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The coevolution of parasite virulence, and host investment in constitutive and induced defense

Abstract

Given their ubiquity in nature and their importance to human and agricultural health it is important to gain a better understanding of the drivers of the evolution of infectious disease. Across vertebrates, invertebrates and plants, defence mechanisms can be expressed either constitutively (always present and costly) or induced (activated and potentially costly only upon infection). Theory has shown that this distinction has important implications to the evolution of defence due to differences in their impact on both individual fitness and the feedback of the population level epidemiological outcomes such as prevalence. However, despite the fact that pathogens evolve in response to host immunity and that this can have important implications to the evolution of host defence, the implications of coevolution on constitutive and induced immunity have not been examined. Here we show theoretically how and when incorporating host-parasite coevolution between host defences and parasite growth strategies plays an important role in determining the optimum outcome. A key result is that whether the parasite affects host reproduction critically impacts host-parasite coevolution; when the parasite impacts fecundity, selection on the host is largely geared towards minimizing reproductive costs, through reducing investment in reproductively costly constitutive defense when the parasite prevalence is low, but also by investing in immunity to avoid infection or recover when prevalence is high. Our work emphasizes the importance of coevolution and epidemiological feedbacks to the coevolution of hosts and parasites and provides testable predictions of the determinants of constitutive verses induced defence.

Introduction

Parasites are ubiquitous in nature, impacting evolution and ecology at all phylogenetic levels (Wood and Johnson, 2015). As such, a good understanding of how parasites and their hosts coevolve is critical for human and animal health, as well as for our understanding of how infectious disease shapes natural systems (Woolhouse *et al.*, 2002; Jack and Du Pasquier, 2019). Parasites influence host life history traits (e.g., mortality rates), investment in immunity (Schmid-Hempel,

2009; Rabajante *et al.*, 2015) and population level characteristics (e.g., carrying capacities/population sizes). Hosts have evolved a range of diverse immune defenses against parasites including both tolerance and resistance (Roy and Kirchner, 2000; Restif and Koella, 2003; Miller, White and Boots, 2005; Råberg, Sim and Read, 2007). Resistance mechanisms, which act to reduce the fitness of the parasite while increasing that of the host, can be usefully divided into two types: constitutive mechanisms, which are persistently active and typically act to prevent infection in the first place such that hosts do not become infectious, and induced mechanisms, which are only activated during an infection and typically drive the recovery process (Kamiya *et al.*, 2016; Boots and Best, 2018). In this definition, constitutive defenses include innate mechanical barriers, complement and antimicrobial proteins, and phagocytic, granulocyte, and natural killer (NK) white blood cells, as well as the natural antibodies which bridge innate and adaptive immunity—whereas induced defenses include innate inflammatory responses, as well as adaptive cytokines and antibody responses (Lee, 2006). This distinction between constitutive and induced defense is important to host evolution at both the individual and population level. At the individual level, maintaining constitutive defenses that are always ready to act is costly even in the absence of parasites, but avoids damage by preventing infection altogether; in contrast, activating induced defenses during an infection may be more energetically efficient since they are only used in the presence of the parasite, but risks incurring damage from both the infection itself and very typically from the immune response (immunopathology) (Schmid-Hempel and Ebert, 2003; Paludan *et al.*, 2021). At the population level, constitutive defense reduces the infection rate, while induced defense only shortens the infectious period and therefore there is the potential for different epidemiological feedbacks. These population level effects create important feedbacks to selection because effectively the host immune investment influences parasite epidemiological traits such as the prevalence and force of infection, which feedbacks into selection for immune defense in the first place (Boots *et al.*, 2009; Boots and Best, 2018).

It is also clear that host characteristics, and in particular immunity and other defences, in turn, influence parasite evolution—in particular, modulating the transmission costs and benefits of virulence (Day, Graham and Read, 2007; Gandon, Jansen and Van Baalen, 2007). Classic evolution of infectious disease theory assumes a tradeoff between virulence and transmission rate on the basis that while high within-host growth rates increase infectiousness, they also increase damage to the host, thus shortening the infectious period and reducing opportunities for future

transmission through increasing mortality (virulence) (Anderson and May, 1982; Ewald, 1983). Host mortality rates and carrying capacities impact the density of susceptible individuals available to the parasite, regulating opportunities for transmission and thus the transmission cost of virulence (Gandon, Jansen and Van Baalen, 2007). Importantly, the form of host defence will also impact selection on the parasite: constitutive defense reduces infectiousness—heightening the transmission benefit of virulence—whereas induced defense introduces host damage from immunopathology—heightening the transmission cost of virulence. Thus, understanding evolution in parasite-host systems requires taking into account the costs and benefits of different parasite and host strategies, as well as parasite-host coevolution—at both the individual level and in the broader epidemiological and population dynamic context. Empirical work has described a complex web of interactions between parasite-host coevolution and ecological feedbacks (Woolhouse *et al.*, 2002; Rabajante *et al.*, 2015; Jack and Du Pasquier, 2019). Eco-evolutionary theory (Otto and Day, 2007) allows us to parse how these interactions actually shape the diversity of parasite and host strategies that we observe in nature (Restif and Koella, 2003; Boots and Best, 2018). Given that both parasites and their hosts can evolve and critically, their evolution selects the other partner in such a tightly coupled interaction, it is critical to examine the impact of this co-evolution in order to understand the evolutionary dynamics of infectious disease.

Here, we develop theory that makes general predictions regarding how the interplay between parasite-host coevolution, population dynamics, and epidemiology impact host investment in constitutive and induced defense, and parasite exploitation. Theory has been developed demonstrating how parasites create selection for a combination of both constitutive and induced immune defense in hosts (Shudo and Iwasa, 2001; Hamilton, Siva-Jothy and Boots, 2008), and how selection is for greater host defence (through recovery) if the costs are facultative (induced) or constitutive (Cressler, Graham and Day, 2015) as well as effects on parasite growth (Schmid-Hempel and Ebert, 2003). However, few theoretical studies on constitutive and induced defence have incorporated parasite-host coevolution in their models. In one exception, an invertebrate system-specific protein network model showed how parasite coevolution leads to a shift in investment from induced to constitutive defence(Kamiya *et al.*, 2016). Furthermore, to our knowledge, only one evolutionary model of host constitutive and induced defense has accounted for the evolutionary feedbacks that result from changes of epidemiology and population dynamics. Key results were that high parasite virulence selects for more induced defences despite the cost to

immunopathology. It also demonstrated that a simple trade-off between the two arms of defence is not enough to lead to evolutionary branching to polymorphism. However, this model did not consider parasite-host coevolution (Boots and Best, 2018). Given previous theoretical models have highlighted that the coevolution of parasites can alter selection on hosts and lead to fundamentally different evolutionary outcomes (Buckingham and Ashby, 2022), it is important that we address this lack a general theory on the evolution of host constitutive and induced defense and parasite growth that accounts for both coevolution and population and epidemiological dynamics. Our goal is to address this gap and provide a framework for understanding host immune defense and parasite growth strategies in natural systems.

1. Methods

The focus of our analysis will be on the coevolution of two host defence traits (respective investment in constitutive defence, *c,* and induced defence, *h*) and one parasite infectivity trait (investment in transmission, *p*). We explore epidemiological and coevolutionary feedbacks to the evolution of host constitutive and induced immune defense, and parasite growth using a classic compartmental epidemiological model (Kermack, McKendrick and Walker, 1927; Anderson and May, 1979; Boots and Haraguchi, 1999):

$$\frac{dS}{dt} = \big(a[c] - q(S+I)\big)(S+fI) - bS - \beta[c,p]SI + \gamma[h]I$$

$$\frac{dI}{dt} = \beta[c,p]SI - (b + \alpha[h,p] + \gamma[h])I$$

Square brackets are used to denote functions of host and parasite investment. All hosts reproduce at rate a, which is reduced due to competition by a density-dependent factor, q. Infected hosts can potentially suffer an additional reduction in birth rate by a sterilizing factor, f (when $f = 0$, the parasite is a castrator). Specifically, when the parasite castrates the host ($f = 0$), infected hosts lose their reproductive capacity unless they recover back to the susceptible class. Note any disease from which there is no recovery would not be relevant to our modeling framework as there is no induced defence in our framing. All hosts die at a natural mortality rate, b. Transmission is a density-dependent mass-action process with a coefficient, β, which is a function of host constitutive defence (c) and parasite investment (p). Infected hosts suffer increased mortality, or

virulence, at rate α, which is a function of host induced defence (h) and parasite investment (p). Infected hosts can recover back to susceptibility at rate γ.

We allow both host and parasite parameters to evolve. Specifically, three key traits are subject to selection: 1) host constitutive defense (c), defined as reduced susceptibility to infection (resistance); 2) host induced defense (h), defined as an increased ability to clear disease (an increased recovery rate); and 3) the parasite growth rate (p). Each of the three evolving traits carries a cost. We assume that constitutive defense—persistently active and thus energetically costly to maintain—reduces the birth rate (Restif and Koella, 2003; Boots *et al.*, 2009; Cressler, Graham and Day, 2015; Donnelly, White and Boots, 2017; Boots and Best, 2018). In contrast, we assume that induced defense—activated only after infection—incurs an immunopathology cost from immune activation, increasing mortality in infected hosts (Lee, 2006; Boots and Best, 2018). Thus, only infected hosts pay the cost of induced defense, whereas all hosts pay the cost of constitutive. Induced defense may incur some costs in the absence of disease (Cressler, Graham and Day, 2015), but we deliberately maintain simplistic assumptions to develop a baseline model from which future work that includes more complex assumptions about costs can be developed. Lastly, we assume that parasite growth leads to higher transmission (β), but also increases virulence (α) (Hamilton, Siva-Jothy and Boots, 2008; Boots and Best, 2018). All three evolving traits are also tied to the population-level epidemiology—constitutive defense reduces transmission (β), induced defense shortens the infectious period (by increasing the host recovery rate, γ), and parasite growth increases transmission (β) (Boots *et al.*, 2009; Boots and Best, 2018).

We define the host recovery rate as a simple function of induced defense, such that,

$$y[h] = h + \gamma_0$$

where γ_0 is a constant. Transmission and virulence are functions of both host and parasite parameters. Specifically, we assume the transmission coefficient, β, is a multiplicative, 'universal' function of constitutive defense and parasite growth, such that,

$$\beta[c,p] = (\beta_0 - c)B[p] + k$$

where k is a constant and $B[p]$ is the parasite's contribution to transmission (defined below), which has been commonly used in previous studies (Restif and Koella, 2003; Boots *et al.*, 2009). Similarly, we define virulence as a multiplicative function of immunopathology (the cost of induced defense) and parasite growth, such that,

$$\alpha[h,p] = \Gamma[h]p + \alpha_0$$

where α_0 is a constant and $\Gamma[h]$ is the host's contribution to virulence (defined below). Thus, constitutive defense trades off with host reproduction, induced defense trades off with increased mortality of infected hosts, and parasite growth trades off with transmission. These three trade-offs are given by exponential functions, such that:

$$\mathrm{a}[c] = \mathrm{a}_0 - \frac{(\mathrm{a}_1)^2}{\mathrm{a}_2}\left(1 - \exp\left[\frac{\mathrm{a}_2}{\mathrm{a}_1}(c - c_0)\right]\right),$$

$$\Gamma[h] = \Gamma_0 - \frac{(\Gamma_1)^2}{\Gamma_2}\left(1 - \exp\left[\frac{\Gamma_2}{\Gamma_1}(h - h_0)\right]\right),$$

and,

$$\mathrm{B}[p] = \mathrm{B}_0 - \frac{(\mathrm{B}_1)^2}{\mathrm{B}_2}\left(1 - \exp\left[\frac{\mathrm{B}_2}{\mathrm{B}_1}(p - p_0)\right]\right),$$

where $\mathrm{a}_1 = {da}/{dc}$, $\mathrm{a}_2 = {d^2a}/{dc^2}$ and similarly for Γ_1, Γ_2, B_1 and B_2 . The advantage of this form is that for a chosen singular point at (h_0, Γ_0) we can fix the gradient as Γ_1 and the curvature as Γ_2, allowing us to easily manipulate the trade-off (Hoyle, Best and Bowers, 2012) (an example plot of the trade-off is included in supplementary figure S1). Importantly, constitutive and induced defense do not trade off with each other and instead evolve independently.

We model evolution using the adaptive dynamics framework ((Geritz, 1998; Geritz *et al.*, 1998). As such, we assume that rare mutants with a small phenotypic difference attempt to invade a (monomorphic) resident at endemic equilibrium. The success of the mutant depends on its invasion fitness, defined as the growth rate in the environment set by the resident. For the parasite, this is simply the growth of mutant-infected individuals and denoted by r. For the two arms of host defence, we instead use the fitness proxy of the negative determinant from the mutant's part of the

Jacobian, which has been shown to be sign equivalent to the true fitness (Hoyle, Best and Bowers, 2012). These are respectively denoted s_{ind} and s_{con}. In isolation, each of the traits will evolve in the direction of its local selection gradient; for example, for the parasite, $[\partial r/\partial p_m]_{p_m=p}$ where p_m is the mutant trait. The three mutant fitness gradients together then form a dynamical system of ordinary differential equations (for simplicity we assume equal mutation rates), where asterisks denote equilibrium population densities:

$$\left.\frac{\partial s_{ind}}{\partial h_m}\right|_{h_m=h} = (a[c] - q(S^* + I^*) - b - \beta[c,p]I^*)\left(\frac{d\gamma[h_m]}{dh_m} + \frac{\partial \alpha[h_m,p]}{\partial h_m}\right) + \frac{d\gamma[h_m]}{dh_m}\beta[c,p]I^*$$

$$\left.\frac{\partial s_{con}}{\partial c_m}\right|_{c_m=c} = \left(\frac{da[c_m]}{dc_m} + \frac{\partial \beta[c_m,p]}{\partial c_m}\right)(b + \alpha[h,p] + \gamma[h]) - \frac{\partial \beta[c_m,p]}{\partial c_m}\left(y[h] + f(a[c] - q(S^* + I^*)\right) + \frac{da[c_m]}{dc_m} f\beta[c,p]I^*$$

$$\left.\frac{\partial r}{\partial p_m}\right|_{p_m=p} = \frac{\partial \beta[c,p_m]}{\partial p_m}S^* - \frac{\partial \alpha[h,p_m]}{\partial p_m}$$

When all three equations are zero simultaneously (i.e., none of the traits are experiencing directional selection), there will be an 'equilibrium' of the evolutionary dynamics, termed a singular strategy in adaptive dynamics. The behavior at this point depends on second-order fitness terms (Geritz, 1998; Geritz *et al.*, 1998). In particular, if the strategy for each trait cannot be invaded by any nearby mutants, then it is termed evolutionarily stable. If the singular strategy is locally attracting from nearby initial conditions, then it is termed convergence stable. Here, we check for these stability conditions numerically. We focus on strategies that satisfy both stability conditions here, called continuously stable strategies (CSSs), which are long-term stable attractors of evolution (as such we always choose our trade-offs above to be 'accelerating'). Code to produce the plots in Python is available on Github (https://github.com/abestshef/coev_const_induced) and Zenodo (DOI: 10.5281/zenodo.14795457).

Our aim is to explore the trends of investment in the two arms of host defence and parasite infectivity as we vary the free model parameters. As such, we can understand under what ecological conditions we are likely to see relatively more or less investment in either constitutive or induced defences, or high parasite infectiousness. We will contrast our results with earlier work where only the host evolved (Boots and Best, 2018) to understand whether the coevolution of the parasite alters any of the trends.

Results

a) Coevolution of parasite growth and host investment in constitutive and induced defense when the parasite has no impact on host fertility ($f = 1$)

i. Varying mortality (b) when $f = 1$

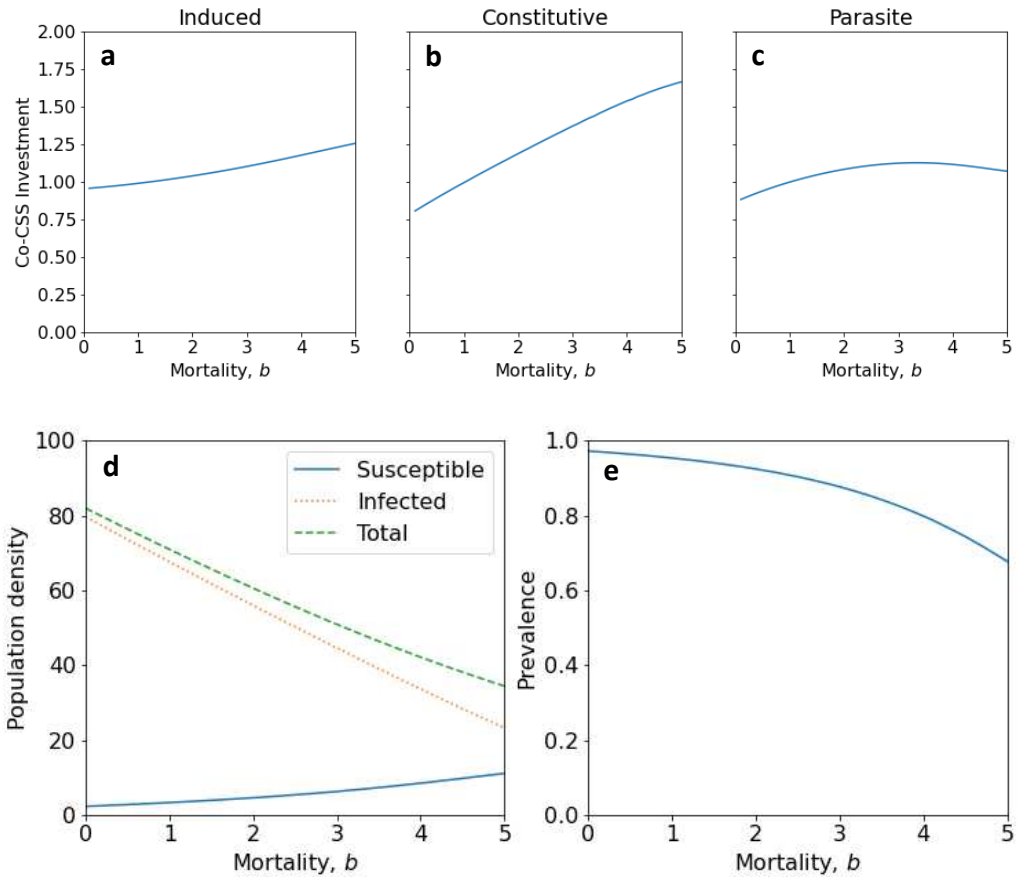

Figure 1. Plots of the optimal (continuously stable) strategy in (a) induced defense, (b) constitutive defense, and (c) the parasite growth rate against the natural host mortality rate, b, when the parasite

has no impact on host fertility ($f = 1$); and the equilibrium host population densities (d) and parasite prevalence (e). Parameter values: $q = 0.1, \alpha = 1, \gamma = 1, \beta = 2, f = 1$. Constitutive trade-off: $a_0 = 10, a_1 = -0.05, a_2 = -0.1, c_0 = 1$. Induced trade-off: $\gamma_0 = 1, \gamma_1 = 0.02, \gamma_2 = 0.1, h_0 = 1$. Parasite trade-off: $B_0 = 1, B_1 = 0.3, B_2 = -0.4, p_0 = 1$.

We first consider coevolutionary dynamics when the parasite has no impact on host fertility ($f = 1$). In response to increased background mortality in the host population, there can be selection for investment in both higher constitutive and induced defense (Figure 1a-b) which means that shorter rather than longer lived hosts invest in more defence. Notably, there is a faster increase in constitutive defense, such that shorter-lived hosts invest relatively more in constitutive than induced defense; and longer-lived hosts invest relatively more in induced than constitutive defense. Although it is often thought that longer lived organisms are more at risk of infection, these results reflect how immune defenses incur fewer total costs over shorter lifespans, particularly with respect to the constant reproductive cost of constitutive defense. Furthermore, heightened background mortality rates reduce the host population density (Figure 1d), reducing transmission risk in a density dependent parasite and furthermore higher background mortality also reduces parasite prevalence (Figure 1e) again reducing risk. The key to these effects is that with long lived hosts, prevalence is very high and therefore the risk of infection is so high, even with strong immunity, that the costs of defense may outweigh the benefits. Our other key result is that counter to classic theory, the parasite is not strongly selected to increase exploitation as host mortality increases. Furthermore, once host investment in induced defense reaches a threshold (Figure 1a), immunopathology costs select for reduced parasite growth (Figure 1c). This result is interesting since in a simple evolution of virulence model higher background mortality always selects for higher exploitation as would higher constitutive resistance. In our model, defence is costly and, in particular, induced immunity comes at the cost of higher virulence. These assumptions mean that selection on the pathogen becomes more complex with the costs of higher resistance selecting against higher virulence as mortality increases.

Our result that decreasing lifespan selects for higher overall immune investment—with a steeper increase in constitutive defense—is consistent with results from our previous model in which only the host evolved (Boots and Best, 2018). However, in this prior modeling analysis,

hosts invested relatively more in constitutive than induced defenses across all natural mortality rates. In contrast, here, with parasite-host coevolution, we find that as the background mortality rate decreases, the relative investment between induced and constitutive defense flips such that longer-lived hosts invest relatively more in induced than constitutive defenses (Figure 1a-b). This result is a product of coevolutionary dynamics. Lower background mortality increases host population density (Figure 1d), which supports a higher parasite prevalence (Figure 1e)—as a result, the parasite reduces its growth rate (Figure 1c), decreasing virulence, which simultaneously reduces the advantage of constitutive avoidance (Figure 1b) and the immunopathology cost of induced defense (Figure 1a). Furthermore, longer lifespans lead to higher costs from investing in immune defense, particularly constitutive.

ii. Varying competition (q), f = 1

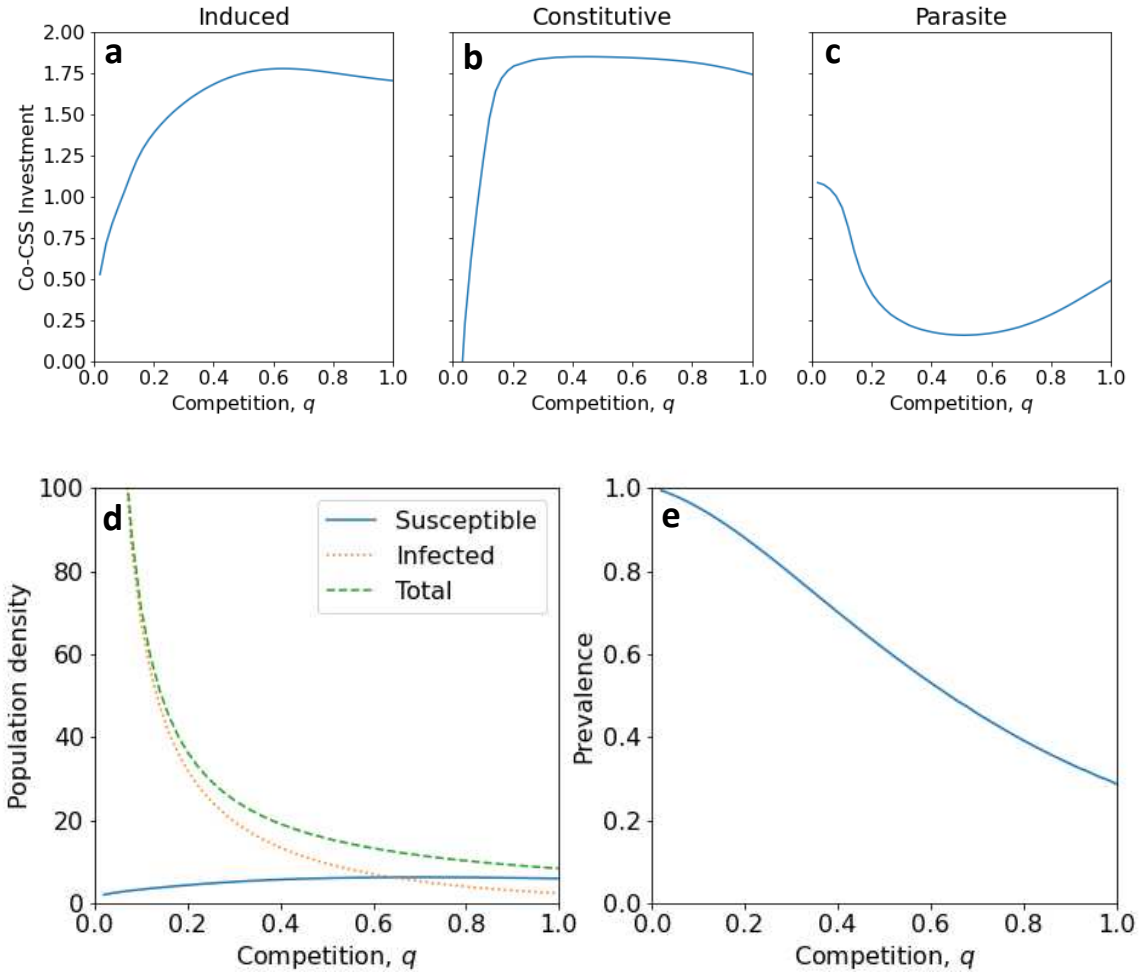

Figure 2. Plots of the optimal (continuously stable) strategy in investment in (a) constitutive defense, (b) induced defense, and (c) the parasite growth rate against the host birth rate susceptibility to crowding (competition) when the parasite has no impact on host fertility ($f = 1$) and c_2 = -0.1; and the equilibrium host population densities (d) and parasite prevalence (e). Parameter values: $b = 1, \alpha = 1, \gamma = 1, \beta = 2, f = 1$. Constitutive trade-off: $a_0 = 10, a_1 = -0.05, a_2 = -0.1, c_0 = 1$. Induced trade-off: $\gamma_0 = 1, \gamma_1 = 0.02, \gamma_2 = 0.1, h_0 = 1$. Parasite trade-off: $B_0 = 1, B_1 = 0.3, B_2 = -0.4, p_0 = 1$.

Increasing the host birth rate sensitivity to crowding (i.e., increasing competition, or decreasing the carrying capacity) reduces the host population density (Figure 2d), leading to a pattern where investment in immunity is somewhat constant until we reach very high densities (low q), and the hosts reduce investment in defence (Figure 2a-b). A key driver of this is that extreme host population densities (Figure 2d) and parasite prevalence (Figure 2e) begin to make

infection inevitable, selecting for low investment in immune defense as hosts "give up" to reduce costs (Figure 2a-b). Parasite growth (Figure 2c) is selected to be high at very high densities, then falls off before increasing again with very strong competition. Notably, we previously found that when only the host evolves, there are monotonic increases in both arms of defense (Boots and Best, 2018). In contrast, adding parasite-host coevolution produces non-monotonic changes such that investment in both induced (Figure 2a) and constitutive (Figure 2b) defense begins to decrease slightly when competition exceeds a threshold.

The parasite strategy is independent of competition itself and is thus purely driven by the host evolutionary response. Specifically, in response to the immunopathology costs from increasing host induced defense, there is selection for reduced parasite replication (Figure 2c), which reduces prevalence (Figure 2d). However, as the host immune investment levels off, selection on the parasite reverses such that the replication rate increases (Figure 2c), which subsequently increases immunopathology costs, selecting for a reduction in host immune investment (Figure 2a).

b) Coevolution of parasite growth and host investment in constitutive and induced defense when the parasite is a castrator ($f = 0$)

i. Varying mortality (b), $f = 0$

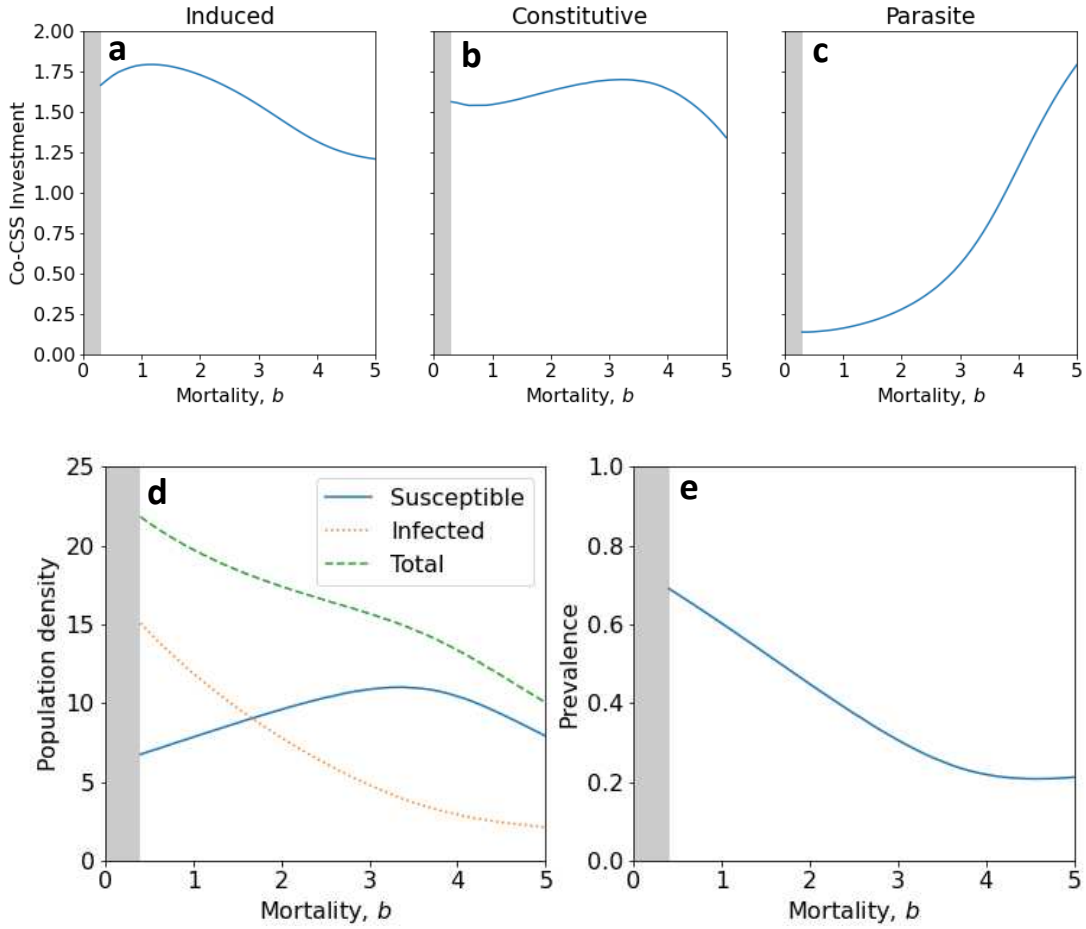

Figure 3: Plots of the optimal (continuously stable) strategy in (a) induced defense, (b) constitutive defense, and (c) the parasite growth rate against the natural host mortality rate when the parasite is a castrator ($f = 0$). Parameter values: $q = 0.2, \alpha = 1, \gamma = 1, \beta = 2, f = 0$. Constitutive trade-off: $a_0 = 10, a_1 = -2, a_2 = -0.5, c_0 = 1$. Induced trade-off: $\gamma_0 = 1, \gamma_1 = 1.5, \gamma_2 = 2.5, h_0 = 1$. Parasite trade-off: $B_0 = 1, B_1 = 0.5, B_2 = -0.4, p_0 = 1$.

Overall, the castrating parasite generally selects for higher host defense with longer lifespans (Figure 3a-b), which is in clear contrast to when the parasite is non-castrating (Figure 1a-b). This reflects the strong selective pressure for hosts to protect their reproduction. However, because immune defense is costly, hosts moderate their investment in immunity in response to the infection risk—reducing constitutive defense (Figure 3b) to avoid unnecessary reproductive costs as parasite prevalence declines (Figure 3e)—and the parasite virulence—reducing induced defense (Figure 3a) to avoid immunopathology as parasite growth rate increases (Figure 3c). In contrast to

the case where there is no castration, although prevalence still increases with reduced mortality, it does not reach such high levels that the host begins to 'give up' on immune defense until host are very long lived, when there is some evidence of induced defenses declining (Figure 3a). The key difference between the case when infecteds reproduce and when they don't is the much stronger selection for higher parasite growth rates when hosts suffer higher background mortality in castrators. A key cause of this is the difference in the selection for immune defence in the host in the two cases.

Parasites that castrate the host flip trends across host natural mortality rates. Notably, when only the host is allowed to evolve, castrators select for increased investment in induced defense, but decreased investment in constitutive defense (Boots and Best, 2018). This occurs because increasing host background mortality and infection-induced castration makes the additional reproductive cost of constitutive defense unsustainable; but then, given that only susceptible hosts can reproduce, induced defense is critical for allowing infected individuals to recover and reproduce. However, here, when the parasite is allowed to coevolve, there is selection for higher parasite growth (Figure 3c). This increasing parasite growth in turn selects for declining investment in induced defense after immunopathology costs exceed a threshold (Figure 3a). Once investment in induced defense begins to decline (Figure 3a), preventing infection-induced castration becomes the key mechanism for maintaining host reproduction and thus, there is selection for higher constitutive defense (Figure 3b). However, investment in constitutive defense peaks at intermediate host lifespans—because host castration increases with parasite growth and reaches a threshold at which the reproductive cost of constitutive immunity outweighs its infection avoidance benefit (Figure 3b-c), especially given the decline in parasite prevalence (Figure 3e).

ii. Varying competition (q), $f = 0$

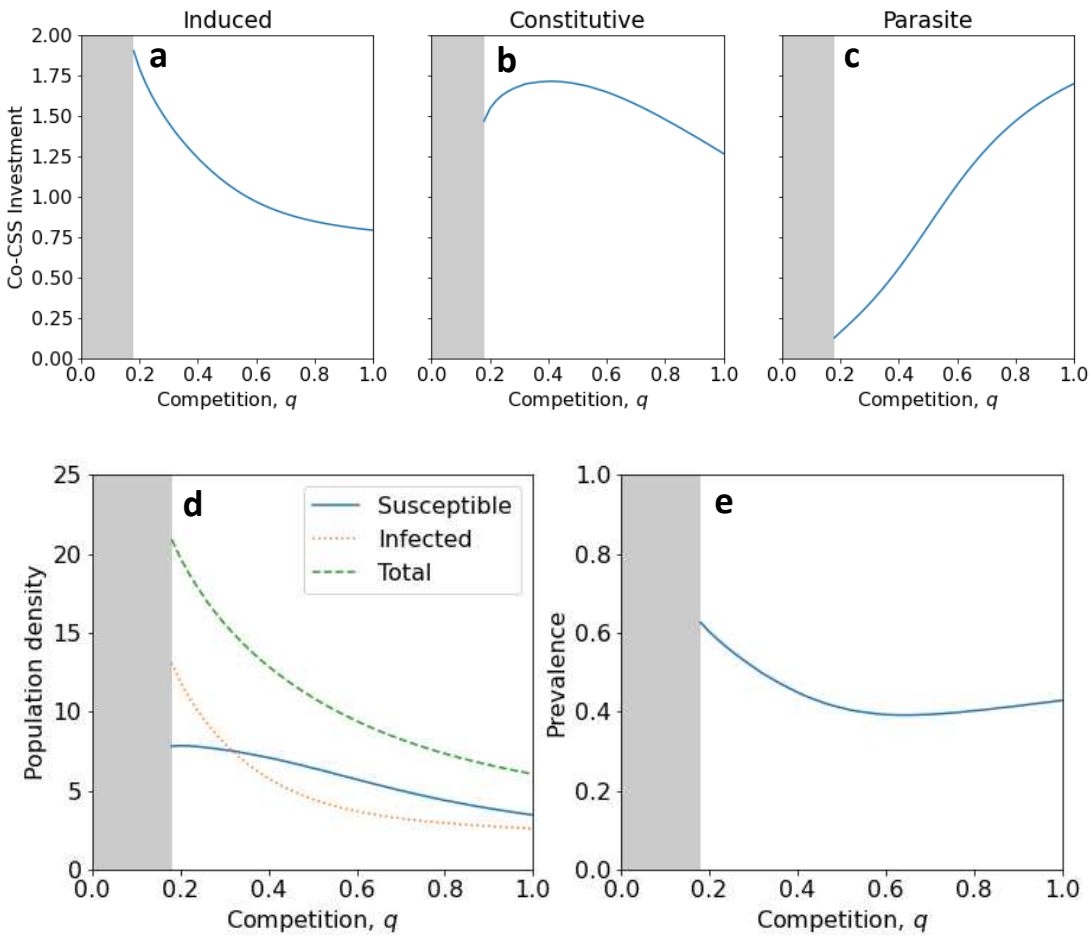

Figure 4. Plots of the optimal (continuously stable) strategy in (a) constitutive defense, (b) induced defense, and (c) the parasite growth rate against the host birth rate susceptibility to crowding (competition) when the parasite is a castrator ($f = 0$). Parameter values: $b = 1, \alpha = 1, \gamma = 1, \beta = 2, f = 0$. Constitutive trade-off: $a_0 = 10, a_1 = -2, a_2 = -0.5, c_0 = 1$. Induced trade-off: $\gamma_0 = 1, \gamma_1 = 1.5, \gamma_2 = 2.5, h_0 = 1$. Parasite trade-off: $B_0 = 1, B_1 = 0.5, B_2 = -0.4, p_0 = 1$.

Parasites that castrate the host also flip trends across levels of host birth rate susceptibility to crowding. At low competition levels, extreme host population densities (Figure 2d and Figure 4d) and parasite prevalence (Figure 2e and Figure 4e) make infection inevitable. When the parasite does not affect host reproduction, this heightened infection risk selects for low investment in immune defense as hosts "give up" to reduce costs (Figure 2a-b). However, when the parasite is a castrator, hosts cannot afford to "give up"—instead, this heightened infection risk selects for high

investment in immunity (Figure 4a-b) to protect reproduction, at whatever cost. However, again, because immune defense is costly, hosts moderate investment in induced and constitutive immunity in response to the parasite infection risk and virulence. Increasing competition decreases the host population density (Figure 4d) and consequently, the risk of infection (Figure 4e), which allows hosts to reduce investment in defense (Figure 4a-b). Initially, at mid to low levels of competition, there is selection for increased investment in constitutive defense, as only preventing infection altogether directly protects the host from castration (Figure 4b). However, as competition increases and further reduces the birth rate, constitutive defense becomes too reproductively costly and is selected against (Figure 4b). It is energetically impossible to achieve complete constitutive immunity, or absolute infection avoidance—thus, infection-induced reduction of the birth rate is unavoidable, making the additional reproductive cost of constitutive defense unsustainable, especially as the infection risk declines (Figure 4e).

Induced defense acts on the recovery rate after the host is already infected; thus, while hosts can regain their reproductive ability through recovering, induced defense itself does not directly protect against castration. Notably, when only the host is allowed to evolve, there is selection for decreased investment in constitutive defense, but induced defense remains unaffected (Boots and Best, 2018). However, when the parasite is allowed to coevolve, the decreasing host birth rate selects for higher parasite growth (Figure 4c), increasing immunopathology costs and selecting for decreasing investment in induced defense (Figure 4a).

Discussion

We have analyzed how the interplay between parasite-host coevolution, population dynamics, and epidemiology influence the optimal parasite growth strategy and host investment in constitutive (always present and costly) as opposed to induced (activated and costly only upon infection) defense. Critically, we provide the first theoretical framework that considers both coevolution and eco-evolutionary feedbacks. We examine trends across host competition and natural mortality rates when the parasite does not directly affect host fertility, as well as when the parasite is a castrator. We show that incorporating host-parasite coevolution into our model reveals feedbacks between the host immune and parasite growth strategies that are missed when only the host is allowed to evolve. Our results show that coevolution leads to predictions that match established ideas such as the pace of life hypothesis but that also there is a rich range of outcomes

that emerge from the interplay of coevolution and population level feedbacks. Our results may therefore help explain the wide range of outcomes that we see in nature. Furthermore, a key result is that we find that whether the parasite affects host reproduction significantly impacts host-parasite coevolution; when the parasite is a castrator, selection on the host is often largely geared towards minimizing reproductive costs—either by investing in immunity to avoid infection or recover when parasite prevalence is high, or by reducing investment in reproductively costly constitutive defense when the parasite prevalence is low. This contrast between the outcomes depending on the disease impact on fecundity is often ignored, but our results show that it is critical.

When hosts coevolve with a non-castrating parasite, increasing host background mortality selects for overall higher investment in immunity, with a faster increase in constitutive defense. These results, as well as the results from our prior host evolution model, are consistent with the Lee (Lee, 2006) pace-of-life prediction, which posits that fast-living species should invest relatively more in constitutive than induced defense because short lifespans neither accumulate the energetic costs of non-specific constitutive defense nor benefit from more specific induced defenses. The first important insight is that coevolution is needed to recapture this key pace-of-life prediction that slow-living species should invest relatively more in induced rather than constitutive defense because constitutive immunity is particularly costly over long lifespans. We did not find these effects in the simpler evolutionary model (Boots and Best, 2018) which emphasizes how even qualitative outcomes can be fundamentally changed once coevolution is included. Given that co-evolution is likely to occur in most natural systems this suggests results from evolutionary models may sometimes be misleading. Empirical support for these Lee (Lee, 2006) predictions has been found in mammals (Previtali *et al.*, 2012), birds (Lee *et al.*, 2008), and invertebrates (Pinzón C. *et al.*, 2014) while short-lived stickleback populations demonstrated higher overall immune activity relative to their long-lived counterparts (Whiting *et al.*, 2018), and crucian carp shifted immune investment to the cheapest constitutive defense in response to increasing mortality rates (Vinterstare *et al.*, 2019). Nevertheless, the empirical literature is not conclusive—some studies have supported a contrasting theory that shorter lifespans may instead constrain immune investment overall, prioritizing resources to meet development and reproductive demands (Norris, 2000; Irene Tieleman *et al.*, 2005; Martin, Weil and Nelson, 2007; Pap *et al.*, 2015). In natural systems, the relationship between lifespan and immune strategies is likely confounded by

environmental factors, parasite diversity, and other host life history strategies such as reproductive strategies and body size (Lee, 2006; Whiting *et al.*, 2018). Furthermore, our modeling shows that in fact there are different predictions when the parasite impacts host reproduction, and this insight has not typically been considered in these discussions.

With respect to parasite evolution, increasing natural mortality in the host population initially selects for increased parasite growth, until, at intermediate host lifespans, immunopathology costs select for reduced parasite growth. This result that short host lifespans select for reduced parasite growth contradicts previous theory that the rate of parasite growth is slower in larger-bodied, slower-living species (Smith *et al.*, 2015; Banerjee, Perelson and Moses, 2017). The impact of background mortality on the evolution of parasite exploitation becomes much more complex in our coevolutionary model where the defence mechanisms, and in particular their costs, impact the parasite evolutionary outcome. Furthermore, this previous theory is based on a body of work that compares parasite replication rates with host metabolism and body mass—metrics that are generally correlated with lifespan, but ultimately reflect physiology. The physiological conditions within fast-living hosts may indeed select for increased parasite replication rates. However, our model indicates that the ecological and coevolutionary processes associated with fast-living hosts—higher background mortality rates and immune investment—select for parasites with reduced growth rates to avoid depleting the susceptible host population. Nevertheless, the relationship between host mortality and parasite replication rates remains largely unexplored in empirical systems, and future research is needed to test our eco-evolutionary model predictions.

Increasing host competition (i.e., host birth rate sensitivity to crowding) selects for overall increasing host investment in defense; although when competition is intense, investment falls again. Notably, this non-monotonic trend in defense is only recovered by our model when allowing parasite-host coevolution and is likely a more realistic representation of real-world trends. There is a lack of empirical literature on how parasite-host coevolution is influenced by birth rate sensitivity to crowding; however, there is literature on the effects of crowding more generally. Specifically, the density-dependent prophylaxis (DDP) theory posits that high host density increases the risk of infection, selecting for higher immune investment (Wilson and Reeson, 1998). Empirical support for the DDP theory has been derived primarily from insect systems (Wilson and Cotter, 2009), but has also been found in some animal populations such as elk (Downs, Stewart

and Dick, 2015). At extreme host densities, our model finds the opposite of the DDP theory—"give up" on immune defense to reduce costs. It is possible that the extreme densities in our model are not observed in real world systems—at intermediate densities, our model trends in host defense are more consistent with the DDP theory, suggesting that these intermediate density levels may reflect more realistic conditions. However, potentially consistent with the non-monotonic trends observed in our model, empirical work suggests that the stress and limited resource availability of high density host populations can also reduce immune function (Goulson and Cory, 1995; Svensson, Sinervo and Comendant, 2001; Piesk *et al.*, 2013). Critically, the empirical literature reports that the relationship between host competition and investment in immune defense is driven by density-dependent changes in parasite risk and resources available to support the energetic demands of immune function, whereas our model only accounts for density-dependent changes in the birth rate. Thus, our results highlight that density-dependent decreases in birth rate may also contribute to the observed correlation between high host density and increased immune investment. Notably, the empirical literature has identified a possible tradeoff between reproduction and immune function, where, in line with our model results, lower reproductive output may increase energetic resources for immune investment (Ardia, 2005; Martin, Weil and Nelson, 2007). Additionally, our model may explain why empirical pace-of-life predictions regarding immune function are inconclusive. Host pace-of-life is determined by a combination of natural mortality and birth rate, and our model suggests that these two factors have opposing effects on immune investment—we found that decreasing host pace-of-life by decreasing natural mortality reduces overall immune investment, whereas decreasing pace-of-life through density-dependent decreases in birth rate (i.e., increasing birth rate sensitivity to crowding) increases overall immune investment.

Critically, these trends flip when the parasite castrates the host— we find that there is a clear distinction between parasites that castrate their hosts and those that do not. Specifically, we found that castrators select for overall lower host investment in immune defense. When the parasite is a castrator, the reproductive cost of constitutive immunity often outweighs its infection avoidance benefit. When the castrator itself is allowed to coevolve, selection for higher parasite growth heightens immunopathology costs, selecting for decreased investment in induced defense. To our knowledge, immune defense strategy in empirical host systems affected by castrating parasites remains unexplored. Nevertheless, snail populations exposed to castrating nematodes

have been found to invest more in reproduction (Hechinger, 2010), mature and reproduce at smaller sizes (Lafferty, 1993; Jokelai and Lively, no date), and increase reproductive output (Krist, no date), suggesting that if reproduction trades off with constitutive immunity (as in our model), hosts exposed to castrating parasites would be expected to decrease investment in constitutive defense as observed in our analyses of both mortality rates and competition. Nevertheless, the direct relationship between infection-induced host castration and parasite-host coevolution remains, to our knowledge, unexplored in empirical systems and thus future research is needed to test our eco-evolutionary model predictions.

Importantly, our model does not capture how multiple exposures to the same parasites changes with lifespan—hypothesized to be a key mechanism underlying observed variation in immune defense strategies. While short-lived hosts can rely on non-specific constitutive defense, long-lived hosts are likely to live to encounter parasites more than once and thus benefit from specific adaptive induced defense (Lee, 2006). For future analyses, incorporating model structure that allows the level and specificity of parasite exposure to vary with lifespan and other host life history characteristics may help parse contrasting results in the empirical literature. Furthermore, our model assumes that constitutive and induced defense do not directly trade off with each other and instead, evolve independently. However, in some systems, there is evidence of a constitutive-induced trade-off, which has been hypothesized to generate and maintain observed diversity in host defense both within and between species (Moreira *et al.*, 2014; Rasmann *et al.*, 2015; Boots and Best, 2018). When only the host evolves, we found that assuming a direct trade-off between constitutive and induced defense does not generate evolutionary branching and coexistence between genotypes (Boots and Best, 2018). Future modeling analyses should assess whether incorporating parasite-host coevolution allows a direct constitutive-induced tradeoff to generate evolutionary branching in host defense and parasite growth strategies.

We have applied eco-evolutionary theory to make a series of predictions regarding the coevolution of parasite growth and host defense strategies. Our analysis demonstrates the importance of considering coevolution and population-level dynamics and provides a framework for future research. In particular, our work would benefit from modeling analyses that examine whether our trends change when adding additional dynamics such as spatial structure (Boëte, Seston and Legros, 2019) and multiple infections (Alizon, de Roode and Michalakis, 2013). There is also a need to experimentally test our theoretical predictions, as well as collect comparative data

in natural systems. Overall, we have provided the theoretical groundwork for building a mechanistic understanding of how parasites and hosts coevolve at both the individual and population level, contributing to the study of human and animal health, as well as how infectious disease shapes natural systems.

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