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Letter

Sex-specific immunocompetence: resistance and tolerance can both be futile but not under the same circumstances

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Abstract

Immunocompetence evolution can involve a "resistance is futile" scenario if parasite encounter rates are so high that high investment in resistance only marginally delays infection. Here, we investigate two understudied aspects of "futility": the mode of immunocompetence and sexual selection. First, immunocompetence is usefully categorized as reducing the rate of becoming infected (resistance) or reducing the negative fitness consequences of infection once it happened (tolerance). We compare the prospects of futility for resistance, tolerance, and their joint occurrence, showing that resistance futility arises with respect to parasite encounter rates, while tolerance futility arises with respect to parasite virulence. However, if the same host trait improves pleiotropically both resistance and tolerance, futility disappears altogether and immunity investment remains profitable when increasing parasite encounter rates, virulence, or both. Second, we examine how sexual selection strength impacts these findings. If one sex (typically males) is near the faster end of a fast-slow continuum of life histories, then life history patterns reflecting futility can evolve sex-specificity. The solutions often feature sexual dimorphism in immunocompetence, but not always in the direction of strong sexual selection yielding low immunity: sexual selection can select for faster and "sicker" lives, but if sexual selection also favors traits that impact parasite encounter rates, the results are strongly dependent on whether futility (along any axis) plays a role.

Keywords: Sexual selection, parasites, resistance, tolerance, virulence, sex-specific immunocompetence

Lay Summary

Intuition suggests that investment in immunity is higher when hosts frequently encounter parasites. While there are examples that confirm this, in other cases, hosts have been shown to abandon immune defenses under high parasite pressure. We reconcile these findings by modeling the optimal host resource allocation towards immunity under varying parasite pressure and strength of sexual selection. Our results show two axes along which immunity investments are futile and should therefore be abandoned in favor of investing in reproduction: resisting infection becomes futile under high parasite abundance, while tolerating the harmful effects of infection is not beneficial under ever increasing parasitic virulence. However, investments of organisms that are capable of both resistance and tolerance mechanisms yield fitness payoffs also when parasites are highly virulent and abundant. This work highlights the impact of parasites and immune defenses on optimal immunity investment levels in hosts, an insight which also complements theory on sex-specific immunity.

Introduction

Hosts employ various strategies to fend off parasites, ranging from behavioral avoidance (Gibson & Amoroso, 2022), to a variety of physiological mechanisms summarized as the immune system (Nicholson, 2016). Immunocompetence, i.e., the ability of a host to resist the establishment of a parasite and/or to limit and possibly eradicate parasite growth once infected, can be broadly divided into resistance and tolerance. The former improves host fitness by limiting parasitism (perhaps by preventing infection altogether or by reducing parasite loads). The latter keeps host fitness intact (or partially intact) without diminishing the presence or abundance of the parasite (Martins et al., 2019; Råberg et al., 2009). Note, however, that terminology varies between authors: Miller et al. (2007) define tolerance as above but consider it a subcategory of resistance. Jokela et al. (2000) use tolerance to refer to a scenario where any type of defense has evolved to be low, and Best et al. (2010) use resistance and tolerance to model two different traits that both take effect in infected hosts only, excluding the possibility that resistance may prevent infection in the first place.

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An interesting theoretical finding is a scenario where "resistance is futile," typically discussed with respect to resistance. The "futility" cases are a counterexample to the intuition that more abundant parasites lead to stronger host immune defenses (see Lindström et al., 2004 for an example of the said intuition). If parasite encounter rates are so high that strongly resistant hosts still become infected, then, assuming a trade-off between resistance and current reproduction, reduced investment into resistance, i.e., futility, is selected for (Jokela et al., 2000; Walsman et al., 2023). This may involve "classical" resistance via animal immunocompetence, but also any behavioral avoidance of parasites (Walsman & Cressler, 2022, Walsman et al., 2023; see also Kokko et al., 2002 for a sexually transmitted context), as well as plant resistance against plant pathogens (Thrall & Burdon, 2000). Theoretical findings of "resistance is futile" are supported by experimental data and field observations in animals (Walsman et al., 2023) and plants (Ericson & Burdon, 2009; Laine, 2004). Whether futility can also apply to tolerance is rarely discussed, though it is known that tolerance can be lost under certain conditions, such as short host lifespans (Miller et al., 2007).

A host that has given up immunity when it is futile makes the most of its (potentially brief) time being still parasite-free and/or still living despite being infected. This yields a connection between futility and sex-specific life histories. Strong sexual selection can make males invest in a "live fast, die young" manner (Kokko, 2025). Whether this creates sex-specific prospects for futility is unknown, even though sexually dimorphic immunocompetence (Zuk et al., 2004) has been reported in a wide variety of taxa: birds (Møller et al., 1998; Sauer et al., 2024; Vincze et al., 2022), mammals (Guerra-Silveira & Abad-Franch, 2013; Klein, 2012; Moore & Wilson, 2002; Wilkinson et al., 2022), fishes (Dong et al., 2017; Shepherd et al., 2012), and insects (Belmonte et al., 2020; Kurtz et al., 2000); for a review, see Kelly et al. (2018). Although males are not always the "sicker sex" (Hillegass et al., 2008; Sanchez et al., 2011; Sheridan et al., 2000; Stoehr & Kokko, 2006), there is a general expectation that strong sexual selection should make males favor high mating success even if it comes with a shortened lifespan. The links to futility, however, remain unexplored.

Here, we investigate two understudied aspects of "futility": (1) types of immune mechanisms (resistance or tolerance) that hosts employ as their defense traits, and (2) varying levels of sexual selection strength. In our study, we operationally define resistance as any immune mechanism reducing the infection probability after encountering a parasite (thus we do not model varying parasite loads), while tolerance captures the host's ability to minimize parasite-imposed harm once infected. We develop a model that assumes a trade-off between immunity and reproduction and solve it numerically for varying levels of sexual selection strength, parasite encounter rate, and virulence. We do this for two defense mechanisms—resistance and tolerance, whose impact is assessed separately as well as jointly, to examine whether either of them, or both, can become futile.

Model

Our continuous-time model optimizes the allocation of resources x ($0 \le x \le 1$) into immunity that trades off with reproduction. Resources not allocated towards immunity, $1–x$, are invested into reproduction. All hosts are assumed to reproduce continually, whether infected or not. Since the rate of reproduction is $1–x$, host fitness in a stationary population is $(1–x)L(x)$, where $L(x)$ denotes the expected lifespan. Most of the modeling effort below deals with deriving $L(x)$. After the expression for the lifespan expectation is known, the numerical search for the fitness-maximizing value of $(1–x)L(x)$ is simple to conduct.

To work towards $L(x)$, we assume that each host starts its life in a susceptible state (S) with baseline mortality μ and a constant parasite encounter rate $k > 0$. The method follows continuous-time rates impacting fitness (see Kokko, 2024 for an extensive tutorial; for the current model, we visualize a high rate of transitioning away from the current state—by dying or by becoming infected—as many parallel arrows in Figure 1; low rates have few arrows). Not every parasite encounter leads to the host becoming infected (state I), as infections can be fended off by high resistance (Figure 1B: resistant hosts have some parasite encounters where the arrow does not "work" to create an infected individual, but one of the many encounters still does result in infection). Once infected, parasite virulence $\omega > 1$ elevates multiplicatively the mortality of their hosts, shortening the expected lifespan (more arrows in Figure 1 leading to death once infected), but this effect may be counteracted by tolerance (Figure 1C has fewer death-inducing arrows from the infected state than Figures 1A, B). Our choice of a multiplicative effect makes the interpretation of ω easy across wide ranges of mortality μ (e.g., $\omega = 1.2$ always increases mortality by 20%, regardless of μ). All parameters are listed in Table 1.

We consider three scenarios. In the *resistance* scenario, investment into immunity x reduces infection probability upon parasite encounter (Figure 1B). In the *tolerance* scenario, x instead mitigates harm imposed by parasites after infection (Figure 1C). Finally, in the *pleiotropic* scenario, x feeds into both immunity mechanisms simultaneously.

Solving the model requires deriving expectations of times spent in different states when different types of events (becoming infected, or death) "compete to happen" to an individual (Kokko, 2024). We derive the expected lifespan L of a host capable of resistance (R), tolerance (T), or both (P, for pleiotropy) as the sum of the time a host is expected to spend in the S and the I states:

$$L_R = \underbrace{\frac{1}{k\left(1-x^{\beta}\right)+\mu}}_{L_{RS}} + \underbrace{\frac{k\left(1-x^{\beta}\right)}{k\left(1-x^{\beta}\right)+\mu}}_{\substack{\text{transition}\\ \text{probability}}} \times \underbrace{\frac{1}{\omega\mu}}_{L_{RI}} \quad [1]$$

$$L_T = \underbrace{\frac{1}{k+\mu}}_{L_{TS}} + \underbrace{\frac{k}{k+\mu}}_{\substack{\text{transition}\\ \text{probability}}} \times \underbrace{\frac{1}{\mu+(\omega\mu-\mu)\left(1-x^{\gamma}\right)}}_{L_{TI}} \quad [2]$$

$$L_P = \underbrace{\frac{1}{k\left(1-x^{\beta}\right)+\mu}}_{L_{PS}} + \underbrace{\frac{k\left(1-x^{\beta}\right)}{k\left(1-x^{\beta}\right)+\mu}}_{\substack{\text{transition}\\ \text{probability}}} \times \underbrace{\frac{1}{\mu+(\omega\mu-\mu)\left(1-x^{\gamma}\right)}}_{L_{PI}} \quad [3]$$

In scenarios involving resistance (Equations 1 and 3), the probability of infection upon each parasite encounter equals $1–x^{\beta}$, where lower values of β imply more efficient reduction in risk (Supplementary Figure S1B). If β is high, substantial allocation (x) is required to yield a considerable reduction. These assumptions translate into a transition rate $k(1–x^{\beta})$ from S to I.

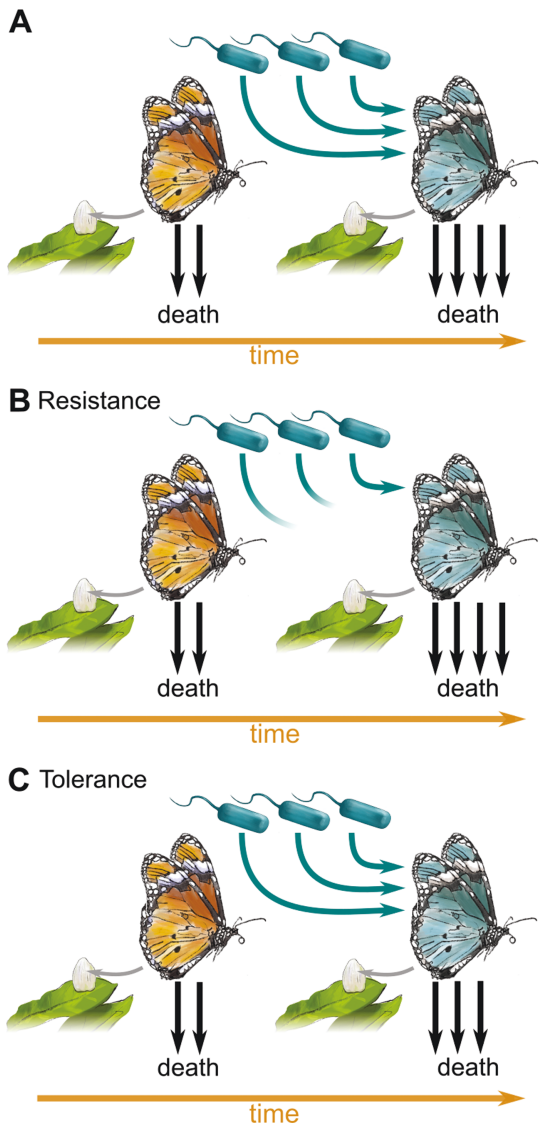

Figure 1. Schematic of the model. In our continuous-time model, a susceptible individual (orange butterfly) encounters parasites continually, which may or may not lead to infection: curved arrows are all capable of causing infection in (A) where there is no resistance, but some contacts do not cause this transition in (B) where there is investment in resistance. Both susceptible (orange) and infected (blue) hosts can die, but the latter do so at a higher rate (more black arrows impacting the infected host); this increase in death rate can, however, be mitigated by tolerance (fewer black arrows in C than in B for infected hosts). An individual can reproduce regardless of infection status, as symbolized by egg-laying (dark gray arrows).

An individual remains in the S state as long as it avoids both infection and death. In cases where immunocompetence x improves resistance, the expected time spent in S is longer if x is high (Equations 1 and 3), while if x only confers tolerance (Equation 2), the time to infection depends on k without involving x. In all settings, the expected time spent in an S state is also limited by death rates μ.

The expected time spent in the I state depends on the lifetime probability of transitioning from S state to I state in the first place (second term in Equations 1, 2, and 3), multiplied by the expected lifespan conditional on ever entering that state (the last terms in Equations 1, 2, and 3). Since we do not include recovery in our model, the only way to leave the I state is through death. In scenarios with no tolerance, virulence ω elevates multiplicatively the death rate from μ to $\omega\mu$ and thus the expected lifespan from the point of infection onwards is $1/(\omega\mu)$.

In scenarios including tolerance (Equations 2 and 3), immunity investment x mitigates the mortality changes caused by virulence: we assume it diminishes the difference between mortality rates while infected and uninfected ($\omega\mu - \mu$ in the absence of tolerance) through a multiplication by $1-x^{\gamma}$, where γ modulates how allocation x translates into longer lifespan once infected ($\gamma > 0$) (Supplementary Figure S1C). Thus, mortality changes from μ to $\mu+(1-x^{\gamma})(\omega\mu-\mu)$ upon infection. Note that even with mortality reduction through tolerance, mortality in the I state does not fall below mortality in the S state. Immunity investment x into both resistance and/or tolerance leads to a proportional reduction of the chance of infection and/or mortality in the infected state, respectively, regardless of the absolute parasite encounter rate or virulence.

We assume that host reproductive success is contingent on the fraction of resources invested into reproduction $(1-x)$, both in the S and in the I states. Reproductive output per time unit equals $(1-x)^{\alpha}$, where α describes the strength of sexual selection ($\alpha > 0$) (see, e.g., Stoehr & Kokko, 2006, for this way of modulating the strength of sexual selection, though in their notation this was δ). High values of α indicate that a small marginal investment difference creates little marginal change in reproductive success when investment into reproduction $(1-x)$ is low to begin with, while the improvement in reproductive success is considerable if the investment has already reached high levels. A biological example for this are males that need to invest heavily into reproduction before achieving any meaningful mating success. Small values of α behave in the opposite way to the above statements (Supplementary Figure S1A). In species that are not sex role reversed, low α fits female life history, where modest investment into reproduction is required, but ever-higher investment leads to diminishing returns.

The expected fitness of a host of a specific sex is a product of reproductive output per time unit, $1-x$, multiplied with the expected lifespan. For each scenario, "resistance," "tolerance," and "pleiotropic," this yields the following equations describing the expected lifetime fitness:

$$W_R = \frac{(1-x)^{\alpha}}{k(1-x^{\beta})+\mu} + \frac{k(1-x^{\beta})}{k(1-x^{\beta})+\mu} \times \frac{(1-x)^{\alpha}}{\omega\mu} \quad [4]$$

$$W_T = \frac{(1-x)^{\alpha}}{k+\mu} + \frac{k}{k+\mu} \times \frac{(1-x)^{\alpha}}{\mu+(\omega\mu-\mu)(1-x^{\gamma})} \quad [5]$$

$$W_P = \frac{(1-x)^{\alpha}}{k(1-x^{\beta})+\mu} + \frac{k(1-x^{\beta})}{k(1-x^{\beta})+\mu} \times \frac{(1-x)^{\alpha}}{\mu+(\omega\mu-\mu)(1-x^{\gamma})} \quad [6]$$

We numerically derive the optimal immunity investment x^* that maximizes fitness for a host, and then interpret the resulting dependencies on α, β, and γ.

Results

Futility in response to parasite encounter rate, virulence, or neither?

When reproduction trades off with resistance only, the lowest and highest parasite encounter rates k produce similar outcomes, where investment into immunity remains low (red line, Figure 2A). It is easy to understand why immunity is neglected with low

Table 1. The list of parameters and notions used in the model.

Symbol	Description	Values (when applicable)
a	Strength of sexual selection	See Figure captions
β	Resistance investment payoff	See Figure captions
γ	Tolerance investment payoff	See Figure captions
μ	Baseline mortality	See Figure captions
ω	Parasite virulence	See Figure captions
k	Parasite encounter rate	See Figure captions
x	Immunity investment	Model outcome
x^*	Optimal immunity investment	Model outcome
L_{SR}	Lifespan of susceptible individuals, "resistance" and "pleiotropic" scenarios	$L_{SR} = \frac{1}{k(1 - x^{\beta}) + \mu}$
L_{ST}	Lifespan of susceptible individuals, "tolerance" scenario	$L_{ST} = \frac{1}{k + \mu}$
L_{IR}	Lifespan of infected individuals, "resistance" scenario	$L_{IR} = \frac{1}{\omega\mu}$
L_{IT}	Lifespan of infected individuals, "tolerance" and "pleiotropic" scenarios	$L_{IT} = \frac{1}{\mu + (\omega\mu - \mu)(1 - x^{\gamma})}$
W_{SR}	Fitness of susceptible individuals, "resistance" and "pleiotropic" scenarios	$W_{SR} = L_{SR}(1 - x)^a$
W_{ST}	Fitness of susceptible individuals, "tolerance" scenario	$W_{ST} = L_S(1 - x)^a$
W_{IR}	Fitness of infected individuals, "resistance" scenario	$W_{IR} = L_{IR}(1 - x)^a$
W_{IT}	Fitness of infected individuals, "tolerance" and "pleiotropic" scenarios	$W_{IT} = L_{IT}(1 - x)^a$
W_R	Total fitness of individuals, "resistance" scenario	$W_R = W_{SR} + \frac{k(1 - x^{\beta})}{k(1 - x^{\beta}) + \mu} W_{IR}$
W_T	Total fitness of individuals, "tolerance" scenario	$W_T = W_{ST} + \frac{k}{k + \mu} W_{IT}$
W_P	Total fitness of individuals, "pleiotropic" scenario	$W_P = W_{SR} + \frac{k(1-x^{\beta})}{k(1-x^{\beta}) + \mu} W_{IT}$
S	Susceptible state	
I	Infected state	

parasite encounter rates—most lives end without entering the infected state, yielding little incentive to invest into immunity. However, immunity remains low at a high parasite encounter rate, with lifespans evolving to be short. This is a classic example of a "resistance is futile" situation: when parasitic encounters are so frequent that even high immunity cannot prevent infection for any substantial amount of time, it becomes optimal to neglect immunity and maximize offspring production before death. Substantial immunity investment in the resistance scenario thus evolves at intermediate values of parasite encounter rate k (Figure 2A).

With tolerance, benefits from immunity investment are based on decreasing the additional mortality induced by parasites. There is no futility pattern for tolerance with respect to parasite encounter rates; instead, allocation into tolerance-conferring immunity increases with parasite encounter rate (yellow dashed line, Figure 2A). Note that this increase only mitigates and does not prevent the lifespan loss associated with parasitism (Figure 2C). Tolerance, however, produces futility with respect to parasite virulence: immunity investment first grows, then shrinks, along the virulence axis (Figure 2B), showing a similar effect as parasite encounter rates had for the resistance scenario.

When the same investment improves both resistance and tolerance (pleiotropy), futility disappears and optimal immunity investment increases with parasite encounter rate as well as with parasite virulence (blue dotted lines, Figures 2A, B). Despite pleiotropic benefits, the investment once again is not sufficient to keep lifespan as long as in the absence of the parasite (blue dotted lines, Figure 2C, D). Note that as a whole, conditions that lead to maximal immunity investment, such as high parasite encounter rate or virulence, associate with either short or intermediate expected lifespans L. The "short life" cases arise because difficulties to cope with abundant, virulent parasites can simultaneously shorten life while also selecting for high immunity. This co-occurrence between shortest lives and strongest immunity is broken under conditions where there is futility: now immunity investment is maximal at intermediate parasite encounter rates and virulence, and lifespans are accordingly at the intermediate range too.

While the above examples show interesting patterns, Figure 2 varies parasite encounter rate k while keeping virulence ω constant, or vice versa; nor is baseline mortality μ varied. Broadening the view to other combinations of k and ω is necessary to infer generality, while μ merely scales the lifespan outcomes and its precise value is less important.

Exploring solutions across varying parasite encounter rates k and virulence ω allows asking whether either parameter promotes futility. Along the encounter rate axis, allocation into resistance-promoting immunity first grows (Figure 3A: colors become lighter) when moving horizontally, in the direction of increasing k, declining thereafter (colors become darker again), such that the optimal investment x^* reaches the highest values at intermediate values of k. Moving vertically, in the direction of increasing virulence, ω, does not show futility in resistance: investment either stays unchanged or increases (moving upwards means moving into lighter-colored regions).

The statements can be reversed for tolerance (Figure 3C): moving along the horizontal axis (increasing k) only leads to lighter colors (increasing investment), while movement along the vertical axis yields futility, where increasing virulence selects for giving up tolerance. To sum up, while resistance futility requires highly abundant parasites, tolerance futility occurs with highly virulent parasites. If parasites significantly shorten life and significant mitigation via tolerance is unachievable, the optimal

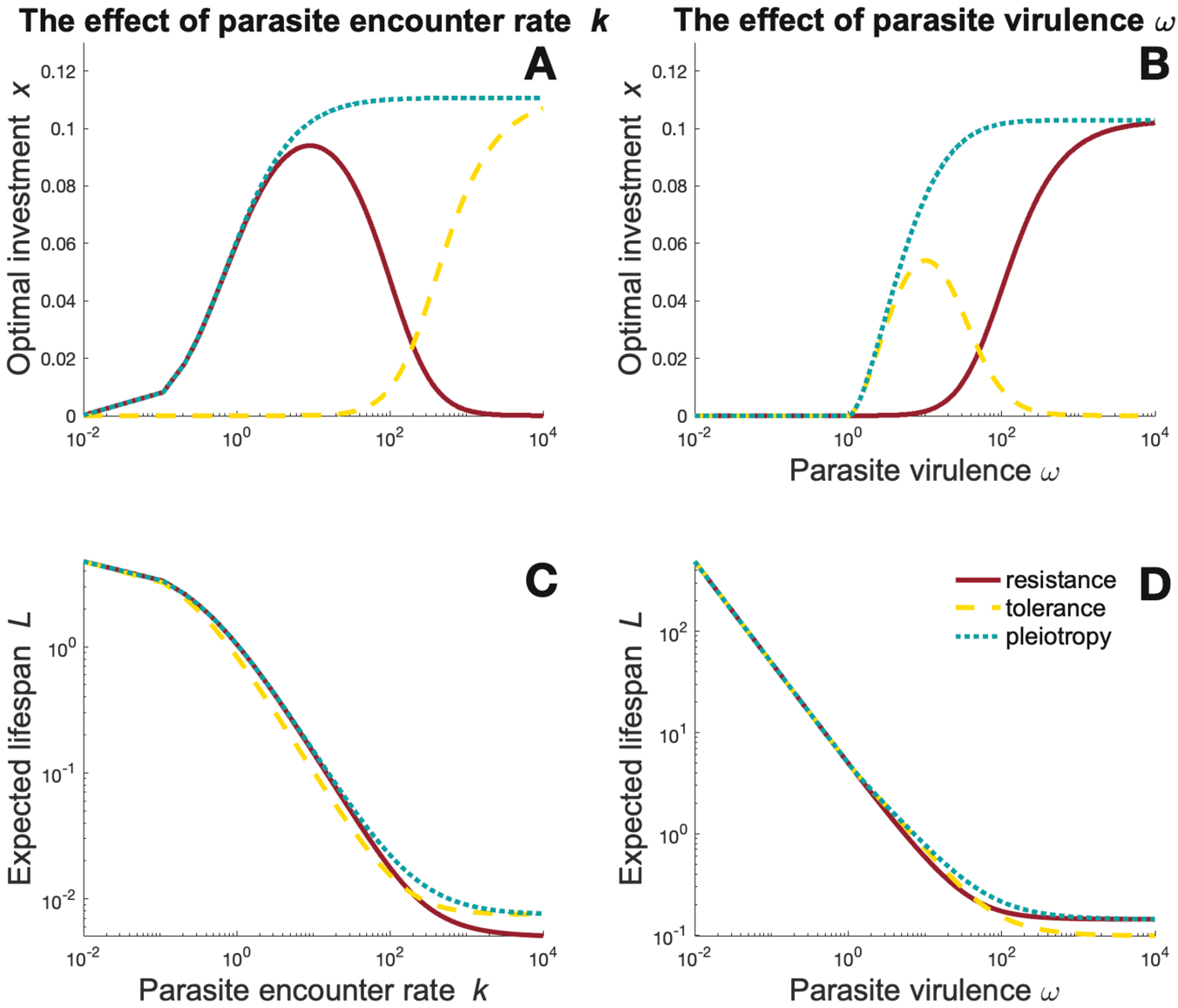

Figure 2. Optimal investment x^* (A, B) and resulting expected lifespan L (sum of expected lifespan in two states, susceptible and infected) (C, D), as a function of (A, C) parasite encounter rates k and (B, D) parasite virulence ω under the three immunity mechanisms scenarios. Line color and shape indicate immunity mechanisms included into a given model scenario: red line—"resistance" scenario; yellow dashed line—"tolerance" scenario; blue dotted line—"pleiotropy" scenario where immunocompetence improves both resistance and tolerance. Other model parameters: $\alpha = 2$; $\beta = 0.5$; $\gamma = 0.5$; $\mu = 0.2$; in (A, C) $\omega = 1{,}000$; in (B, D) $k = 10$.

strategy maximizes fitness with a short life and fast reproduction rather than prolonging it through tolerance.

Finally, when immunity investment improves both tolerance and resistance, the question is whether the system combines both types of "futility," only one, or none. The answer was "none" in the single example of Figure 2, and this also generalizes to Figure 3E. Since Equations (4, 5, and 6) do not yield closed-form solutions for the optimal x^*, the result that futility disappears with pleiotropy deserves an even stronger investigation with respect to its generality. A broad search across parameter values shows this is the case for all 10,000 tested parameter sets (see supplementary information).

The lifespan results of Figure 2 generalize as well: the adaptive responses by the hosts do not fully compensate for the burden of parasitism. The different immunity scenarios yield almost identical results for the expected host lifespan (Figure 3B, D, and F). Total lifespan diminishes with increasing parasite encounter rate as well as with virulence (dark blue areas at the top-right side of Figure 3B, D, and F), despite adaptive changes in immunocompetence that differ between resistance, tolerance, and pleiotropic scenarios (Figure 3A, C, and E). Note also that, should one compare two species differing in their ecologies, it is possible to have little difference in predicted immunity despite widely differing encounter rates and/or virulence of their (potentially species-specific) parasites; this applies whenever the two parameter combinations are within a zone of the same color in Figure 3.

Stronger sexual selection leads to weaker immunity, but the net effect depends on parasite encounter rates

Sexual selection strength interplays with parasite abundance to influence optimal immunocompetence (Figure 4). In general, whenever it is beneficial for a host to invest into immunity (at moderate and/or high parasite encounter rates depending on the

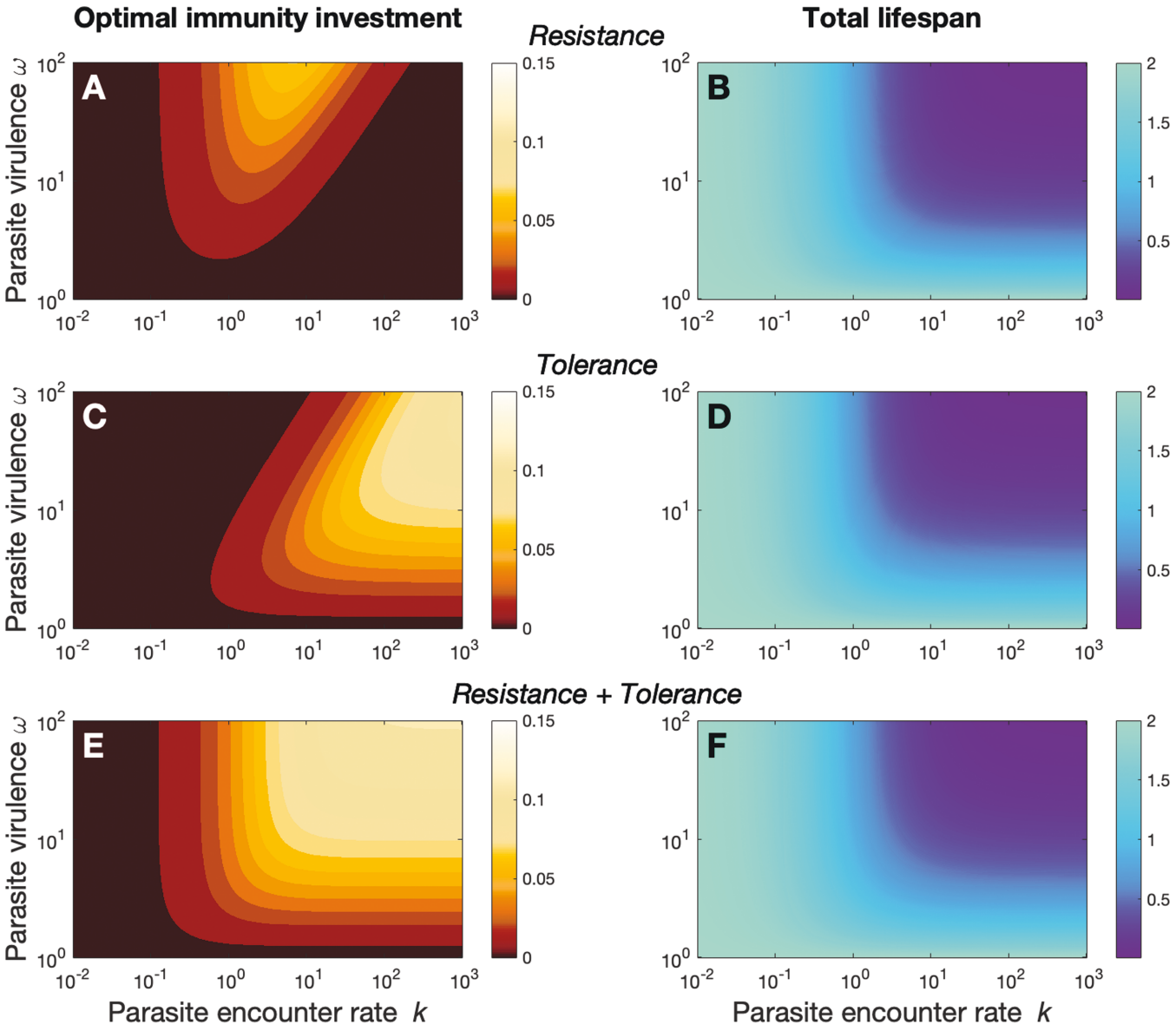

Figure 3. The effect of parasite virulence and parasite encounter rate on (A, C, E) optimal immunity investment and (B, D, F) expected lifespan. Immunocompetence is assumed to improve resistance (A, B), tolerance (C, D), or both (E, F). The investment heatmaps (A, C, E) show the optimal immunity investment x^* for each combination of parasite encounter rate k (x-axis, log scaled) and parasite virulence ω (y-axis). The lifespan heatmaps (B, D, F) assume individuals invest according to the optimal value x^*. Parameter values: $\alpha = 2$; $\beta = 0.5$;$\gamma = 0.5$; $\mu = 0.5$.

immunity mechanism), the relationship between sexual selection strength and investment into immunity is negative (Figure 4A, C, and E: colors darken when sexual selection increases). This is logical: relaxed sexual selection ($\alpha < 1$) implies diminishing returns of reproductive success with ever-higher investment in reproductive traits, rendering the lifespan-extending trait of immunocompetence relatively more beneficial. However, at very low parasite encounter rates, irrespective of the immunity mechanisms in focus, immunity investment remains low regardless of sexual selection strength, as infection risk remains minimal. This is also true when varying the relationship between immunity investment and resistance and tolerance payoffs β and γ (Supplementary Figures S2 and S3).

We do not explicitly specify "males" and "females" in our model. Instead, we consider their situation to differ in two ways: the sex experiencing stronger sexual selection (often males) is located higher up along the α axis (Figure 4A, C, and E); additionally, some sexually selected traits, e.g., fighting (with the possibility of injuries) and increased mobility, may elevate the parasite encounter rate, shifting a given sex towards the right in Figure 4A, C, and E. The optimal investment changes accordingly. While increasing α lowers optimal investment, the effect of increased parasite encounter rate is mechanism-specific, as explained in previous findings (Figures 2 and 3).

Consequently, what matters for the final prediction is the location of a sex in the parameter space. The effects may be subtle: if moving a female to a male life history involves an increase in both k and α, then in some cases (large areas of similar color, Figure 4) not much changes, while in other situations there is much subtlety in predictions. Examples (Figure 4) occur when moving from circles ("female") to either triangles or squares ("male"), and in both cases (triangles and squares), males experience a higher k and are more strongly sexually selected than females are. In the triangle locations, the shift along the k axis is relatively stronger

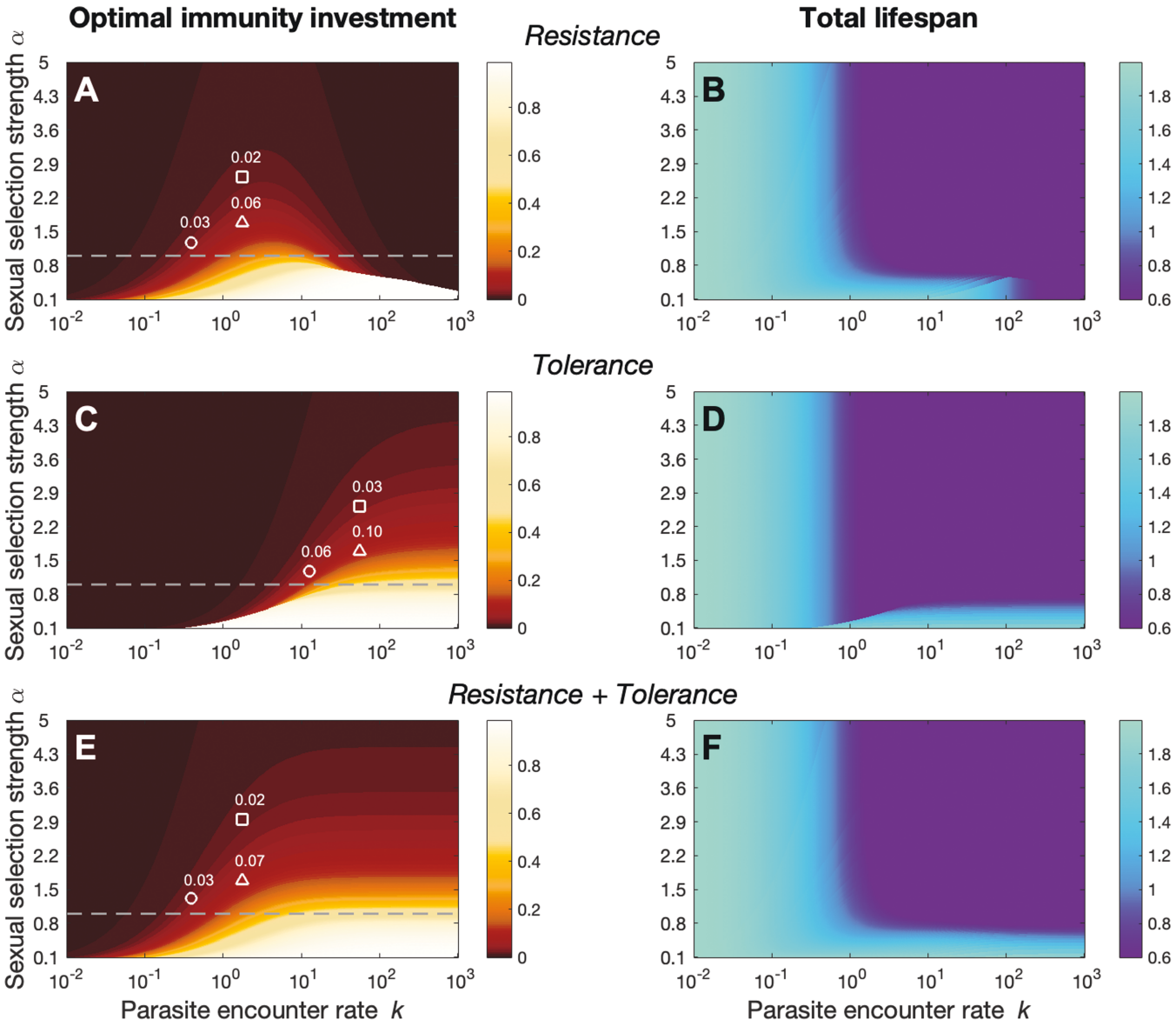

Figure 4. The effect of strength of sexual selection and parasite encounter rate on optimal immunity investment. Immunocompetence is assumed to improve resistance (A, B), tolerance (C, D), or both (E, F). The optimal investment x^* heatmaps (A, C, E) show the nonlinearity of x^* with respect to parasite encounter rate k and strength of sexual selection α. The lifespan heatmaps (B, D, F) assume individuals invest according to the optimal value x^*. Symbols inside the heatmaps point out locations referred to in the main text, with numbers indicating immunity investment x^*. Within each plot, the square and triangle mark higher levels of sexual selection as well as parasite encounter rate compared to the respective circle; triangles have the highest investment, circles medium, and squares the lowest. Other model parameters: $\beta = 0.5$; $\gamma = 0.5$; $\mu = 0.5$; $\omega = 30$.

than the shift along the sexual selection axis, and the result is a strengthening of immunity in males relative to females as a result of an increased parasite encounter rate; the square shows the opposite (male $x^* <$ female x^*) as the difference in sexual selection strength, promoting fast life histories in males, predominates the pattern.

Discussion

The concept of "futility" explains a counterintuitive phenomenon where a host neglects immunocompetence when intuitively it would be most needed. Typically, the axis in question is parasite abundance; futility means a negative relationship between (some values of) abundance and evolved resistance (Walsman et al., 2023). Broadly speaking, a "resistance-is-futile" strategy applies to ineffective defense mechanisms, predicting weaker or possibly abandoned investments into defense (Jokela et al., 2000). In our study, we showed that resistance and tolerance differ in the conditions that create futility.

While our results align with earlier work, showing that resistance can sometimes diminish with very high parasite abundance, our study identifies another axis of futility. With tolerance as the defense trait, parasite virulence—not abundance—serves as the axis of futility. Interestingly, ours is not the first to show futility as a response to parasite traits beyond abundance. Best et al. (2010) modeled a special case of castrating parasites, distinguishing between two traits termed "resistance" and "tolerance," but with important terminological differences between their study and ours. Their resistance does not prevent infection; instead, it is assumed to lower the parasite growth rate, influencing virulence.

Thus, once the terminology is accounted for, their finding of "futile resistance" aligns well with virulence-tolerance futility from our model.

Intriguingly, if we assume that immunocompetence aids both resistance and tolerance, neither axis of futility remains. This holds even if immune investment strengthens one immune mechanism more than the other (supplementary information). Thus, we make the prediction that if the same trait can often help in both contexts, futility should not be observed. Thus, when futility is found, our model suggests that researchers should find little pleiotropy where one trait helps in both contexts—or perhaps even an actual trade-off between resistance and tolerance, should they compete for resources within an organism (see discussion in the context of birds, Arriero et al., 2018; or fruit flies: Vincent & Sharp, 2014). Modeling this scenario explicitly appears a fruitful research avenue.

Our model also has some other limitations. To keep the causalities maximally clear, we made the choice of building an "open" model (*sensu* Cooper et al., 2018) where parasite encounter rates can take any value regardless of host traits. While this makes detecting futility clearer, it also prevents us from making predictions on the role that feedbacks take in host-parasite dynamics (see a review by Boots et al., 2008 for several examples of how the coevolution of a host-parasite system can be modeled). Interestingly, since resistance and tolerance differ starkly in their effects on parasite fitness, we can conjecture that high tolerance can increase parasite abundance, with knock-on effects on the evolution of resistance, a potential outcome resembling results of a coevolutionary model (Baalen, 1998) where hosts lose their resistance under abundant but avirulent parasites. Likewise, we did not consider evolving parasite traits (Cousineau & Alizon, 2014; Gipson & Hall, 2016), creating potentially more complex settings and promising avenues for future models.

We assume a trade-off between reproduction and immunity with the potential for sex-specific optima. There are extreme examples in nature: male semelparity in *Antechinus* is caused by the collapse of male immunocompetence after one intense mating season (Fisher et al., 2013). More generally, fighting off infection negatively impacts a host's reproductive success (as suggested by host traits (Manjerovic & Waterman, 2012) and exposure to infectious agents (Hogg & Hurd, 1995; Fellowes et al., 1999; for a review, see Schwenke et al., 2016). In turn, higher reproductive investment may also suppress immunocompetence (Adamo et al., 2001; Ardia et al., 2003; Fedorka et al., 2004; Uller et al., 2020). Our model, where sexual selection decreases optimal immunity investment, goes in line with previous studies (Sheldon & Verhulst, 1996; Zuk, 1990; Zuk & Stoehr, 2002).

We add, however, new examples to the set of known theoretical counterexamples, such as the known theoretical finding that if a male needs very good condition to have appreciable mating success, and parasites are a major determinant of condition, males may remain the more immunocompetent sex (Stoehr & Kokko, 2006). In our case, sex differences in optimal immunity levels occur when sexes differ in the strength of sexual selection and/or the parasite encounter rate. If parasites are not abundant enough for futility to emerge, the more sexually selected sex is predicted to have lower immunocompetence when sexual selection is the sole difference between sexes, but this sex can switch to higher immunocompetence if sexual selection comes with behaviors increasing parasite encounter rates. In "futile" scenarios, the sexually selected sex is much more clearly predicted to have lower immunocompetence, regardless of parasite encounter rate.

A higher parasite burden in males (Poulin, 1996) may stem either from sex-specific parasite behavior (Duneau & Ebert, 2012; Duneau et al., 2012) or from males offering an easier habitat for the parasites, reflecting sexually divergent immunocompetence (Bacelar et al., 2011; Foo et al., 2017). Documenting parasite encounter rates is probably easier than sex-specific virulence (Hall & Mideo, 2018). Note, however, that while we might expect higher parasite encounter rates for males (e.g., with male-biased mate-searching, Li & Kokko, 2019), females face unique challenges too, e.g., pregnancy-associated transmission risk (Mitchell et al., 2022), traumatic insemination (Reinhardt et al., 2003), or diet differences (De Lisle & Bolnick, 2021).

We did not consider any specific form of sexual selection, where favorable sexually selected traits correlate with superior resistance genes (Dunn et al., 2013; Taskinen & Kortet, 2002). Stoehr and Kokko (2006) considered immunity investment's potential to increase mating success yet without an explicit focus on females preferring resistant males. If females mate preferably with males resisting infection, or tolerant males simply persist longer in the mating pool (an idea akin to "stamina," Kovalov & Kokko, 2022), dynamics are likely to become more complicated; parental care (Venkateswaran et al., 2021; Wittman & Cox, 2021) and sexually transmitted disease (Keiser et al., 2020) offer further challenges.

Overall, we have shown an interesting nonadditivity: two axes of futility both disappear if the same immunity trait can help uninfected hosts avoid infection and improve the performance (here, survival) of infected hosts. Hence, an immune system with pleiotropic effects may avoid scenarios where immune defense becomes futile. Since it is conceivable that mechanisms conferring resistance can also help tolerate the infection once it exists, this may help explain why organisms rarely "capitulate" in the presence of frequently encountered parasites.

Supplementary material

Supplementary material is available online at *Evolution Letters*.

Data and code availability

MATLAB files with the model code and scripts used to generate data and figures are available under the following link: https://zenodo.org/records/14139445.

Author contributions

Conceptualization—all the authors; building and investigating the model—all the authors; writing original draft—F.A.B. and V.K.; reviewing and editing—all the authors; supervision—H.K. All the authors read the final version of the manuscript and approved it for the publication.

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