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Sexual Conflict and Sexually Transmitted Infections (STIs): Coevolution of Sexually Antagonistic Host Traits with an STI

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abstract: In many taxa, there is a conflict between the sexes over mating rate. The outcome of sexually antagonistic coevolution depends on the costs of mating and natural selection against sexually antagonistic traits. A sexually transmitted infection (STI) changes the relative strength of these costs. We study the three-way evolutionary interaction among male persistence, female resistance, and STI virulence for two types of STIs: a viability-reducing STI and a reproduction-reducing STI. A viability-reducing STI escalates conflict between the sexes. This leads to increased STI virulence (i.e., full coevolution) if the costs of sexually antagonistic traits occur through viability but not through reproduction. In contrast, a reproduction-reducing STI de-escalates the sexual conflict, but STI virulence does not coevolve in response. We also investigated the establishment probability of STIs under different combinations of evolvability. Successful invasion by a viability-reducing STI becomes less likely if hosts (but not parasites) are evolvable, especially if only the female trait can evolve. A reproduction-reducing STI can almost always invade because it does not kill its host. We discuss how the evolution of host and parasite traits in a system with sexual conflict differs from a system with female mate choice.

Keywords: sexual conflict, sexually transmitted infection, virulence evolution, coevolution, sexually antagonistic traits, host-parasite interactions.

Introduction

Sexual conflict over mating rate arises when male reproductive success increases with mating rate while female reproductive success is maximized at some intermediate rate (Bateman 1948; Arnqvist and Rowe 2005). To increase their mating or fertilization rate, males evolve persistence traits that often cause harm to females physically or physiologically. Females, in turn, evolve resistance traits that deter males or offset the physiological harm. This conflict gives rise to sexually antagonistic (SA) coevolution between male persistence traits and female resistance traits, the outcome of which determines the mating rate. Sexually transmitted infections (STIs), by definition, are transmitted during mating and thus may play an important role in the evolution of host mating strategies. Here, we explore the interplay between STI virulence evolution and the evolution of host traits mediating sexual conflict over mating rate.

STIs are ubiquitous in nature and have been found in more than 48 families and 27 orders of invertebrate and vertebrate hosts (Lockhart et al. 1996). Some affect mortality, while others affect host fertility, fecundity, or both (see Sheldon 1993; Lockhart et al. 1996; Knell and Webberley 2004; and references therein). Virulence evolution of STIs that affect host reproduction is relatively poorly understood, although the evolution of intermediate virulence is expected if hosts display transmission-avoidance mate choice (Ashby and Boots 2015). Virulence of STIs that affect host mortality is predicted to evolve in much the same way as that of non-sexually-transmitted diseases; that is, evolutionarily stable virulence is proportional to the natural host mortality rate and depends on the shape of the trade-off between transmission and virulence (Knell 1999). Surprisingly, evolutionarily stable virulence does not depend on the mating rate, although the spread of STIs and overall infection prevalence does (Lipsitch and Nowak 1995; Knell 1999). Models show that the mating system and the resulting heterogeneities in sexual contact patterns affect overall disease prevalence as well as the difference in prevalence between the sexes (Thrall et al. 2000; Ashby and Gupta 2013). For example, in populations with strong mating skews, the choosy sex tends to have higher infection prevalence because STI prevalence in

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the other sex is limited to a small group of attractive individuals (Thrall et al. 2000). Moreover, heterogeneities in contact rates can affect the evolution of virulence. For example, Ashby and Gupta (2013) found that lower levels of virulence were favored when there was higher heterogeneity in contact rates. They attributed this to the benefit of persisting in individuals with high levels of sexual activity without killing such a high-value host. Their study demonstrates the importance of heterogeneity in contact rates but does not explicitly model why such heterogeneities exist or how the mating system might evolve in response to an STI.

Other studies have investigated how an STI can affect the host mating system, typically in the context of hosts with conventional sexual selection involving female mate choice. Traditionally, STIs were thought to select for monogamy (Immerman 1986; Immerman and Mackey 1997), but subsequent models showed that STIs can maintain both monogamy and promiscuity in a population as well as select for risky female choice (Thrall et al. 1997; Boots and Knell 2002; Kokko et al. 2002; female choosiness based on attractiveness of males is considered a risky strategy because the most popular males have the highest mating rate and are more likely to be infected). By selecting on mating system, the STI changes its own ecological landscape, possibly setting the stage for coevolution. The outcome of coevolution can be hard to intuit. Indeed, there are several examples in the host-parasite literature of coevolution leading to different or unexpected outcomes compared with the evolution of either the host or the parasite in isolation (Gandon et al. 2002; Day and Burns 2003; Best and White 2009). In a model where only STI virulence evolved, Knell (1999) showed that an STI evolved to be less virulent if hosts displayed transmission-avoidance mating behavior. He then speculated that hosts would subsequently lose disease-avoidance behaviors such as mate choice based on the degree of parasitism of potential mates. However, when the level of host choosiness based on parasitism was allowed to coevolve with STI virulence, Ashby and Boots (2015) found that intermediate levels of disease-avoidance behavior and virulence could evolve, and under some conditions coevolutionary cycling could occur between host choosiness and STI virulence. These unexpected results emphasize the importance of considering possible coevolutionary feedbacks of an STI with the host mating system.

Over the past 30 years it has become clear that, in many systems, sexual conflict over mating rate plays at least as large a role in shaping the evolution of male-female interactions as conventional sexual selection processes (Rice and Holland 1997; Arnqvist and Rowe 2005). In the absence of an STI, there are several possible outcomes of SA coevolution depending on the biology of the system. If male persistence and female resistance carry no inherent cost, traits will continually escalate in an evolutionary arms race (Gavrilets and Hayashi 2006). Incorporating natural selection against persistence and resistance traits prevents runaway evolution (Gavrilets et al. 2001), and allowing for the evolution of female sensitivity can lead to female indifference to male traits, halting the coevolutionary process (Rowe et al. 2005). In all of these cases, only females suffer the cost of mating. Given that an STI increases the cost of mating to both males and females, it is not obvious how an STI will affect SA host interactions. Although classic theory indicates that evolutionarily stable STI virulence is unaffected by mating rates, there remains the potential for host-parasite coevolution. Because the traits mediating sexual conflict are themselves costly, evolutionary changes in these traits driven by the emergence of an STI might create epidemiological feedbacks that drive subsequent STI evolution.

We model an STI in a host system with sexual conflict over mating rate; that is, the STI can coevolve with SA host traits (male persistence and female resistance). We examine how an STI changes the escalation of SA traits in the host as well as how the evolution of these host traits affects whether an STI can establish and, if so, the evolution of STI virulence. In exploring these scenarios, it is worth considering how fitness costs occur. For hosts, fitness costs of the same relative magnitude are equivalent whether they occur through a reduction in survival or reproduction. In classic models of non-sexually-transmitted (horizontally transmitted) infections, reductions in the survival of its host are costly to the parasite, but in most circumstances, reductions in the reproduction of its host are not. This is why the rich transmission-virulence tradeoff literature focuses almost exclusively on virulence defined as disease-induced reductions in host viability (Cressler et al. 2016). For STIs, a reduction in host reproduction can be costly to the parasite if it involves a reduction in mating success (i.e., STI transmission opportunities), as may occur if parasites reduce the energy male hosts can allocate to mate search or sexual display (sensu Rowe and Houle 1996) or if females discriminate against infected males (Hamilton and Zuk 1982; Knell 1999). For this reason, we separately examine an STI that reduces host fitness via mortality and one that reduces sexual fitness (i.e., female fecundity and male mating success); we refer to these as viability-reducing STI and reproduction-reducing STI models, respectively. In addition, the host traits that mediate sexual conflict over mating rate are also assumed to be costly; we likewise consider cases where these costs occur through viability versus reproduction because the form of this cost affects the potential for coevolution with the STI.

Model Setup

We take as our focal case the model with a viability-reducing STI where the costs of SA traits are manifest through

reductions in viability (hereafter, "viability-reducing STI" and "viability costs for SA traits"). Other cases are subsequently described with respect to how they differ from this focal case. The results presented are from individual-based simulations. Numerical solutions of an analytical model of the focal case are similar (app. B; apps. A, B are available online).

Host Life Cycle without the STI

We model an interlocus sexual conflict over mating rate by assuming sex-limited expression of male and female traits. Each trait is controlled by a single diploid autosomal locus; the loci are unlinked. For each locus, we assume a continuum of alleles. A male is characterized by his persistence trait and a female by her resistance trait; these traits may be morphological (e.g., male grasping and female antigrasping traits of water striders; Arnqvist and Rowe 2002) or behavioral (e.g., harassment by males or vigorous struggles by females in water striders; Arnqvist 1989). Resistance (x) and persistence (y) levels expressed by a host are calculated as the average of the allelic values from each chromosome. Because an individual is either male or female, each individual expresses only the persistence or the resistance trait, although all individuals carry alleles for both loci. Definitions of key parameters are provided in table 1.

Each breeding season, a female encounters a certain number of males, randomly drawn from a Poisson distribution with mean α. The probability of mating during an encounter between a male with persistence y and a female with resistance x is an increasing function of the difference $u = y - x$ as given by equation (1), following Gavrilets et al. 2001 and Rowe et al. 2005:

$$\phi[u] = \frac{1}{(1 + e^{-u})}. \tag{1}$$

The probability of mating $\phi[u]$ plays several roles in the model. Importantly, it affects female mortality because females pay a viability cost d per mating. Fixed per-mating viability costs for females have been observed in systems with sexual conflict over mating rate and can arise from factors ranging from toxic ejaculates (Rönn et al. 2006) to increased predation risk while mating (Rowe 1994). The mating probability is also assumed to affect female fecundity in that a given female can have zero fitness if she remains unmated (at low mating probabilities) by the end of the breeding season.

Mortality occurs after mating but prior to offspring production. For the ith female who has mated with m_i males in the current breeding season, her probability of mortality is

$$1 - e^{z_i}, \tag{2a}$$

where

$$z_i = \mu_f + dm_i \tag{2b}$$

and μ_f is the baseline mortality rate for females. For the ith male we replace equation (2b) with

$$z_i = \mu_m, \tag{2c}$$

where μ_m is the baseline mortality rate for males. The mortality model shown above assumes no viability costs associated with the SA traits.

However, for the focal case we assume that both sexes suffer viability costs of expressing SA traits. While there are documented examples of SA traits affecting male mortality via predation (e.g., Arnqvist 1994), little is known about the costs of SA traits in females (Perry and Rowe 2015) or whether these costs increase linearly or nonlinearly. We follow Gavrilets et al. (2001, 2006) and Otto and Day (2007) in assuming nonlinearly increasing viability selection because linearly increasing costs lead to indefinitely escalating coevolutionary arms races (not shown). Specifically, we assume that a male pays a cost for his persistence trait; the strength of this cost is ce^y, where c is the persistence cost parameter. Likewise, a female pays a mortality cost for her resistance trait given by δe^x, where δ is the resistance cost parameter. Viability selection against these SA traits, together with the cost of mating experienced by females, results in three costs incurred by hosts

Table 1: Parameters and variables

Parameter	Definition
y	Male persistence trait
x	Female resistance trait
$u = y - x$	Mating rate metric
$\phi[u]$	Mating probability function
c	Persistence cost to males
δ	Resistance cost to females
d	Mating cost to females
α	Number of males encountered
b	Maximum fecundity
K	Carrying capacity
M	Number of males in the population
F	Number of females in the population
m	Number of males a given female mates with
μ_i	Baseline mortality coefficient of sex i
v	Virulence of the STI
$\beta[v]$	STI transmission function
w	Transmission-virulence trade-off parameter

Note: STI = sexually transmitted infection.

(persistence costs to males as well as resistance and mating costs to females). With these costs, we replace equation (2b) with

$$z_i = \mu_f + dm_i + \delta e^{x_i} \tag{2d}$$

and replace equation (2c) with

$$z_i = \mu_m + ce^{y_i}. \tag{2e}$$

Surviving females produce offspring. A mated female has a maximum fecundity b (per breeding season) that is decreased by density dependence if population size exceeds the carrying capacity K. Specifically, the expected number of offspring born to the ith mated female in the current breeding season is

$$O_i = b\left(1 - \frac{M + F}{K}\right), \tag{3}$$

where M and F are the number of adult males and females in the population. The actual number of offspring produced by this female is drawn from a Poisson distribution with mean O_i. (As given here, O_i is the same for all mated females, but this will not be so in modifications of the model described below.) Unmated females produce no offspring.

If a female has mated with m males, a given male sires an average of $1/m$ of her offspring, with the actual sire of each offspring chosen at random from the m males. For simplicity, we ignore sperm precedence. Gametes are formed with free recombination between loci, and alleles experience mutation with probability U_{hosts} per locus. The effect size of a mutation is chosen from a normal distribution with a mean of 0 and standard deviation of 0.1. If the mutational step yields a negative trait value, the trait value is assumed to be 0. The surviving adults and newborn offspring make up the next generation, whose mean and variance in host trait values are recorded before another round of mating, mortality, reproduction, and mutation is conducted.

Inclusion of a Viability-Reducing STI

If an STI is present in the population, it can be transmitted from an infected individual to an uninfected (susceptible) individual with probability $\beta[v]$, given a mating between them. $\beta[v]$ is a function of STI virulence; v is a parasite trait encoded by a single haploid locus. Following convention, we assume a convex trade-off between transmission and virulence. We proceed by setting $\beta[v] = v/(w + v)$, where w is a shape-determining parameter (see chap. 12 in Otto and Day 2007), and assume that infected hosts suffer additional mortality v that augments the probability of death, such that we add v to right-hand side of the appropriate version of equations (2b–2e). For example, in the model where hosts pay viability costs for SA traits, if the ith female is infected by a pathogen with virulence v_j, then we replace equation (2d) with

$$z_i = \mu_f + dm_i + \delta e^{x_i} + v_j. \tag{4}$$

A newly infected host cannot infect other hosts during the same breeding season in which it became infected; that is, the newly infected host must survive to the next breeding season before it is infectious. Because of the discrete ordering of events in our simulation model, if STIs were immediately infectious, then a highly virulent (and thus highly transmissible) STI could rapidly spread within the mating phase of a single breeding season before suffering any consequences of high virulence that affect the host after the mating period. (Preliminary versions of this model that allowed for immediate transmission resulted in extremely high virulence.) During this uninfectious period, the clonally reproducing STI undergoes mutation with probability U_{STI}. The effect size of a mutation is chosen from a normal distribution with a mean of 0 and standard deviation of 0.01. If the mutational step yields negative virulence, virulence is assumed to be 0. At the start of each generation, the population mean and variance in virulence are recorded.

Reproduction Costs for SA Traits

Simulations proceed as described above except that the cost of SA traits affects aspects of reproduction instead of viability. We model these costs on reproduction in a manner parallel to how they are modeled when costs occur through viability. Given the same cost parameter (δ) and trait value (x), a female's fitness should be affected by the same amount regardless of whether costs occur via reproduction or viability. As discussed below, reproductive costs in males occur via a reduction in competitive siring success and, thus, will approach equivalence with the viability model only if females typically mate with multiple males. Higher resistance trait values reduce female fecundity, such that the number of offspring born to the ith mated female in the current breeding season is drawn from a Poisson distribution with mean

$$O_i = e^{-\delta e^{x_i}} b\left(1 - \frac{M + F}{K}\right) \tag{5}$$

Reduced fecundity for females might be expected if there are physiological/energetic costs of investing in resistance traits that reduce investment in reproduction.

Higher persistence trait values reduce male fertility by decreasing siring success (i.e., the male's persistence trait increases his expected number of matings but decreases his postcopulatory competitive ability). Similar reproduction costs have been observed in flour beetles, a system

characterized by male-male competition, where investment in weapons comes at the expense of testes size and ejaculatory volume (Yamane et al. 2010). Specifically, having mated with a given female, a male sires an average of $e^{-ce^y}/\sum_{i=1}^{m} e^{-ce^{y_i}}$ of her offspring, where m is the total number of males she mated with and y_i is the persistence trait of male i. When the cost of the male persistence trait is manifest through reproduction rather than viability, we have explicitly chosen this cost to occur through siring success rather than mating success. Because increased values of the persistence trait increase mating success (eq. [1]), it would be self-defeating if the cost reduced the same fitness component that it also improves.

Reproduction-Reducing STI

Simulations with a reproduction-reducing STI proceed as described for a viability-reducing STI except that disease virulence affects host fitness through aspects of reproduction. We model virulence for a reproduction-reducing STI parallel to how virulence is modeled for a viability-reducing STI (i.e., for a given level of virulence, a host's fitness should be reduced by the same amount for either type of STI model). In the current breeding season, the expected number of offspring produced by the ith mated female infected with a pathogen of virulence v_j is

$$O_i = e^{-(\delta e^{x_i} + v_j)} b\left(1 - \frac{M + F}{K}\right) \tag{6}$$

if the cost of female resistance occurs through reproduction (if not, then δ in the equation above is set to 0).

In principle, a reproduction-reducing STI could affect males through either mating success or siring success, but we consider only the former. A reproduction-reducing STI faces no virulence-transmission trade-off in females and would also not experience a trade-off in males if it only reduced siring success. Thus, we assume that a reproduction-reducing STI affects male mating success, or else we would expect virulence to escalate without bound. Specifically, the probability that a mating occurs when a female encounters a male infected with a pathogen of virulence v_j is $e^{-v_j}\phi[u]$ (it is conceptually equivalent to view this form of virulence as reducing the number of females that an infected male encounters due to a disease-induced reduction in search effort). Reduction in mating effort of infected individuals has been observed in some species due to energetic trade-offs with immune response (Hart 1988; Dantzer 2004; Lawniczak et al. 2007), although we are aware of no examples for populations infected with a sexually transmitted disease. The reduction in the mating success of infected males could be interpreted as resulting from (nonevolving) female choice in which females discriminate against infected males, although such a view would be somewhat at odds with the sexual conflict premise of our model. Note that like a viability-reducing STI, individuals show symptoms of the disease immediately but are not infectious until the next breeding season.

Simulations

Individual-based simulations were carried out in Python (code available from the Dryad Digital Repository: http://dx.doi.org/10.5061/dryad.142p9j6 [Wardlaw and Agrawal 2018]) for 50,000 generations, well after the trait values appeared to reach evolutionary equilibrium. To initiate the population, 2,000 diploid hosts (with an equal sex ratio) were assigned trait values at the resistance and persistence loci by drawing random values from a normal distribution with mean $\bar{x}$ and $\bar{y}$, respectively, and standard deviation 0.5. In host populations infected with an STI, the STI was introduced into 5% of hosts with the virulence of each infection drawn from a normal distribution with mean $\bar{v}$ and standard deviation 0.1. Standard deviations were chosen such that the initial coefficient of variation in both host and parasite traits was near 10% (following Rowe and Houle 1996 and Criscione et al. 2005). Values from the last 1,000 generations were averaged. Rare extinctions of the host population (representing <0.4% of all simulations) were excluded from the average. There is one combination of model assumptions and parameter values that led to a 30% host extinction probability. This unique case is discussed in appendix A.

Results

Evolution of Host Traits without an STI

To understand how a coevolving STI affects the outcome of SA coevolution, we first consider how the host evolves in the absence of an STI (which has been previously studied for viability costs of SA traits; e.g., Gavrilets et al. 2001). Rather than reporting the SA traits directly, it is more useful instead to consider two other metrics. The average of the two trait values, $(y + x)/2$, is an indicator of the degree of escalation in the SA traits (hereafter, conflict escalation) and is plotted in figure 1*A*–1*C*. Second, we plot the difference between male persistence and female resistance, $u = y - x$ (hereafter, the mating rate metric), because the mating probability is an increasing function of this difference (fig. 1*D*–1*F*). The evolutionary equilibrium trait values presented in figure 1 and all subsequent figures are stable to different initial trait values.

For the range of parameters shown in figure 1, male persistence y always exceeds female resistance x, so the mating rate metric u is positive and mating probabilities are not too low. The extent of conflict escalation, as reflected

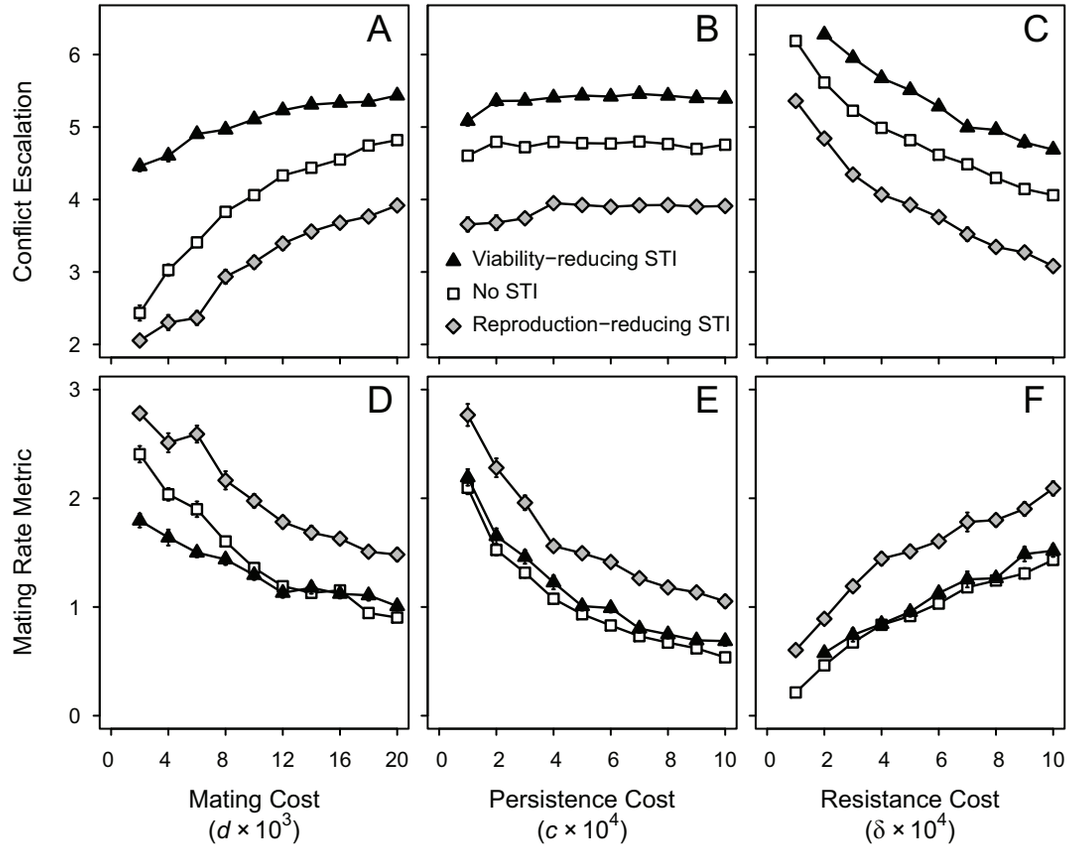

Figure 1: Outcome of coevolution between males and females in the absence of a sexually transmitted infection (STI) and in the presence of two types of evolving STIs. Both sexes pay viability costs for expressing sexually antagonistic (SA) traits. Shown here are the degree of escalation in sexual conflict, measured as the average of male persistence, y, and female resistance, x (*A*–*C*), and the difference between y and x (*D*–*F*); values are at evolutionary equilibrium. The mating rate is an increasing function of the difference between male persistence and female resistance ($y - x$); thus, we label this difference the mating rate metric. Simulations with an evolving STI began at the STI-absent host trait values, and the results for a reproduction-reducing STI (diamonds) and a viability-reducing STI (triangles) are a three-way evolutionary equilibrium with the STI at evolutionary equilibrium virulence v (see fig. 3). Parameter values (unless shown otherwise): $\alpha = 10$, $\mu = 0.2$, $b = 4$, $K = 1{,}000$, $w = 1$, with $c = 0.0005$, $\delta = 0.0005$, $d = 0.02$. Each point represents the average of 20 independent simulations (±SE). Simulations in which the disease became extinct are excluded from calculating the average. At very low resistance costs, a viability-reducing STI became extinct in 100% of simulations (see fig. 4), and there are no data for the three-way evolutionary equilibrium. Qualitatively similar patterns are observed when hosts pay reproduction costs for expressing SA traits (see fig. A1).

by average trait values, increases substantially as the mating cost to females increases (fig. 1*A*). This is driven by the female trait increasing to reduce the mating rate, while the male trait increases only slightly in response because of the nonlinearly increasing cost of natural selection. Because female resistance increases more than male persistence, the mating rate metric u declines (fig. 1*D*) with increased mating cost. Conflict escalation does not change drastically with increasing cost of male persistence (fig. 1*B*), but there is a reduction in the mating rate metric (fig. 1*E*). In contrast, increasing the cost of female resistance leads to a decline in conflict escalation (fig. 1*C*) accompanied by an increase in the mating rate metric (fig. 1*F*). At high resistance costs, females with lower resistance better balance the costs of mating with the costs of their SA trait. Qualitatively similar patterns are observed when the costs for SA traits occur through reproduction (fig. A1; figs. A1, A2, B1, B2 are available online) rather than viability (fig. 1).

Evolution of Host Traits with an Evolving STI

Viability-Reducing STI. We now consider the evolution of host traits in the presence of an evolving STI and then later discuss virulence of the STI. We begin by examining a viability-reducing STI in a host where the costs of SA traits occur through viability. The introduction of an evolving viability-reducing STI escalates the conflict between the sexes (fig. 1; a viability-reducing STI also causes an increase

in conflict escalation if costs of SA traits occur through reproduction, although the increase is smaller; fig. A1). This increase is driven by females. If only females are allowed to evolve (not shown), female resistance will evolve to be higher than male persistence to reduce the additional cost of mating arising from the risk of an STI. In this case, $u = y - x$ is negative, and the mating rate drops to low levels. A viability-reducing STI cannot persist at low mating rates. In contrast, if only males are allowed to evolve (not shown), male persistence increases from its STI-absent equilibrium, presumably because males are selected to more quickly obtain additional mates in the face of higher mortality rates due to infection (although the change is smaller compared with the case where only females evolve). The STI does not become extinct because mating rates remain high (as u increases). When females and males can both evolve, the increase in female resistance invokes a subsequent increase in male persistence that ensures male mating (fig. 2*A*). As such, the net effect of coevolutionary feedback tends to be increased average trait values (i.e., increased conflict escalation). It is worth emphasizing that the evolution of male persistence in response to the escalation in female resistance allows the STI to remain in the system for almost all parameter values except very low resistance costs (see fig. 1*C* and further discussion in the section on establishment of the STI). If a lack of genetic variation in the male trait prevented its coevolution, the STI would become extinct after female resistance increased and caused a decrease in mating rates.

Reproduction-Reducing STI. A reproduction-reducing STI has qualitatively different consequences for the outcome of sexual conflict. Again, this outcome can be understood by first thinking about the evolution of each sex in isolation. If only females are allowed to evolve (not shown), female resistance decreases in the presence of a reproduction-reducing STI. A prevalent STI results in less mating pressure on females because infected males exhibit reduced mating effort compared with uninfected males. Consequently, females do not need to invest as much in costly resistance traits. If only males are allowed to evolve (not shown), there is no observed change in the male persistence trait. When males and females can both evolve, the decrease in female resistance allows male persistence to decrease slightly (although to a lesser extent). Thus, in contrast to a viability-reducing STI, a reproduction-reducing STI decreases the degree of conflict escalation (figs. 1*A*–1*C*, 2*B*). This is also true if the costs of the SA traits occur through reproduction (fig. A1) rather than viability (fig. 1). In contrast to a viability-reducing STI, evolution of either host sex never drives a reproduction-reducing STI extinct for the parameter values examined here.

Virulence of a Viability-Reducing STI

Conditional on establishment of a viability-reducing STI, three-way evolution of the STI with male and female host traits can give rise to quantitatively different results than if the STI is introduced into a nonevolving host population (fig. 3*A*–3*C*). A viability-reducing STI becomes more virulent if hosts coevolve than if they do not, but only if the cost of SA traits occurs through viability. This is because the addition of the STI to the system causes evolutionary increases in female resistance and, consequently, male persistence, thereby increasing the host mortality rate; optimal STI virulence is expected to increase with

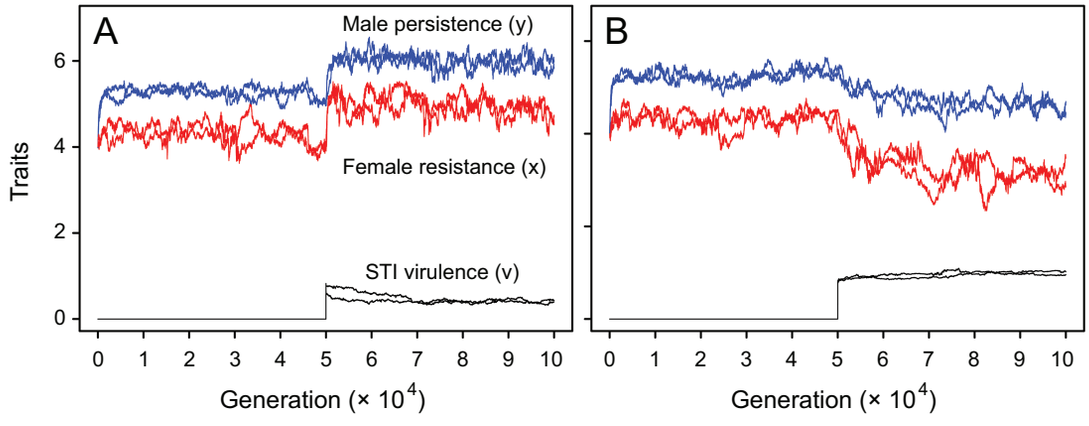

Figure 2: Sample runs from two independent replicates of the individual-based simulations where hosts evolve to their disease-absent equilibrium values before a viability-reducing sexually transmitted infection (STI; *A*) or a reproduction-reducing STI (*B*) is introduced at generation 50,000. Male persistence is shown in blue, female resistance is shown in red, and STI virulence is shown in black. Parameter values: $\alpha = 10$, $\mu = 0.2$, $b = 4$, $K = 1{,}000$, $w = 1$, $d = 0.02$, $c = 0.0005$, $\delta = 0.0005$.

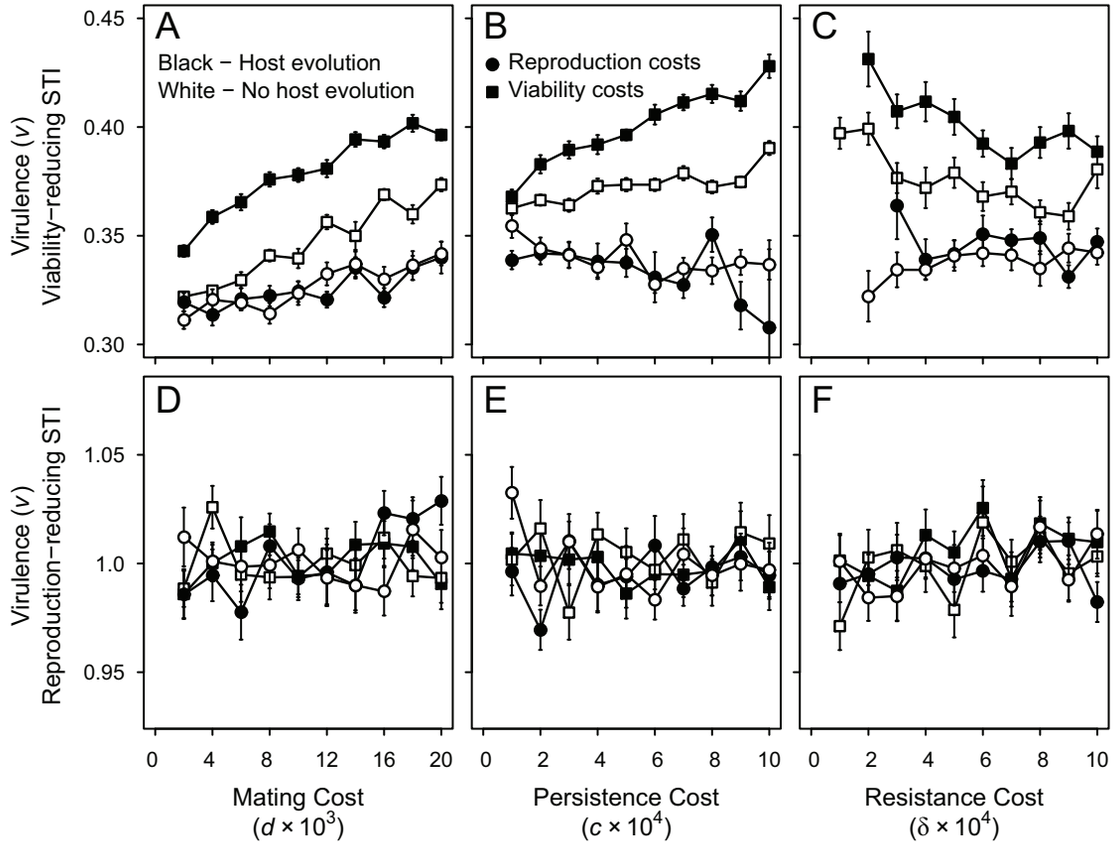

Figure 3: Evolutionary equilibrium virulence of two types of evolving sexually transmitted infections (STIs) in a population where hosts do not evolve (white symbols) or do evolve (black symbols). Shown is the virulence of a viability-reducing STI (*A*–*C*) and a reproduction-reducing STI (*D*–*F*). In both cases, the parasite was introduced with $\nu = 0.8$ at the STI-absent male persistence and female resistance host trait values. Parameter values (unless shown otherwise): $\alpha = 10$, $\mu = 0.2$, $b = 4$, $K = 1{,}000$, $w = 1$, with $c = 0.0005$, $\delta = 0.0005$, $d = 0.02$. Each point represents the average of 20 independent simulations (±SE). Simulations in which the disease became extinct are excluded from calculating the average and can lead to larger error bars at high extinction probabilities. At very low resistance costs, there are no data for the three-way evolutionary equilibrium when a viability-reducing STI became extinct in 100% of simulations (see figs. 4*C*, A2*C*).

host mortality rate (Knell 1999). The equilibrium virulence of a viability-reducing STI increases as the average host trait values increase and does not depend on the difference in trait values. The difference in trait values affects only the establishment and prevalence of the STI. In contrast, when the cost of SA traits occurs through reproduction, the virulence of a viability-reducing STI does not increase with an evolving host (fig. 3*A*–3*C*) even where there is host conflict escalation in the presence of the STI (fig. A1*A*–A1*C*). Escalated male and female trait values do not increase host mortality and invoke subsequent coevolution of the STI.

Virulence of a Reproduction-Reducing STI

Virulence evolution of a reproduction-reducing STI is shaped by its effects on males. In infected females, a reproduction-reducing STI does not face a transmission-virulence trade-off because the consequences of infection (decreased fecundity) do not reduce transmission opportunities. However, infected males in our model suffer reduced mating success with females. Thus, males infected with a highly virulent reproduction-reducing STI do not mate as often as uninfected males with similar persistence trait values. This reduction in transmission opportunities creates a transmission-virulence trade-off in one sex (males) that limits virulence evolution. The transmission-virulence trade-off is not affected by the host trait values themselves, regardless of whether costs of SA traits are paid through viability or reproduction. Consequently, the evolution of SA host traits induced by the presence of a reproduction-reproducing STI does not invoke a corresponding response in STI virulence evolution. Because there is no coevolutionary response, virulence of a reproduction-reducing STI is the same in host populations that can and cannot evolve (fig. 3*D*–3*F*).

Comparison with a Non-Sexually-Transmitted Disease

In our focal case, a viability-reducing STI coevolves with a host population paying SA costs through viability. As noted, STI virulence evolution depends on host mortality, much like a non-sexually-transmitted disease or ordinary infectious disease (OID). Furthermore, STI virulence in our model causes disease-induced mortality. Given that both STI and OID virulence affect viability and are shaped by the same parameters, we might expect similar coevolutionary outcomes if we model an OID infecting hosts with sexual conflict over mating rate. An OID, however, is not transmitted sexually and therefore will not exert direct selection on females to reduce the mating rate. We find that an OID has the same effect on the outcome of the conflict as increasing the baseline mortality rate μ (not shown). In contrast to a viability-reducing STI, an OID has little effect on the extent of conflict escalation. However, an OID drives an increase in the mating rate metric because male persistence increases and female resistance decreases.

Establishment of the STI

In the preceding sections on STIs, we focused on cases where both hosts and parasites can evolve and the disease establishes itself within the host population. (We use the term disease "establishment" rather than the more typical term "persistence" to avoid confusion with the host male's "persistence" trait.) We now consider how a lack of genetic variation that prevents evolution of either host or parasite traits affects both the establishment and the virulence of the STI. We discussed one important case above in which a lack of genetic variation in the male trait but not the female trait prevents the establishment of an evolving viability-reducing STI. Here we focus on contrasts between hosts and parasites in their evolvability (rather than on differences in evolvability between male and female host traits).

When neither the host nor the parasite can evolve, a viability-reducing STI near its equilibrium virulence always establishes when introduced into host populations at equilibrium except for rare stochastic extinctions (for the parameter values considered here). In comparison, a relatively avirulent viability-reducing STI almost always becomes extinct and a highly virulent one (shown in fig. 4, white symbols) establishes, unless mating rates are very low (i.e., when mating costs are high and there are high persistence costs to males or low resistance costs to females). In contrast, in all cases examined a reproduction-reducing STI establishes regardless of whether it was introduced at low, high, or equilibrium virulence. By virtue of not killing its host, a reproduction-reducing STI has a long duration of infection and can establish and spread at very low mating rates through rare transmission events. Because of the ease of establishment of a reproduction-reducing STI (for all combinations of evolvability), further discussion about extinction rates and the accompanying figure (fig. 4) pertain only to a viability-reducing STI.

If the host but not the parasite can evolve, then females are selected to increase their SA resistance trait in the presence of a viability-reducing STI, driving an increase in average

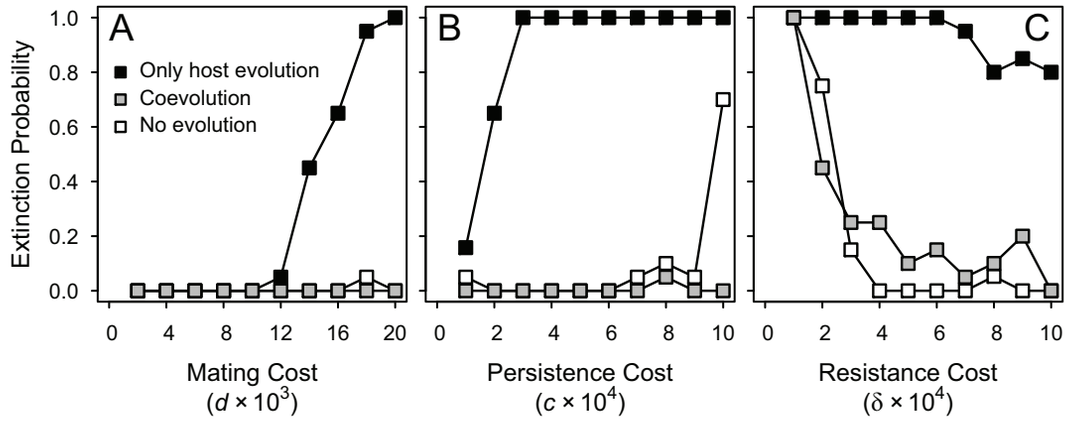

Figure 4: Fraction of simulation runs where a highly virulent viability-reducing sexually transmitted infection (STI) was driven extinct in hosts paying viability costs. The parasite was introduced with $v = 0.8$ at the STI-absent male persistence and female resistance host trait values, and neither host nor parasite evolved (white symbols), host traits evolved in the presence of a nonevolving parasite (black symbols), or hosts and STI both evolved (gray symbols). Parameter values (unless shown otherwise): $\alpha = 10$, $\mu = 0.2$, $b = 4$, $K = 1{,}000$, $w = 1$, with $c = 0.0005$, $\delta = 0.0005$, $d = 0.02$. The extinction probability was determined from 20 independent simulations. STI extinction probability was slightly higher, on average, in hosts paying reproduction costs for sexually antagonistic traits, but overall patterns of extinction probability were qualitatively similar (fig. A2).

host trait values and a decrease in the difference between the SA traits (not shown). The accompanying decrease in mating rate can drive a highly virulent, nonevolving STI extinct (i.e., at high persistence costs to males, low resistance costs to females, and high mating costs to females). In figure 4, we show the fraction of runs in which the parasite became extinct when hosts can evolve but parasites cannot (black symbols). Extinction rates are higher over a wider range of parameter values when female resistance costs are low ($\delta = 0.0001$; data not shown). As described above, STI extinction is even more likely if the female trait can evolve but the male trait cannot. For any of the parameter values shown in figure 4, a viability-reducing STI is unable to invade if only the female host trait evolves (not shown). If the STI can evolve but hosts cannot evolve, an initially virulent viability-reducing STI only becomes extinct for very low mating rates (not shown).

Finally, we consider evolution in both the host and the STI (fig. 4, gray symbols). STI extinction occurs most often when the cost of resistance to females is low (fig. 4*C*). At low resistance costs, elevated female trait values quickly evolve in the presence of the STI, which lowers the mating rate enough (albeit transiently) that a viability-reducing STI becomes extinct due to a lack of transmission opportunity. When the STI can coevolve with an evolving host, it is likely to successfully establish across a wide range of conditions under which it would otherwise become extinct (fig. 4). Contrasting the case where the costs of sexual antagonism are paid through viability (fig. 4) rather than reproduction (fig. A2), the STI is more likely to become extinct in the latter scenario for most parameter values. Differences between these scenarios in STI establishment probability are likely driven by the pronounced decrease in mating rate accompanying the introduction of the STI in host populations paying costs for SA traits through reproduction (compare fig. 1*D*–1*F* with fig. A1*D*–A1*F*).

Discussion

Although the evolution of STI virulence and sexual conflict have each been studied in isolation (e.g., STIs: Lipsitch and Nowak 1995; Knell 1999; sexual conflict: Gavrilets et al. 2001; Gavrilets and Hayashi 2006), the link between them has received little attention. The models presented here aim to understand this connection. In some cases, each species reciprocally affects the evolution of the other (i.e., true coevolution), whereas in other cases only one species evolves in response to the other. Whether and in which direction each species evolves in response to the other depends on how trade-offs are structured.

We found that an STI affects the level of escalation of traits mediating sexual conflict within the host but that viability-reducing STIs and reproduction-reducing STIs do so in opposite ways. The introduction of a viability-reducing STI escalates the conflict. Female resistance increases to reduce the additional cost of mating imposed by the risk of disease infection. Male persistence increases to stay above increasing female resistance levels. Thus, average host trait values increase; that is, there is elevated conflict escalation. If the cost of SA traits occurs through viability, then a coevolving viability-reducing STI increases its virulence level in response to these changes in the host not because of a change in host mating rate but rather because of the increased host death rate resulting from the escalated sexual conflict. In contrast, if the cost of SA traits occurs through reproduction, then increased conflict escalation evolves in response to a viability-reducing STI—but in this case there is no feedback affecting virulence evolution.

In both cases described above, the three traits reach a stable equilibrium. We find no evidence of cycling, as has been observed under some conditions in a coevolution STI model involving conventional sexual selection (Ashby and Boots 2015). Based on our understanding about why the observed changes occur, cycling is not expected. Stabilizing selection maintains the evolutionary equilibrium. Male persistence increases male reproductive success at the expense of costs associated with persistence, such as increased predation risk (Rowe 1994) and reduced foraging time (Robinson and Doyle 1985). Females suffer costs of mating but must balance these with the direct cost of expressing the resistance trait and the risk of remaining unfertilized if resistance is too high. In the presence of a viability-reducing STI, males experience stronger selection to obtain mates quickly in the face of higher total mortality, and females experience stronger selection to reduce the additional cost of mating associated with a prevalent STI. The escalation of sexual conflict increases total host mortality, selecting for higher STI virulence, which in turn should drive further escalation of the sexual conflict traits. However, the faster-than-linear increasing costs to hosts of the escalating sexual conflict traits and the slower-than-linear increasing transmission benefits of increased STI virulence ensure that the system reaches an equilibrium rather than evolving to ever-higher levels of all three traits. (Such nonlinear costs are a common assumption in both sexual conflict and virulence models and are necessary to have sensible equilibria; e.g., Gavrilets et al. 2001; Otto and Day 2007.) Evolutionary equilibrium is even easier to understand when hosts pay costs of SA traits through reproduction because then conflict escalation does not select for higher STI virulence and create the potential for a host-STI arms race.

Compared with viability-reducing STIs, reproduction-reducing STIs have the opposite effect on the outcome of sexual conflict: a reproduction-reducing STI de-escalates the conflict. Females evolve lower resistance in response

to the alleviation in mating pressure they experience because infected males have reduced mating success. The accompanying (but smaller) decline in the male trait contributes to conflict de-escalation. Regardless of whether hosts pay the cost of SA traits through viability or reproduction, the virulence of a reproduction-reducing STI does not seem to be affected by the decrease in average host trait values. All three traits reach evolutionary equilibrium due to stabilizing selection. Continual de-escalation of the conflict is prevented by selection on females to resist costly matings and selection on males to stay competitive, given that they will enter fewer matings if they are infected.

When the costs of SA traits occur through viability, conflict escalation occurs in response to either a viability-reducing STI or a reproduction-reducing STI. However, a coevolutionary response from the STI occurs only with a viability-reducing STI. As known from past virulence theory (Anderson and May 1982; Ewald 1983), the transmission-virulence trade-off can be thought of as a trade-off between current and future transmission for the STI, the latter of which requires the current host's survival. In cases where host mortality is higher for reasons not directly due to the disease (e.g., higher extrinsic mortality or higher investment in SA traits carrying viability costs), future transmission is downweighted and the disease evolves higher virulence (i.e., increased investment in current transmission). This logic does not apply to a reproduction-reducing STI. As modeled here, the transmission-virulence trade-off in a reproduction-reducing STI occurs because increased transmission given a mating comes at the expense of reducing a male's probability of successfully obtaining a mate. That is, the two components of this trade-off both affect current transmission. Thus, their value relative to one another is unaffected by extrinsic factors that alter the value of future transmission.

The models presented here are an initial investigation, rather than an exhaustive analysis, of the evolutionary interplay of STIs in hosts with sexual conflict. We have assumed specific functional forms for (i) the mating probability as a function of male and female SA traits, (ii) the direct fitness costs of SA traits, and (iii) the relationship between virulence and transmission. There are little to no data providing a strong empirical justification for specific forms of these relationships. Rather, our choices have been made out of mathematical convenience or following previous models (e.g., Gavrilets et al. 2001; Rowe et al. 2005; Otto and Day 2007). Based on our understanding of the results, we speculate that the reported patterns should be robust to other functional forms if the sign of curvatures of the relationships are not changed (i.e., functions remain linear, accelerating, or decelerating, as appropriate). Formal examination of other functional forms or a more general analysis would be needed to confirm this. Although we did not explore a variety of functional forms, we did examine fundamentally different biological models in a comparable framework (i.e., costs of SA traits through viability vs. reproduction, STI virulence manifest through viability vs. reproduction). These alternative models behave differently from one another, broadening our understanding of this topic. Of course, there are many biological possibilities we did not consider that could influence model outcomes and would be worthy of future study (e.g., multiple transmission pathways, coinfection, age-dependent effects). Below we discuss a few possibilities similar to, but not covered by, the models we did explore.

One of the costs we did not explore in depth is the risk of females remaining unfertilized. In the simulation model, a female achieved her full fecundity provided that she mated with at least one male. However, if fertilization was not guaranteed by mating, the increased risk of being left unfertilized would be expected to affect the evolution of female resistance. Thrall et al. (1997) constructed a model investigating how male and female mating behavior affected reproductive success in the presence of an STI. At high disease prevalence, females could achieve the same fitness by being monogamous and minimizing infection risk or by being promiscuous and minimizing the risk of being left unfertilized but increasing the risk of infection. It is possible that if there were higher probabilities of females being unfertilized in our model, divergent female strategies (low and high resistance) would be maintained.

We investigated the full three-way evolutionary interaction over a range of mating costs to females. However, many empirical investigations into sexual conflict in natural systems have reported that females suffer a cost of harassment instead of, or in addition to, the cost of mating (Alcock et al. 1977; Rowe 1994; Stone 1995; Jormalainen 1998; Watson et al. 1998). At high male densities or male-biased sex ratios, the cost of rejecting harassing males can become so great that females are selected to decrease resistance, increasing overall mating activity in these systems (Rowe 1992; Rowe et al. 1994; Lauer et al. 1996). However, the introduction of an STI would effectively increase the cost of mating, possibly tipping the balance in favor of high resistance for females.

The majority of models that have investigated the evolution of host mating strategies in the presence of an STI have assumed that there is sexual selection but no sexual conflict. The distinction between male attractiveness and female preference versus male persistence and female resistance has important consequences for the evolution of an STI. Choosiness may help females gain indirect benefits from mating with a preferred male. Resistance, in contrast, helps females avoid the direct costs of mating (Gavrilets et al. 2001). Unless indirect benefits are strong (Thrall et al. 1997; Boots and Knell 2002), the presence of an STI

will cause selection for nonchoosy females because the most popular males have high infection prevalence (Thrall et al. 2000). In a system with sexual conflict, those males with the highest persistence traits would be more likely than average males to be infected, adding to the cost of mating for females. Females do not reduce their risk of mating with such males by having lower resistance (i.e., lower resistance is not equivalent to being less choosy because the latter can mean less discriminant mating without changing mating frequency). A female with lower resistance may have a lower fraction of her matings with high-persistence (probable STI-carrying) males, but she will not have a fewer number of matings with such males. Moreover, she will have more total matings, increasing her infection risk. Consistent with this fact, we found that the presence of a viability-reducing STI resulted in increased female resistance, which might be construed as increased choosiness, opposite of what is observed in sexual selection models. In contrast, a reproduction-reducing STI results in decreased female resistance, which might be construed as decreased choosiness. Although this would appear to match the outcome of sexual selection models, the reason for this result is very different. In the sexual conflict model, reduced female resistance evolves not to avoid infection but rather because the STI reduces the mating effort exhibited by infected males so that females do not need to invest as heavily in their resistance trait.

For the most part, we have assumed that infection does not directly alter a male's persistence or a female's resistance. However, in some cases STIs manipulate host behavior in ways that directly affect sexual conflict. An STI that influences male competitive ability or propensity to mate could change the relative costs of mating. For example, parasitized males can be less competitive (Siva Jothy and Plaistow 1999; Thomas et al. 1999), decreasing the risks of mating for females in a population with a highly prevalent STI. This is the scenario we modeled by allowing a reproduction-reducing STI to decrease mating probability for infected males. Conversely, as in the milkweed leaf beetle (Abbot and Dill 2001), males with an STI can be more aggressive than their uninfected counterparts, which could increase the number of matings and therefore the costs to females. It is worth noting, however, that although disease prevalence is very high in this milkweed leaf beetle system (~90%), the STI is relatively avirulent, suggesting that STIs that increase male mating propensity may not strongly increase selection on female resistance despite increasing the total mating rate. Alternatively, the STI may manipulate host behavior in such a way that its interests are aligned with one sex. It has been suggested that an STI that reduced the female remating rate would be beneficial for males (Knell and Webberley 2004) because a male that infects his mate would reduce her remating rate and ensure his own paternity. If the benefits of reducing sperm competition outweigh the costs of the STI, males may be selected to increase persistence and consequently their likelihood of acquiring an STI. Similarly, there is some evidence that STIs increase oviposition rates in the fall army worm moth, meaning that males could benefit from acquiring and transmitting an STI (Simmons and Rogers 1994). There are numerous ways males and females could evolve in response to these changes in host mating behavior. Overall, these examples suggest that a change in the cost structure in the presence of an STI could affect the outcome of sexual conflict in natural systems.

There are many well-known examples of STIs and sexual conflict, but we are aware of no systems where both are well studied. Evidence of sexual conflict and sexually transmitted diseases has been reported in ungulates (conflict: Bro-Jørgensen 2010; STI: Lockhart et al. 1996), *Drosophila* (conflict: e.g., Rice et al. 2006; STI: Knell and Webberley 2004), and the two-spot ladybird *Adalia bipunctata* (conflict: Haddrill et al. 2013; STI: Webberley et al. 2002; Ryder et al. 2005). Studies of SA traits in populations with a viability-reducing or reproduction-reducing STI should look for escalated or de-escalated trait values, respectively, compared with populations where the STI is absent. Research on viability-reducing STIs should compare different populations or closely related host species that experience different persistence, resistance, or mating costs. Variation in the costs of SA host traits could arise between populations if, for example, the persistence or resistance trait made the bearer more vulnerable to predation in an open versus a closed habitat (for a discussion of the dependence of SA selection on environmental conditions, see Fricke et al. 2009). Higher mortality rates in one habitat should select for higher virulence in an endemic viability-reducing STI. Additionally, we expect lower disease prevalence in populations where male persistence is strongly selected against and there are high costs of mating or low costs of resistance for females; that is, low mating rates will limit STI transmission.

We have shown that an STI has the potential to influence the outcome of SA coevolution. Because STIs are ubiquitous in nature (Lockhart et al. 1996), they should co-occur with sexual conflict often enough that it is worth considering how STIs change SA selection. Furthermore, considering the full coevolutionary interaction has important implications for both the susceptibility of a host population to invasion of a new STI and the level of virulence expected to evolve.

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