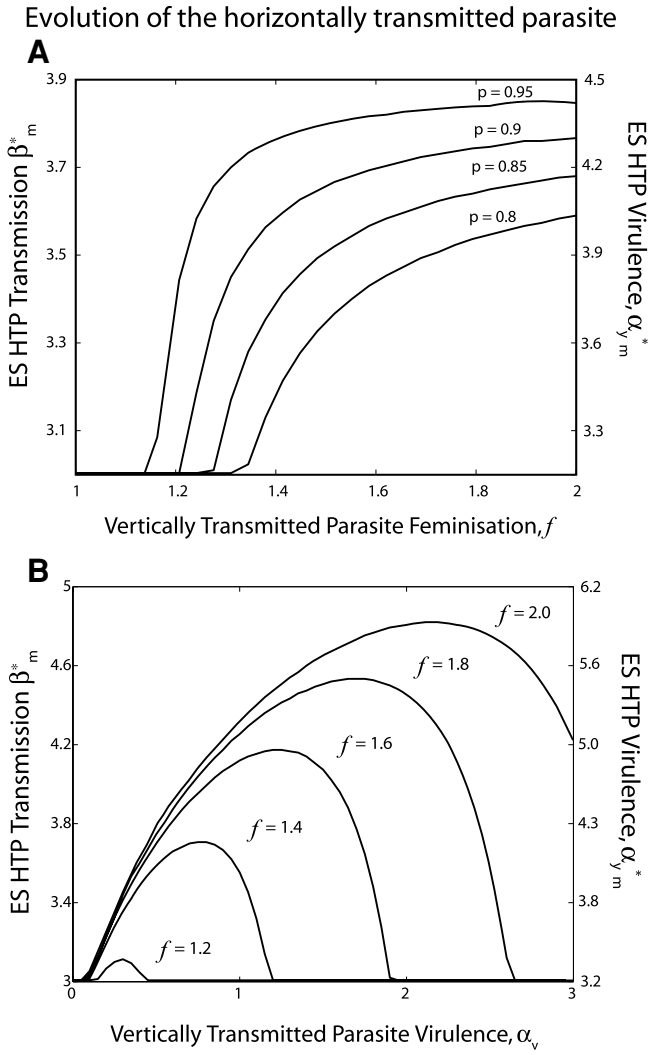

Figure 1. (A) The evolutionarily stable (ES) horizontally transmitting parasite (HTP) transmission rate when coinfecting with vertical transmitting parasites (VTPs) with different feminization rates, and different rates of vertical transmission. (B) The ES HTP transmission rate at varying values of VTP virulence and with varying amounts of feminization. The parameters are $a = 4$, $b = 1$, $\kappa = 0$, $q = 1$ and unless varied in the figure $\alpha_V = 0.5$ $p = 0.9$. The trade-off relationship is, $\alpha_Y = 15 - 4.5(8 - \beta)^{0.6}$.

EVOLUTION OF THE VERTICALLY TRANSMITTED PARASITES

We now examine the evolution of the VTP when faced with an HTP to examine how different characteristics in the HTP alter the optimal strategy of the VTP. Trade-offs in VTPs are less well

established than the transmission virulence trade-off in HTPs, although there are now data to suggest that the high replication rates needed for vertical transmission (Power 1992; Mouton et al. 2004; De Roode et al. 2008) and feminization (Min and Benzer 1997) are detrimental to the hosts. We therefore assume a two separate trade-offs in the VTP, first between the vertical parasites feminization ability and its virulence and second, between the vertical parasites vertical efficiency and its virulence (which is analogous to the standard one in an HTP). As before the trade-offs are assumed to have accelerating costs leading to CSS strategies. We examine how different characteristics of the HTP influence these optimal CSS strategies.

For the VTP feminization-virulence trade-off the invasion exponent of the rare mutant strain (f_m, α_{vm}) invading a resident strain (f_r, α_{vr}) at equilibrium is given by the following expression

$$I_m = (p(af_m - qH) - (\beta Y + \alpha_{vm} + b)) + \frac{(1-\kappa)p\beta Y(af_m - qH)}{(\alpha_y + \alpha_{vm} + b)}. \quad (6)$$

Similarly for the VTP efficiency-virulence trade-off with mutant (p_m, α_{vm}) resident (p_r, α_{vr}) the invasion exponent is

$$I_m = (p_m(af - qH) - (\beta Y + \alpha_{vm} + b)) + \frac{(1-\kappa)p_m\beta Y(af - qH)}{(\alpha_y + \alpha_{vm} + b)}. \quad (7)$$

In biological terms, invasion occurs when the input of new VTPs from the singly infected hosts plus the reproductive output from the coinfected class are greater than the loss from HTP infection and the increased vertical and horizontal virulence.

FEMINIZATION AND VIRULENCE TRADE-OFF

There is a decrease in feminization (and virulence) in the VTP at intermediate levels of castration (Fig. 2B). This results because reducing feminization and increasing life span of the host is more beneficial when the HTP negates the advantage of feminization. This decrease in feminization occurs until a threshold point where castration becomes so punitive that the coinfected individuals becomes less important to VTP fitness. In general, an increase in HTP transmission leads to selection for less feminization and virulence in the VTP (Fig. 2A), whereas a highly virulent HTP selects for greater feminization and VTP virulence (Fig. 2C). This response is linked to the prevalence of the HTP: prevalence increases as the HTP transmission increases since a greater proportion of VTP are infected by the HTP. In contrast, an increase in HTP virulence will decrease its prevalence.

VERTICAL TRANSMISSION EFFICIENCY AND VIRULENCE TRADE-OFF

With a vertical transmission efficiency and virulence trade-off, the VTP life history is defined by an equivalent relationship to the

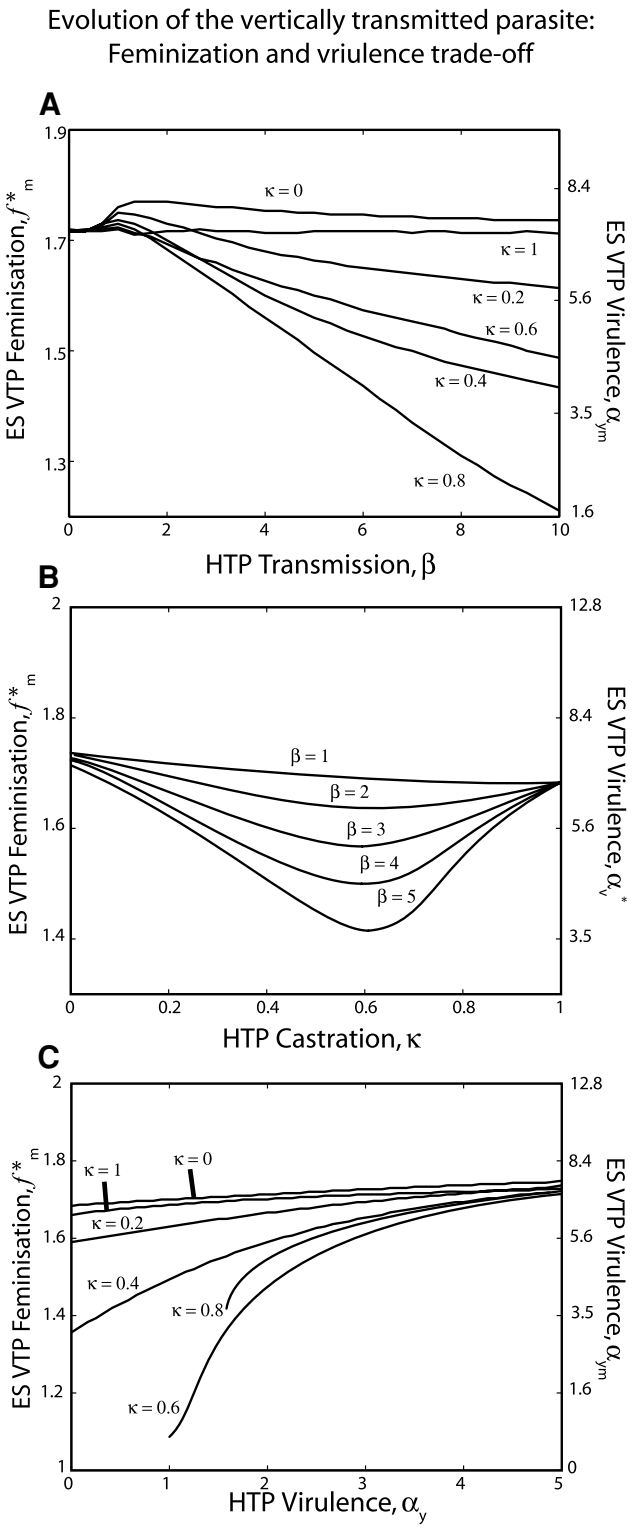

Figure 2. (A) The evolutionarily stable ES vertical parasite feminization against horizontal castration at varying horizontal transmission values. (B) ES vertical parasite feminization against horizontal castration at varying horizontal transmission values. (C) ES vertical parasite feminization against horizontal virulence (on death rate) at varying horizontal castration values. Parameter values unless otherwise stated: $a = 15$; $b = 1$; $r = a - b$; $P = 0.95$; $\beta = 2$; $\alpha_y = 4$; $\alpha_v = 20.8–20(2.1 - f)^{0.4}$.

standard transmission/virulence trade-off of the HTP. In general, high transmission rates (Fig. 3A) or virulence (Fig. 3C) in the HTP select for more transmission and virulence in the VTP. This relates to either an increased risk of coinfection or higher death rate of coinfected hosts, that both select for higher transmission and virulence from hosts that have a higher death rate than the singly infected hosts. Our results are a restating of the standard co-infection theory (van Baalen and Sabelis 1995), which emphasize the equivalence of the selection pressures on VTP and HTPs with this trade-off relationship. In contrast to the feminization trade-off, we also find that the ES vertical transmission level and virulence increases as the horizontal parasites castration level increases. The effect of higher HTP virulence on VTP transmission and virulence is lost once there is complete castration (Fig. 3B). In this case, no transmission can occur from coinfected individuals, so this class becomes unimportant to the VTP fitness.

COEVOLUTION

We now consider coevolution of both the HTP and VTP. The invasion conditions for the evolution of each parasite in isolation (equation 5 and 6 or 7) is used to graphically plot the position of the CSS of each parasite. The position of the coevolutionary stable strategy (CoESS) is determined as the intersection of the CSSs for the HTP and VTP. Numerical simulations were used to ensure that the CoESS is convergent stable and therefore the end point of evolution. We proceeded by looking at coevolution of the HTP with its transmission-virulence trade-off and the VTP with its two trade-offs in turn.

We first examined how the CoESS between the horizontal and vertical parasite varies in hosts with different life spans under the assumption of a feminization-virulence trade-off in the VTP (Fig. 4A). A decrease in host life span (which equates to an increase in natural mortality, *b*) leads to an increase in virulence in both the horizontal and the vertical parasite and consequentially an increase in horizontal transmission and feminization. "Fast" acute pathogens are more likely to be favored in short-lived hosts, since they are more likely to die of other causes before transmission can occur. Both the HTP and VTP exhibit minimum virulence at intermediate levels of castration and maximum virulence when there is no castration (Fig. 4B). As such the coevolutionary response of VTP is similar to its evolutionary one (Fig. 2B), but the HTP is strongly selected by the VTP feminization rate (Fig. 1).

For a trade-off between vertical transmission efficiency and virulence in the VTP as in the case above an increase in host longevity selects for an increase in virulence for both parasites HTP (Fig. 5A). The coevolutionary responses of the VTP to increasing levels of castration (Fig. 5B) are similar to the evolutionary response (see Fig. 3B). The HTP response exhibits minimum virulence at intermediate levels of castration (which HTP will clearly be selected to increase transmission while trying to can

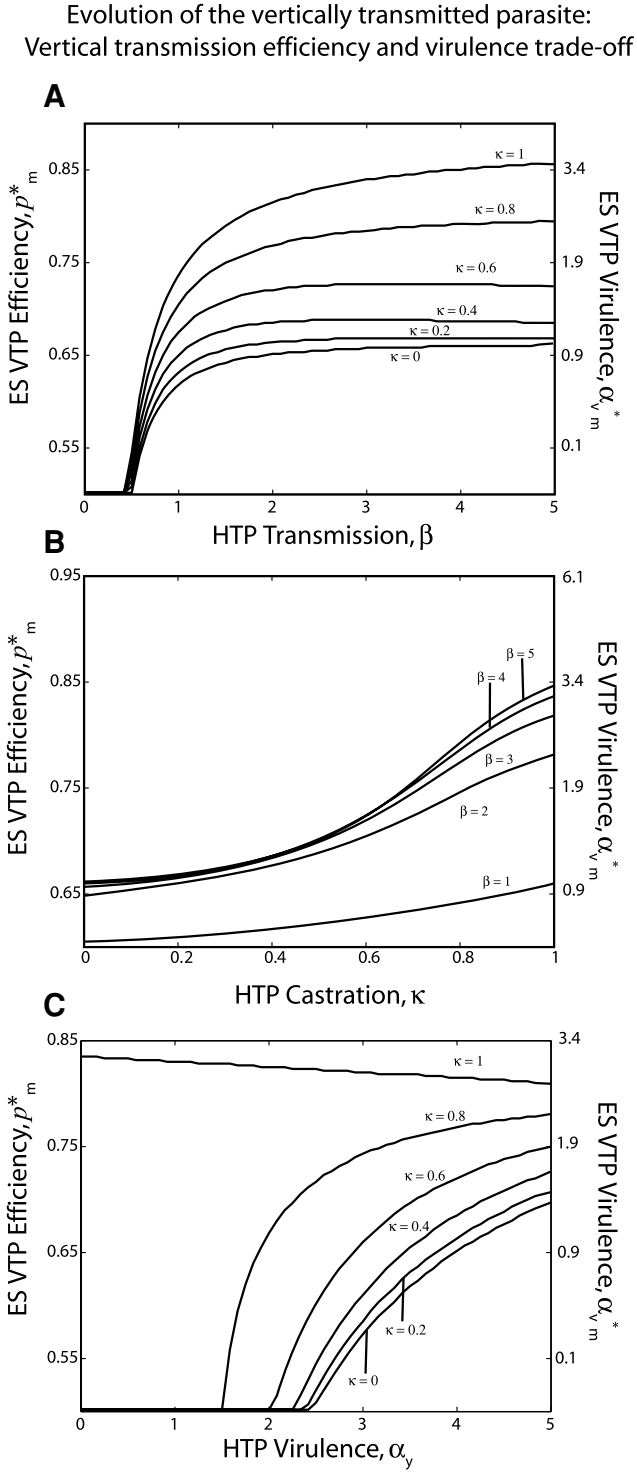

Figure 3. **(A) The evolutionarily stable ES vertical parasite transmission against horizontal castration at varying horizontal transmission values. (B) ES vertical parasite transmission against horizontal castration at varying horizontal transmission values. (C) ES vertical parasite transmission against horizontal virulence (on death rate) at varying horizontal castration values. Parameter values (when not varied in the figure) are, $a = 15$; $b = 1$; $r = a - b$; $\beta = 2$; $\alpha_y = 0$; $\alpha_v = 32.5–35(1.1 - P)^{0.1}$; $f = 1.5$.**

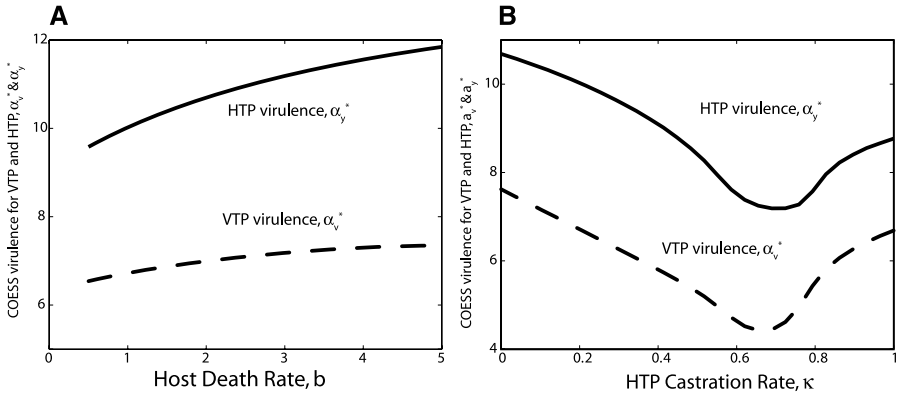

Figure 4. (A) The coevolutionary evolutionarily stable strategy (CoESS) of horizontal parasite virulence (solid line, α_y^*) and vertical parasite virulence (dashed line, α_v^*) (with feminization-virulence trade off), against natural death rate. (B) CoESS (solid line, α_y^*, dashed line, α_v^*) plotted against HTP castration levels. Parameter values (when not varied in the figure) are, $a = 15$; $b = 1$; $P = 0.9$; $\alpha_y = 15–4.5(8 - \beta)^{0.6}$; $\alpha_v = 20.8–20(2.1 - f)^{0.4}$; $\kappa = 0.2$.

be understood by tracing the response of α_V as κ increases in Fig. 3C).

Discussion

We have shown that parasites with different transmission strategies have important selective pressures on each other when competing for the same host. Unconstrained, an HTP will be selected to increase transmission while trying to minimize virulence (Levin and Pimental 1981), unless there is a trade-off between transmission and virulence (Levin and Pimental 1981; Anderson and May 1991; Antia et al. 1994; Mosquera and Adler 1998). It is also clear that an unconstrained optimal VTP would have high feminization, low virulence, and high vertical efficiency. We have shown that such "Darwinian demonic" (Law 1979) VTPs would select for fast transmitting, highly virulent HTPs. Indeed, the presence of a VTP in the system is enough to increase the virulence and transmission of an HTP. This increase in virulence due to coinfection is well known, but our work emphasizes that this will also occur with potentially cryptic VTPs.

Individuals infected with a feminizing VTP can be seen as a form of the host with greater reproductive and death rates. Models have previously shown that this will increase HTP virulence (Gandon et al. 2002). Other multihost parasite models (Regoes et al. 2000; Gandon 2004; Gandon and Day 2009) also have similarities to the model presented here, in that they all have host strains with different life-history traits that can in principle be seen as implicitly reflecting a host with a VTP infection. In our model, we explicitly model a VTP and as such include the epidemiological dynamics of vertical transmission between generations. Our model deals with two different parasite species and hence is also fundamentally different in that only the VTP and HTP affect the evolution of each other. We demonstrate how the increases in vertical transmission efficiency of a feminizing VTP

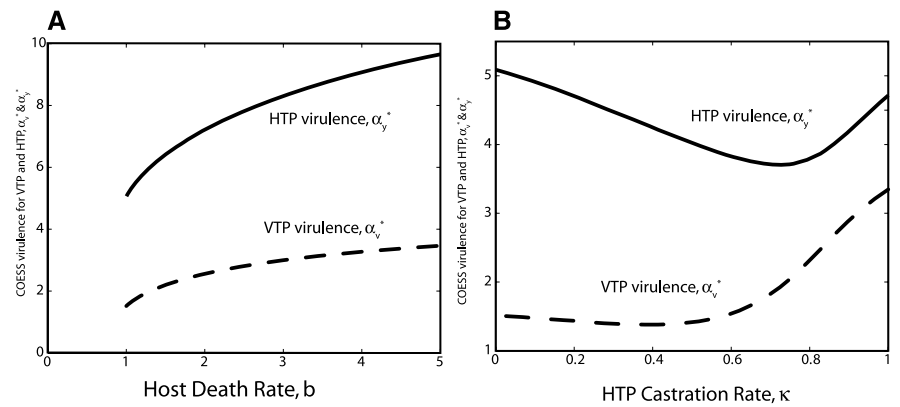

Figure 5. The coevolutionary evolutionarily stable strategy CoESS plots of virulence of VTP with vertical efficiency and virulence trade-off (solid line, α_y^*) and an HTP with a transmission virulence trade-off (dashed line, α_v^*). (A) Change in CoESS with increasing host death rate. (B) Change in CoESS with change in HTP castration ability. Parameter values (when not varied in the figure) are, $a = 15$; $b = 1$; $f = 1.5$; $\alpha_v = 32.5–35(1.1 - P)^{0.1}$; $\alpha_y = 15–4.5^*(8 - \beta)^{0.6}$; $\kappa = 0$.

can increase transmission and virulence of an HTP a result that is absent from the other multihost models as they specify different types of hosts rather than one host that is exposed to infection by a VTP. The rich range of outcomes that we find reflect this explicit modeling of both parasite species and emphasize the importance of ecological feedbacks in evolutionary outcomes. Our models also shed light on conflicts between parasites including bacteriophages with different transmission modes (Brown et al. 2006), where the persistence of the vertically transmitted phage is not through feminization (Jones et al. 2007). Indeed previous theoretical studies on bacteria and phage are similar to ours (Brown et al. 2006). However, here the VTP maintains itself in the population by protecting from further phage infection. The ecological implications of this protection have been considered in previous models (Lipsitch et al. 1995; Jones et al. 2007) but the evolutionary implications warrant further work.

Although there are very few empirical studies on trade-offs in VTPs, their evolution is likely to be constrained due to trade-offs between their key life-history characteristics. In our models, we found that when feminization is traded off against virulence, high transmission rates and low virulence in the HTP select for low feminization rates and virulence in the VTP. In contrast when the VTP has a trade-off between transmission efficiency and virulence, we observe that both low transmission and virulence in the HTP select for low transmission efficiency and virulence in the VTP. When there is a trade-off in the HTP (between transmission and virulence) we would tend to expect high virulence to be associated with high transmission and therefore this will select for intermediate VTP virulence with a feminization and virulence trade-off but high VTP virulence when there is a vertical efficiency and virulence trade-off. The selective pressure of an HTP on a VTP therefore crucially depends on the nature of the trade-off in the VTP. In particular VTPs are selected for intermediate feminization and virulence in the presence of highly infective, highly virulent HTPs. There is now good empirical evidence of the vertical transmission/virulence trade-off in nature (deRoode et al. 2008), but we need more empirical studies on the nature of trade-offs with feminization.

Several theoretical studies have shown that the competition created by multiple infections of HTPs can select for increased virulence (Nowak and May 1994; May and Nowak 1995; van Baalen and Sabelis 1995), with the selection dependent on the force of infection (van Baalen and Sabelis 1995). Other studies have shown that when sublethal effects have been incorporated in simple multiple infection models, the evolution of lower virulence can be found (Schjorring and Koella 2003) and also other mechanisms for varying virulence in multiple infections have been explored (Brown et al. 2002). Here we show that virulence of the HTP would tend to be increased due to the presence of a feminizing VTP. However increasing HTP transmission and virulence, have a counter acting effects on the VTP feminization rate and virulence. It is unclear, therefore, how the virulence of VTPs will be affected by multiple infection of HTPs. The outcome will depend on the trade-off relationships of the life-history characteristics of each parasite.

There is a clear conflict between a VTP and an HTP that reduces the fecundity of its host. High rates of castration significantly reduce VTP transmission, but may have no effect on the HTP fitness (O'Keefe and Antonovics 2002). The degree of castration can therefore have profound effects on the evolution of the VTP. When virulence is traded off against feminization, the minimum level occurs at intermediate levels of castration, whereas when it is traded off against vertical efficiency the minimum occurs at low castration levels. When we examine the coevolutionary dynamics we find a similar pattern such that for an HTP and a VTP with a feminization/virulence trade-off, virulence in minimized at intermediate levels of castration. With a vertical efficiency/virulence trade-off, coevolution also leads to minimum virulence for the HTP at intermediate levels of castration, but minimum VTP virulence at low castration.

For an HTP, many studies have shown that castration should be maximized if the hosts energy is then used to further the parasite transmission (Jokela et al. 1993; Jaenike 1996; O'Keefe and Antonovics 2002). However, in nature many parasites do not completely castrate their hosts (Young and Yearian 1982). This may of course reflect the fact that parasites cannot "choose" where the damage occurs. In addition, the host will be selected to defend itself from the loss of its reproductive potential (Rothman and Myers 1996; Gandon et al. 2002; Bonds 2006). Our work emphasizes that given the conflict between VTPs and HTPs, host reproduction may be maintained in part by the presence of VTPs. The implications of castration and shared defense to host resistance should be considered in more detail.

There are few natural systems where the interactions between feminizing VTPs and HTPs have been studied in detail. Generally the focus of research in most systems is on one parasite host interaction. However we would argue that our model can be applied to most if not all feminizing VTPs in nature. There are an increasing number of systems where feminizing VTPs have been found. Vertically transmitted *Wolbachia* strains have been shown to feminize infected hosts, in many isopod species (Bouchon et al. 1998), and in particular *Armadillidium vulgare* (Rigaud et al. 1991; Cordaux et al. 2004). *Wolbachia* has also been shown to feminize a number of insect species, the leafhopper *Zyginida pullula* (Negri et al. 2006) and the Asian corn borer, *Ostrinia furnacalis* (Kageyama et al. 2002), which in itself is susceptible to the parasitoid attack (Liu et al. 1998) and most probably other horizontally transmitted bacouloviruses. There are also the feminizing microsporidians that infect *Gammarus duebeni* and *Gammarus roeseli* (Terry et al. 2004; Haine et al. 2007). In most of these systems, specific HTPs

have not been extensively studied; however they are ubiquitous in nature. It is unlikely therefore that any feminizing VTP is not selected by one or more HTPs. Our model suggests that more research effort should be directed at explicitly examining the interactions that are found. Furthermore, we would also argue that it is also important to look for VTPs in systems where the main focus is on HTPs. Given the increasing number of VTPs that are being reported, it is likely that they remain to be found in a number of systems.

Our model has assumed that both parasites evolve at a similar rate, and that host resistance itself is not relevant on an evolutionary time scale. Future studies should address the evolution of host resistance to multiple infections, especially when the infections act quite differently on the host. The evolution of a resistance strategy would undoubtedly depend on the interactions between the infections and how they impact on the fitness of the host. Systems in the wild often have multiple infections and therefore it will be vital understand how these influence the coevolution of the host and its shared parasites.

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