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Pathogen evolution under host avoidance plasticity

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Host resistance consists of defences that limit pathogen burden, and can be classified as either adaptations targeting recovery from infection or those focused upon infection avoidance. Conventional theory treats avoidance as a fixed strategy which does not vary from one interaction to the next. However, there is increasing empirical evidence that many avoidance strategies are triggered by external stimuli, and thus should be treated as phenotypically plastic responses. Here, we consider the implications of avoidance plasticity for host–pathogen coevolution. We uncover a number of predictions challenging current theory. First, in the absence of pathogen trade-offs, plasticity can restrain pathogen evolution; moreover, the pathogen exploits conditions in which the host would otherwise invest less in resistance, causing resistance escalation. Second, when transmission trades off with pathogen-induced mortality, plasticity encourages avirulence, resulting in a superior fitness outcome for both host and pathogen. Third, plasticity ensures the sterilizing effect of pathogens has consequences for pathogen evolution. When pathogens castrate hosts, selection forces them to minimize mortality virulence; moreover, when transmission trades off with sterility alone, resistance plasticity is sufficient to prevent pathogens from evolving to fully castrate.

1. Introduction

Host resistance is broadly defined as the host's ability to limit pathogen burden [1] and includes such diverse defences as physical barriers (e.g. skin), behavioural modifications or a rapid immune response. By limiting pathogen burden, however, resistance necessarily has negative consequences for pathogen fitness [2,3]. Thus, resistance can impose selective pressure upon pathogen attributes such as virulence and transmissibility, with important implications for host–pathogen evolutionary dynamics. Resistance mechanisms can be broadly classified as either adaptations targeting recovery from infection or those intended to prevent infection [4,5]. The latter category is typically referred to as avoidance mechanisms and will be our focus here. Although there is a substantial body of literature on host avoidance evolutionary and coevolutionary dynamics (e.g. [2,3,5–14]), a key assumption of this theory is that the host has a fixed resistance strategy, which does not exhibit plasticity. As a result, when considering the host–pathogen coevolutionary dynamics, the focus is upon a *symmetric* game [15]: the pathogen strategy (e.g. expression of virulence/transmissibility) and the host resistance strategy are played simultaneously.

Assuming fixed resistance and a symmetric game makes sense if the resistance mechanism is passive, as in the case of physical barriers like skin or in gene-for-gene models (e.g. [16]). However, there is increasing empirical evidence that many mechanisms of avoidance resistance are inducible defences, triggered by external stimuli. For example, images of sick people cause an increased immune response in humans [17,18], reducing the likelihood of infection establishment, while visual and olfactory stimuli are used by numerous species as cues to limit direct contact with infected conspecifics [19–24]. In fact, the human disgust emotion has been argued to be an adaptive response intended to encourage disease avoidance [25–27]. Logically, when presented with an external stimuli, the elicited organismal response will tend to be related to the strength of the stimulus. Thus, when resistance is triggered by external cues, the host

response will vary with the strength of the signal (e.g. how sick an individual appears). In game theory, this is an *asymmetric* game [15], in which the pathogen 'goes first', causing an expression of symptoms in the host to which other hosts plastically respond. It is well known that asymmetric games can yield very different evolutionary predictions [28–31], yet the implications of this have not been considered for host–pathogen avoidance coevolution.

Here, we investigate the coevolution of a host–pathogen population when avoidance is phenotypically plastic. We allow pathogen transmissibility, pathogen-induced sterility and pathogen-induced mortality to evolve. We first outline general expectations for pathogen evolution under resistance plasticity before linking these predictions to host–pathogen coevolution in a specific system. In doing so, we show that the evolutionary outcomes differ substantially from those when resistance is fixed in three key ways. First, when pathogen transmissibility has no explicit trade-offs, avoidance plasticity is sufficient to restrain pathogen evolution. Additionally, by 'going first' the pathogen is able to exploit situations in which the host would otherwise invest less in resistance, causing resistance escalation. Second, when pathogen transmission trades off with pathogen-induced mortality, we find that host plasticity selects for reduced virulence. As a consequence, this yields an evolutionary outcome more favourable for both parties: the pathogen is less virulent, the total host population density increases, and there is an increase in both the proportion of hosts infected and the pathogen's relative fitness. Third, while pathogen-induced sterility has a limited effect on fixed resistance models [12,32,33], we show that under transmission–mortality trade-offs, if a pathogen castrates a host, the pathogen is forced to minimize mortality virulence. Moreover, when pathogen transmissibility trades off with sterility alone, resistance plasticity is sufficient to prevent the pathogen from becoming completely sterilizing.

2. Preliminaries

We focus upon a susceptible-infected host–pathogen system with no recovery. Denote the densities of wild-type susceptibles and infecteds at time t as $x(t)$ and $y(t)$, respectively. Pathogen transmission is exclusively horizontal and individuals can manipulate transmission: with probability $1-\epsilon$, an individual is able to successfully resist an infection that would otherwise occur. For example, if the resistance mechanism is a more aggressive immune response, then the pathogen is unable to become established in the host. Thus, our focus is upon resistance mechanisms in which a host *avoids* infection, rather than resistance through recovery [4,30]. We assume individuals are aware of their own infection status; as the population is well mixed and we do not allow multiple infection, there is no adaptive reason for infecteds to resist infection.

During infection, the actions of the pathogen upon its host produce cues, providing information to other conspecifics. Examples of such cues could include: sores, sluggishness, sneezing, vomiting or olfactory signals. Upon contact with an infected individual, a susceptible host evaluates the cues and mounts an appropriate resistance response (e.g. aggressive immune system activation or behavioural modification). For simplicity, we assume perfect information transfer and that no misidentification errors occur. Thus in the monomorphic host–pathogen system, infecteds transmit the pathogen at a *per capita* rate of $\beta\epsilon\lambda(x, y)$, where β is a transmissibility parameter under pathogen control, and $\lambda(x, y)$ governs the rate at which susceptibles are encountered. For density- or frequency-dependent transmission, $\lambda(x, y) = x$ or $\lambda(x,y) = x/(x+y)$, respectively. Upon infection, hosts may suffer from reduced fecundity and increased mortality. As such, let δ be the probability an infected host is sterile, and let γ control the magnitude of pathogen-induced mortality. In particular, we suppose infected hosts die at a *per capita* rate of $\mu(\gamma, v, x, y)$, where v is a parameter controlling background mortality and the population densities indicate some portion of mortality may be density-dependent. We assume μ is a continuously differentiable function in γ, and for notational brevity we will write $\mu(\gamma)$.

Now consider the coevolutionary process. Our general approach is to find the optimal resistance strategy for the host in terms of static pathogen quantities, and then given that response, find the optimal pathogen strategy (e.g. [28–30]). To make this more concrete, if we let κ serve as a dummy variable specifying the pathogen strategy (i.e. if any of β, δ and γ are evolving, they have a functional dependency upon κ such that $\beta'(\kappa)$, $\delta'(\kappa)$, $\gamma'(\kappa) \geq 0$), then using the tools of adaptive dynamics [34], we can obtain the optimal host resistance function, $\epsilon(\kappa)$. We then wish to find the pathogen strategy, $\tilde{\kappa}$, which maximizes pathogen fitness subject to the optimal host resistance response. The pair $(\epsilon(\tilde{\kappa}), \tilde{\kappa})$ is known as the *Stackelberg outcome* [35]. If both $\epsilon(\tilde{\kappa})$ and $\tilde{\kappa}$ are evolutionarily and convergence stable strategies (CSS; [36]), then the Stackelberg outcome is an evolutionary attractor; such outcomes will be our focus here. For mathematical simplicity, we assume separation of evolutionary and ecological timescales and that mutations are of small effect. Therefore, each time a mutant host or mutant pathogen appears in the population, the population is allowed to re-equilibrate at the demographic attractor before another mutation occurs. As a consequence, the host and pathogen are effectively adapting to monomorphic pathogen and host populations, respectively.

Note that we have not as of yet specified the population dynamics of susceptibles. The reason is because whenever the pathogen is not fully sterilizing, obtaining analytic predictions regarding host evolution is more difficult than for pathogen evolution since there are necessarily more equations. As such, we will first suppose we have obtained the CSS host resistance response function, $\epsilon(\kappa)$, and provide general predictions for how we should expect the pathogen to evolve subject to this response function while specifying as little as possible about the host population dynamics. We will then relate these predictions to a specific host population in order to better understand the evolutionary outcomes. We have restricted all in-depth mathematical analyses to the electronic supplementary material, and where necessary we will reference the relevant section of the electronic supplementary material as S.X.X.

3. Effects of host plasticity upon pathogen evolution

Let $(\bar{x}, \bar{y})$ denote a locally stable wild-type endemic equilibrium. Then at this equilibrium, the rare mutant pathogen dynamics are governed by

$$\dot{y}_m = [\beta(\kappa_m)\epsilon(\kappa_m)\lambda(\bar{x}, \bar{y}) - \mu(\kappa_m)]y_m, \tag{3.1}$$

where the dot indicates differentiation with respect to time, y_m is the density of hosts infected with the mutant pathogen and κ_m is the mutant pathogen strategy. Note that in (3.1), $\epsilon(\kappa_m) = \epsilon(\beta(\kappa_m), \gamma(\kappa_m), \delta(\kappa_m))$; this represents host phenotypic plasticity. If resistance were instead fixed, $\epsilon(\kappa_m)$ would be replaced by ϵ and so would not vary with the phenotype of the encountered pathogen. The term in (3.1) enclosed in square brackets represents the invasion fitness of the rare mutant pathogen: if positive, the mutant pathogen will invade.

Now what is the impact of plasticity? First, suppose that the pathogen strategy has no effect on host mortality (i.e. $\partial_{\kappa_m}\mu = 0$, where ∂_{κ_m} indicates the partial derivative of the function with respect to κ_m). Then by applying the tools of adaptive dynamics [34] and taking the derivative of the invasion fitness of the rare mutant pathogen with respect to κ_m, the pathogen singular strategy, $\tilde{\kappa}$, is the solution of

$$\underbrace{\frac{\beta(\tilde{\kappa})}{\epsilon(\tilde{\kappa})}\left[\frac{\partial\epsilon}{\partial\beta}\frac{\mathrm{d}\beta}{\mathrm{d}\kappa_m}+\frac{\partial\epsilon}{\partial\delta}\frac{\mathrm{d}\delta}{\mathrm{d}\kappa_m}\right]_{\kappa_m=\tilde{\kappa}}}_{\text{effect of plasticity}}+\left.\frac{\mathrm{d}\beta}{\mathrm{d}\kappa_m}\right|_{\kappa_m=\tilde{\kappa}}=0, \tag{3.2}$$

where we have highlighted the contribution of host plasticity. The conditions under which such a strategy will be CSS can easily be obtained (see electronic supplementary material, S.2). If resistance is fixed, then the contribution of host plasticity is zero and (3.2) will have no solution. Thus, transmissibility, β, will increase without restraint, as has been observed elsewhere for well-mixed populations lacking transmission–mortality trade-offs ([12,32,33]; although see [37] for an example of when morbidity can restrain pathogen evolution). However, with host resistance plasticity, this is not necessarily true: if an increase in pathogen transmissibility or sterility causes susceptible hosts to be more likely to avoid infected conspecifics ($\partial_\beta\epsilon < 0$ or $\partial_\delta\epsilon < 0$, respectively), then there may exist a pathogen singular strategy. Indeed, even if we suppose that transmissibility does not trade-off with any other pathogen attributes, because $\epsilon(\tilde{\beta})$ will depend upon pathogen-induced mortality, γ, while $\tilde{\beta}$ will necessarily depend upon $\epsilon(\tilde{\beta})$, it follows that $\tilde{\beta}$ will also indirectly depend upon γ. In an empirical study, such a finding (i.e. transmission being correlated with virulence) could be naively interpreted as a trade-off dictated by properties of the pathogen life cycle, rather than from the selective pressure exerted by host plasticity.

Suppose instead that there is the classical trade-off between transmissibility and pathogen-induced mortality, γ, such that transmissibility is an increasing function of γ (i.e. $\beta'(\gamma) > 0$). For simplicity, replace the dummy variable κ with γ. Under such a trade-off, the terms $\lambda(\bar{x}, \bar{y})$ and $\partial_{\gamma_m}\mu(\gamma_m)$ will both appear once we take the derivative of the invasion function with respect to γ_m, and therefore little progress can be made without some specification of how conspecifics encounter one another and how infected mortality occurs. Thus, assume one of three circumstances holds: (i) frequency-dependent transmission with $\mu(\gamma_m) \equiv \gamma_m + \nu$, (ii) density-dependent transmission with $\mu(\gamma_m) \equiv \gamma_m + \nu$, or (iii) density-dependent transmission with $\mu(\gamma_m) \equiv (\gamma_m + \nu)(\bar{x} + \bar{y})$. Note that in case (iii), both background and pathogen-induced mortality are regulated by density-dependence; biologically this implies that being infected exacerbates density-dependent mortality effects. The common attribute of these three cases is that the pathogen evolutionary dynamics are a simple maximization process [38–40], and any pathogen strategy which is evolutionarily stable is also convergence stable and vice versa. As a result, it is not necessary to specify the dynamics of susceptible hosts in order to obtain the pathogen singular strategy. Indeed, it is easy to show that for all three cases, the disease-free equilibrium is unstable if $\mathcal{R}(\gamma) = \beta(\gamma)\epsilon(\gamma)/\mu(\gamma) > 1$, and that a rare mutant can invade provided $\mathcal{R}(\gamma_m) > \mathcal{R}(\gamma)$ (see electronic supplementary material, S.2.1). Thus, $\mathcal{R}(\gamma)$ represents the relative fitness of a pathogen. For all three cases, the pathogen singular strategy, $\tilde{\gamma}$, is the solution of

$$\underbrace{\frac{\beta(\tilde{\gamma})}{\epsilon(\tilde{\gamma})}\left[\frac{\partial\epsilon}{\partial\beta}\frac{\mathrm{d}\beta}{\mathrm{d}\gamma_m}+\frac{\partial\epsilon}{\partial\gamma_m}\right]_{\gamma_m=\tilde{\gamma}}}_{\text{effect of plasticity}}=\left(\frac{\beta(\tilde{\gamma})}{\tilde{\gamma}+\nu}-\left.\frac{\mathrm{d}\beta}{\mathrm{d}\gamma_m}\right|_{\gamma_m=\tilde{\gamma}}\right), \tag{3.3}$$

where we have again highlighted the contribution of plasticity. If host resistance is fixed, the left-hand side of (3.3) is zero, and so the optimal pathogen strategy is independent of what the host does, provided pathogen evolution is a simple maximization process. Therefore in a co-evolutionary process, the pathogen evolutionary dynamics are unaffected by host evolution. This result would also hold if the asymmetric game assumed the host went first (e.g. [10]). Under resistance plasticity, however, this is clearly not the case: here, what the host does can have a substantial impact upon pathogen evolution.

An obvious question to ask is what effect plasticity has upon pathogen-induced mortality, γ, when there exists a transmissibility–mortality trade-off. Denote the optimal pathogen strategy under fixed resistance as γ^*. Suppose the optimal pathogen strategy under resistance plasticity, $\tilde{\gamma}$, can be written $\tilde{\gamma} \approx \gamma^* + \Delta\gamma$, where $\Delta\gamma$ represents the change in mortality virulence due to resistance plasticity and we are neglecting higher-order terms in $\Delta\gamma$. Following a Taylor expansion of (3.3) and some simplifications (see electronic supplementary material, S.2.2), whenever host resistance increases with increasing pathogen-induced mortality (i.e. $\partial_\gamma\epsilon < 0$), resistance plasticity will reduce pathogen-induced mortality as compared to when resistance is fixed (i.e. $\Delta\gamma < 0$). Effectively, phenotypic plasticity allows the host to employ the threat of escalating resistance to compel the pathogen to reduce its virulence and transmissibility.

To examine these predictions in more detail, however, we need to obtain the optimal response function, $\epsilon(\kappa)$. To do so requires fully specifying the host population dynamics; this will be the focus of the following section.

4. A specific case of host–pathogen coevolution

Consider a host–pathogen population in which hosts are haploid and asexual reproduction occurs at a *per capita* rate of b. Transmission of infection is density-dependent, as are background and pathogen-induced mortality (case (iii) of preceding section). We opt to regulate the population with density-dependent mortality rather than density-dependent fecundity as has been done elsewhere (e.g. [10]) primarily for mathematical tractability (see electronic supplementary material, S.3.1, for discussion). Although it is known that how host density-dependence is modelled can alter the conditions for evolutionary branching (e.g. [40–42]), here we focus exclusively upon evolutionary endpoints, that is, strategy combinations which are CSS for both host and pathogen. Thus, we do not believe how density-dependent regulation occurs will drastically alter our qualitative predictions

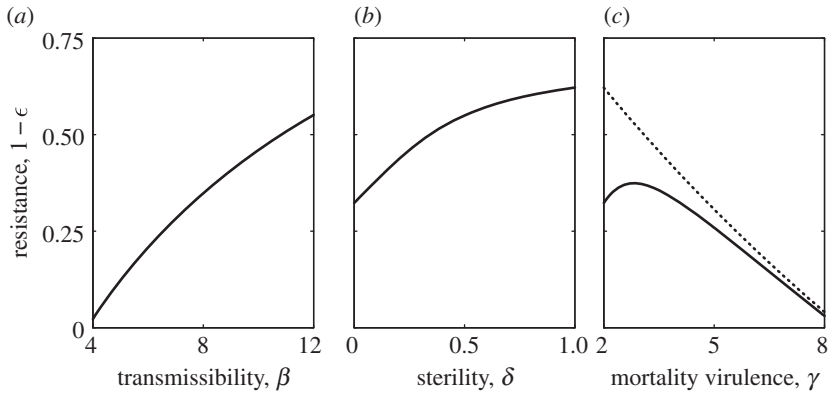

Figure 1. Effect of pathogen transmissibility, sterility and mortality virulence upon the optimal host avoidance strategy when resistance is fixed. In (*c*), the solid curve corresponds to $\delta = 0$ (pathogen causes no sterility), while the dotted curve corresponds to $\delta = 1$ (pathogen castrates host). In all subplots, $\mathcal{D}(\epsilon) = 0.5(1-\epsilon) + 1.5(1-\epsilon)^2 - 0.25(1-\epsilon)^3$, $\nu = 1$, while in (*a*,*b*), $\gamma = 2$, in (*b*,*c*), $\beta = 10$, and in (*a*), $\delta = 0.25$.

here, under the caveat we only consider CSS strategies and pathogen evolution is a maximization process.

Susceptible individuals are continuously alert to infection risk and inspect every contact. By doing so, they could expose themselves to greater predation risk, increased likelihood of starvation, or incur other physiological or metabolic costs from, for example, altering their immune response. As such, each encounter with a conspecific comes with increased mortality risks, and these risks scale with resistance. Hence, the more resistant an individual is, the greater the probability they will die during a contact. For encounters between susceptibles, as time and energy must be spent to evaluate the threat, for simplicity we suppose the likelihood of dying during the encounter is the same as for a contact with a host infected with the wild-type pathogen. Upon encountering a novel pathogen strain, the host will instantaneously adjust its resistance, causing a corresponding change in the likelihood it will die during that encounter. In the one-host, one-pathogen model, the per-contact resistance costs mean that due to resistance, susceptible individuals die at a *per capita* rate of $\mathcal{D}(\epsilon)(x+y)$, where $\mathcal{D}(\epsilon)$ scales cost with resistance, such that $\mathcal{D}'(\epsilon) < 0$ and $\mathcal{D}(1) = 0$.

Under these assumptions, the one-host, one-pathogen model is

$$\left.\begin{aligned} \dot{x} &= bx + b(1-\delta)y - \beta\epsilon yx - (\nu + \mathcal{D}(\epsilon))(x+y)x \\ \text{and} \quad \dot{y} &= \beta\epsilon xy - \mu(x+y)y, \end{aligned}\right\} \tag{4.1}$$

where $\mu \equiv \gamma + \nu$. Let $\mathcal{R} = \beta\epsilon/\mu$. If $\mathcal{R} > 1$, then the disease-free equilibrium is unstable and a unique endemic equilibrium exists satisfying $\bar{y} = (\mathcal{R}-1)\bar{x}$. When the endemic equilibrium exists, it is globally asymptotically stable (see electronic supplementary material, S.3.1).

Provided resistance costs to the host are accelerating, $\mathcal{D}''(\epsilon) > 0$, the optimal host response function is CSS (electronic supplementary material, S.3.2.1; see also [3,13]). Moreover, under the assumption of small mutational steps, the pathogen can never be eliminated by host resistance evolution (electronic supplementary material, S.3.2.1; [2,6,8]): as the number of infected hosts is reduced, so too is the likelihood of infection and hence the benefit of paying a resistance cost.

(a) Fixed host resistance

First, how do the pathogen traits impact host resistance in the *absence* of pathogen evolution? This is equivalent to assuming resistance is a fixed strategy and the focus is upon the coevolutionary process of a symmetric game, or that we are considering the coevolutionary process of an asymmetric game in which the host, rather than the pathogen, goes first (e.g. [10]). The reason why these are identical was discussed previously: provided the pathogen dynamics are a simple maximization process, in the absence of host plasticity the pathogen evolutionary trajectory is determined solely by the transmission–mortality trade-off (see (3.3)). As a result, when focused upon CSS strategies, the coevolutionary outcome is that obtained by simultaneously computing the host and pathogen optimal strategies.

Under fixed resistance, as the pathogen becomes more sterilizing and as transmissibility increases, host resistance will monotonically increase as well (figure 1*a*,*b*; electronic supplementary material, S.3.3.1). The effect of pathogen-induced mortality, γ, is more complex: if the pathogen is fully sterilizing, then any increase to γ causes a decrease in resistance (figure 1*c*; see also [9,10]), whereas when the pathogen does not fully sterilize the host, the relationship depends upon the magnitude of γ (electronic supplementary material, S.3.3.1). In particular, resistance is greatest at intermediate pathogen-induced mortality and declines at low and high values (figure 1*c*). The reason is that while on the one hand any increase in mortality virulence is deleterious to the expected fitness of infecteds, on the other, since increasing γ shortens infection duration, it also causes a decrease in pathogen relative fitness, $\mathcal{R}$, reducing the likelihood of becoming infected. When the pathogen is fully sterilizing, infected hosts have zero future fitness irrespective of the magnitude of γ, so the only selective pressure is the likelihood of infection.

(b) No pathogen trade-offs

Now suppose there is no explicit pathogen trade-off between transmissibility (β) and virulence (δ and γ): virulence is fixed and only transmissibility is evolving; moreover, suppose the host exhibits resistance plasticity. Then, we can explicitly obtain the CSS Stackelberg outcome, $(\epsilon(\tilde{\beta}), \tilde{\beta})$ (see electronic supplementary material, S.3.3.2, for details). Now that resistance is plastic, as pathogen-induced mortality and sterility increases, resistance decreases (figure 2*a*). These predictions run counter to those obtained when the pathogen was not evolving (or resistance was fixed, figure 1*b*,*c*), and are contrary to the general theoretical expectation that resistance

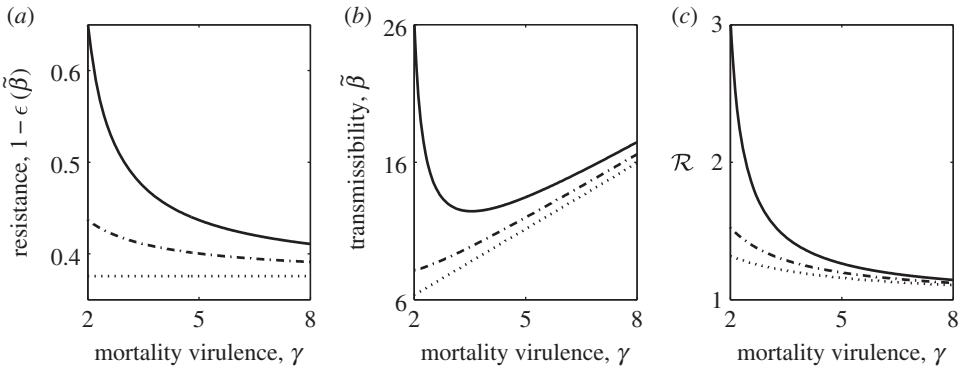

Figure 2. (*a–c*) Effect of varying pathogen virulence, γ and δ, upon the CSS resistance response, CSS pathogen transmissibility and pathogen relative fitness $\mathcal{R}$, when there are no pathogen transmissibility trade-offs. Each curve corresponds to a different value of δ; in particular, the solid line corresponds to $\delta = 0$, the dash-dot curve corresponds to $\delta = 0.5$ and the dotted curve is $\delta = 1$. Thus, the more pronounced the curve, the smaller the δ, and less sterilizing the pathogen. All subplots used $\mathcal{D}(\epsilon) = 0.5(1-\epsilon) + 1.5(1-\epsilon)^2 - 0.25(1-\epsilon)^3$, and $\nu = b = 1$.

should either peak with intermediate virulence before declining (see figure 1*c*; [2,3,10,13]) or for castrating pathogens, resistance should be a declining function of mortality virulence (figure 1*c*; [9]). To understand why, we need to consider how $\tilde{\beta}$ changes with γ and δ: by going first the pathogen is able to shape the host's response. In particular, the pathogen exploits situations in which a host under fixed resistance would invest less, forcing resistance escalation. In the case of δ, as the pathogen becomes less sterilizing, the incentive for the host to resist infection decreases, and thus the pathogen will increase its transmissibility (figure 2*b*). This in turn forces an increase in the host's resistance response. To see this, compare the placement of the curves corresponding to $\delta = 0$ (solid curve) and $\delta = 1$ (dotted curve) in figure 2*a* to those in figure 1*c*: under fixed resistance, host resistance is greater for fully sterilizing pathogens than when the pathogen causes no sterility (figure 1*c*), whereas under resistance plasticity, the opposite holds (figure 2*a*).

The evolutionary behaviour as we vary γ is more complex. If the pathogen is fully sterilizing, then transmissibility is a strictly increasing function of mortality virulence (figure 2*b*). Conversely, as $\delta \to 0$, the pathogen favours low transmissibility at intermediate levels of mortality virulence, while increasing transmissibility at both low and high values (figure 2*b*). These predictions relate to the observations made earlier: changing γ while holding the other pathogen attributes fixed has a twofold effect upon host fitness: any increase reduces the fitness of infected individuals, while simultaneously reducing the pathogen's relative fitness, lessening the likelihood of infection. When γ is small, the host would otherwise favour reduced resistance (figure 1*c*), and so the pathogen increases transmissibility forcing resistance escalation under plasticity (figure 2*a*). When the pathogen is fully sterilizing, the host is only concerned with limiting transmission: any increase to γ, which by itself would cause a decrease in pathogen relative fitness, is offset by the pathogen being forced to increase its transmissibility, thus host resistance is maintained at a constant level (figure 2*a*,*b*).

A consequence of the $(\epsilon(\tilde{\beta}), \tilde{\beta})$ pair for the host population is that increasing γ causes a decrease in $\mathcal{R}$ by shortening the duration of infection. As a result, since the proportion of the population infected is $\bar{y}/(\bar{x}+\bar{y}) = (\mathcal{R}-1)/\mathcal{R}$, the proportion infected decreases as well. Indeed, the proportion infected and $\mathcal{R}$ are lowest as the pathogen becomes fully sterilizing and causes the greatest host mortality (figure 2*c*). Thus resistance plasticity can allow a host population to thrive, particularly in the face of more severe and virulent pathogens, with the caveat that the consequences of infection for an individual are dire. This holds despite the absence of a pathogen transmissibility–virulence trade-off.

(c) Mortality trade-offs

Now suppose transmissibility has a functional dependency upon pathogen-induced mortality such that any increase in β is due to an increase in γ. In figure 3, we contrast the predictions for the CSS strategy pair under plasticity (black curves) to those of the coevolutionary CSS pair generated under fixed resistance (grey curves). The pathogen responds to the selective pressure exerted by host plasticity by becoming less virulent (figure 3*b*; see also electronic supplementary material, S.2.2), causing in turn the host to be less resistant (figure 3*a*). The outcome is greater relative fitness for the pathogen, a higher proportion of the population infected, and greater total population density (figure 3*c*,*d*)—which increases both from reduced pathogen virulence as well as the reduced mortality costs of lower resistance. The end result is resistance plasticity drives a superior outcome for both the pathogen and the host, and delivers an evolutionary result more akin to the classic prediction of pathogens evolving towards avirulence. Indeed, this represents an example of a Stackelberg game exhibiting endogeneous timing [43,44]. Endogeneous timing occurs when both players achieve higher fitness by playing their strategies in a particular sequence, rather than simultaneously. When the host is phenotypically plastic, its strategy by definition is the best response to anything the pathogen does and so going second (i.e. phenotypic plasticity) ensures host fitness is maximal. On the other hand, pathogen fitness is given by $\mathcal{R}$, and this is greater under resistance plasticity (figure 3*c*) as compared to either fixed resistance or by the host going first, since as discussed previously the latter two scenarios generate the same outcome.

Note that the greatest difference between plasticity and fixed resistance occurs as the pathogen becomes fully sterilizing (figure 3). The logic here is clear: as resistance is based upon β, γ, and δ, when pathogen sterility increases, the host will pay the higher costs in order to increase resistance. Since δ is a fixed, non-evolving quantity, as the pathogen becomes more sterilizing and host resistance increases, the pathogen is

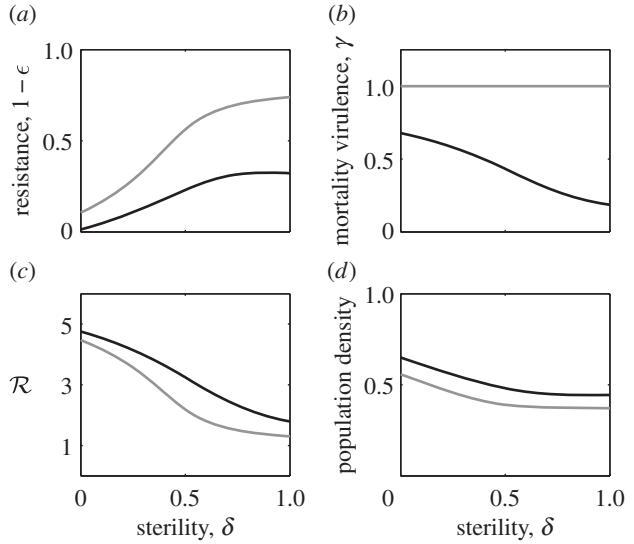

Figure 3. Host–pathogen coevolution under transmissibility–mortality trade-off. The black curves correspond to the CSS strategy pair generated by resistance plasticity, $(\epsilon(\tilde{\gamma}), \tilde{\gamma})$, while the grey curves represent the CSS strategy pair under fixed resistance, (ϵ, γ^*). Population density is $\bar{x} + \bar{y}$. In all subplots, $\mathcal{D}(\epsilon) = 0.5(1-\epsilon) + 1.5(1-\epsilon)^2 - 0.25(1-\epsilon)^3$, $\nu = b = 1$, and $\beta(\gamma) = 20\gamma/(1+\gamma)$.

forced to decrease mortality virulence (and hence β) in order to maintain the product $\beta(\tilde{\gamma})\epsilon(\tilde{\gamma})$ at sufficiently high levels. Therefore, if a pathogen causes complete castration, the expectation under resistance plasticity is that the pathogen should minimize mortality-related virulence. In the absence of plasticity, however, the magnitude of δ has no effect upon pathogen evolution in well-mixed populations (grey curve in figure 3*b*, equation (3.2); see also [12,32,33]).

(d) Sterility trade-offs

Previous work has found that if pathogen transmissibility trades off with sterility instead of mortality, then in well-mixed populations the pathogen should evolve to castrate the host [12,32,33]. When host resistance is phenotypically plastic, however, this is not the case: there can exist an optimal pathogen strategy, $\tilde{\delta}$, provided increases to pathogen-induced sterility are offset by increases to host resistance (equation (3.2)). Because of the complexities of the Stackelberg pair, $(\epsilon(\tilde{\delta}), \tilde{\delta})$, analytic predictions are difficult. However, numerical results indicate that, assuming any increase in transmissibility is due to an increase in sterility (i.e. $\beta'(\delta) > 0$), the optimal pathogen strategy causes the greatest host sterility at high and low levels of pathogen-induced mortality, while being the most benign at intermediate levels (electronic supplementary material, S.3.3.4).

As explained previously, the selective pressure upon the host to increase resistance is greatest when pathogen-induced mortality is intermediate. The pathogen can therefore increase sterility (and hence transmissibility) at low and high pathogen-induced mortality without triggering dramatic increases in host resistance. At intermediate pathogen-induced mortality, the pathogen is sufficiently deleterious that the host will pay a cost to resist infection, yet $\mathcal{R}$ is large enough that the pathogen cannot increase its sterilizing effect without suffering resistance reprisals from the host (see electronic supplementary material, S.3.3.4 and figure S1).

5. Discussion

Conventional models of host avoidance assume resistance is a fixed strategy which does not vary with individual encounters [2,3,5–14]. While such an assumption is logical for gene-for-gene or passive resistance mechanisms, it makes less sense when resistance is in response to external stimuli, as recent empirical evidence suggests is frequently the case [17–27]. When resistance is fixed, host evolution is intuitive: increasing pathogen-related sterility and transmissibility causes host resistance to increase (figure 1*a*,*b*). Increasing or decreasing pathogen-induced mortality also has a well known, if more complex effect: resistance is greatest for intermediate pathogen-related mortality. This is due to the balancing of the two selective pressures caused by varying pathogen virulence: change in fitness of infecteds versus the change in likelihood of becoming infected (figure 1*c*; [2,3,10,13]). The host–pathogen coevolutionary outcome under fixed resistance is similarly straightforward: in the absence of pathogen transmission–mortality trade-offs, pathogen transmissibility will increase without restraint. If there is a transmission–mortality trade-off and pathogen evolution is a maximization problem, then the optimal pathogen strategy is independent of the host's (fixed) resistance level. Here, we have shown that when host resistance is instead phenotypically plastic, none of these expectations hold. In particular, our analysis revealed three main results.

First, even when there is no explicit link between pathogen transmissibility and virulence, under a wide variety of conditions there will exist an evolutionary attracting Stackelberg outcome. When such an outcome exists, as the pathogen goes first and the host responds, the pathogen exploits situations in which the host would, under fixed resistance, favour low investment in resistance. This drives an escalation of host resistance. Second, when there is an explicit pathogen transmission–mortality trade-off, host resistance plasticity will cause a decrease in pathogen virulence and pathogen-controlled transmissibility. Notably, the ultimate evolutionary outcome is preferable to both parties: the pathogen is less virulent, the total host population size increases, as does the proportion of the population infected and the relative fitness of the pathogen. Thus, by behaving plastically, a situation closer to commensalism than would otherwise be expected is generated. Finally, the level of pathogen-induced sterility has important implications for pathogen evolution under resistance plasticity. When transmission trades off with mortality alone and sterility is not evolving, pathogens that castrate their hosts are forced to minimize pathogen-induced mortality to alleviate host resistance selective pressures (figure 3). If transmissibility instead trades off with sterility alone, host resistance plasticity is capable of restraining pathogens from castrating hosts, contrary to current theoretical expectations for resistance in well-mixed populations [12,32,33].

Asymmetric games have been used to study host–pathogen coevolution elsewhere. For example, it has been shown that when both virulence and host recovery are phenotypically plastic [30,45], virulence always decreases, causing an increase in the fitness of both host and pathogen, as observed here. A different model by Restif & Koella [10] used an asymmetric game involving host resistance in which the host went first, and so the pathogen was phenotypically plastic. Because under multiplicative transmission functions, as used here, such a game will generate predictions identical to the symmetric

game with fixed strategies, the authors assumed transmission depended upon both the host and pathogen strategy in a non-multiplicative fashion [10]. Their model indicated host resistance should be maximal at intermediate pathogen virulence [10]. Under a transmission–mortality trade-off, as was used in their model, our results indicate that, for any sterility level, resistance is instead a strictly decreasing function of virulence. The reason for this discrepancy is because of the difference in who goes first: asymmetric games often generate fitness advantages to going first [29], as going first allows the player to exploit its opponent's response.

One of the main simplifying assumptions of our model is of perfect information transfer. In reality, we would expect a host's ability to discern between different pathogen strains to be coarser and identification errors to occur. However, we do not believe that adding this complexity would alter our main qualitative predictions about the selective effect host resistance plasticity has upon pathogen evolution. We do note, however, it is possible that the higher-order evolutionary dynamics may change, since host error may create an additional environmental feedback [38,39] that could lead to evolutionary branching and pathogen diversification. Another simplifying assumption we made was that when we considered the implications of resistance plasticity for pathogens with transmissibility–mortality trade-offs, we focused exclusively upon cases in which pathogen evolution reduced to a maximization problem (e.g. [40,41]). We did so because our goal here was to demonstrate the impact avoidance plasticity can have upon host–pathogen evolutionary outcomes. Relaxing this assumption would complicate the conditions under which the strategy pair are CSS, as well as allowing additional feedbacks from the host population demographics to come into play [42]; without examining specific examples in-depth, it is not known what role plasticity would play—but in general, we would expect plasticity to effect the evolutionary outcomes.

In summary, here we have shown the important implications host avoidance plasticity can have for pathogen evolution. In particular, resistance plasticity generates predictions that are frequently opposite of those generated by fixed resistance models. The mechanism of avoidance, and whether it is plastic or fixed, is therefore of the utmost importance for evolutionary expectations.

Authors' contributions. D.V.M. and T.D. conceived research question and designed model. D.V.M. analysed model. D.V.M. and T.D. wrote paper.

Competing interests. We declare we have no competing interests.

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