The evolution of the age of onset of resistance to infectious disease

Lydia J. Buckingham[1,2,*] and Ben Ashby[1,2,3,4†]

1. Department of Mathematical Sciences, University of Bath, Bath, UK
2. Milner Centre for Evolution, University of Bath, Bath, UK
3. Department of Mathematics, Simon Fraser University, Burnaby, BC, Canada
4. Pacific Institute on Pathogens, Pandemics and Society, Burnaby, BC, Canada

* ORCID 0000-0002-9691-9788

† ORCID 0000-0001-5588-7081

*Corresponding author: ljb74@bath.ac.uk

Keywords: juvenile, adult, resistance, susceptibility, pathogen, parasite

Funding acknowledgements: Ben Ashby is supported by the Natural Environment Research Council (grant nos. NE/N014979/1 and NE/V003909/1). This research was generously supported by a Milner Scholarship PhD grant to Lydia Buckingham from The Evolution Education Trust. We acknowledge the support of the Natural Sciences and Engineering Research Council of Canada (NSERC). Nous remercions le Conseil de recherches en sciences naturelles et en génie du Canada (CRSNG) de son soutien. PIPPS receives funding from the BC Ministry of Health.

ABSTRACT

Many organisms experience an increase in disease resistance as they age but the time of life at which this change occurs varies. Increases in resistance are partially due to prior exposure and physiological constraints but these cannot fully explain the observed patterns of age-related resistance. An alternative explanation is that developing resistance at an earlier age incurs costs to other life-history traits. Here, we explore how trade-offs with host reproduction or mortality affect the evolution of the onset of resistance, depending on when during the host's life-cycle the costs are paid (only when resistance is developing, only when resistant or throughout the lifetime). We find that the timing of the costs is crucial to determining evolutionary outcomes, often making the difference between resistance developing at an early or late age. Accurate modelling of biological systems therefore relies on knowing not only the shape of trade-offs but also when they take effect. We also find that the evolution of the rate of onset of resistance can result in evolutionary branching. This provides an alternative, possible evolutionary history of populations which are dimorphic in disease resistance, where the rate of onset of resistance has diversified rather than the level of resistance.

INTRODUCTION

Many organisms experience changes in their level of resistance to infectious disease as they age, with repercussions for both their own health and transmission to others (Altizer et al. 2004; Apolloni et al. 2013; Clark et al. 2017). Age-related differences in resistance have been recorded across many taxa, including plants (Miller 1983; Panter and Jones 2002; Develey-Rivière and Galiana 2007; Bruns et al. 2017), invertebrates (Sait et al. 1994; Kubi et al. 2006; Armitage and Boomsma 2010; Garbutt et al. 2014; Green et al. 2016; Klemme et al. 2022) and vertebrates (Duca 1948; Zuckerman and Yoeli 1954; Francis 1961), including humans (Baird 1998; Kurtis et al. 2001; Glynn and Moss 2020). In particular, adults are generally more resistant than juveniles (Duca 1948; Zuckerman and Yoeli 1954; Francis 1961; Sait et al. 1994; Baird 1998; Kurtis et al. 2001; Panter and Jones 2002; Kubi et al. 2006; Develey-Rivière and Galiana 2007; Armitage and Boomsma 2010; Green et al. 2016; Bruns et al. 2017), with some species being completely resistant as adults to pathogens which are highly detrimental to juveniles (e.g. nucleopolyhedrovirus in gypsy moths (Elderd et al. 2008)). Precisely when in the host's lifetime these changes in resistance occur varies between systems. This variation in the timing of resistance onset has received little empirical or theoretical attention, with very few studies seeking to explain or even describe the time within a host's lifespan at which resistance changes. A key outstanding question is therefore, 'how should evolution shape the timing of the onset of resistance?'

As there is variation in the age of onset of resistance within species and resistance traits are often heritable, it is reasonable to assume that the age of onset of resistance is an evolvable trait. In this paper, we seek to generate predictions for how the age of onset of resistance might evolve. Intuitively, an earlier onset of resistance will tend to lower disease prevalence

64 and hence reduce the risk of infection, thereby acting as a negative feedback on selection if
65 resistance is costly. However, precisely how this phenomenon affects the evolution of the
66 onset of resistance remains to be determined.
67
68 Several factors are known to contribute towards the onset of disease resistance. Many
69 species' immune systems respond to prior exposure, meaning that resistance may increase
70 substantially following infection. This mechanism can explain some, but not all, observed
71 variation in the age of onset of disease resistance, particularly in the case of species which
72 rely solely or predominantly on innate resistance. For instance, different species of plants
73 experience changes in resistance at different life-stages (Develey-Rivière and Galiana 2007).
74 Alternatively, variation in the age of onset of resistance may have evolved due to contrasting
75 selection pressures at different life-stages. For instance, if a pathogen is more harmful to older
76 hosts than younger hosts then the onset of resistance may be delayed if developing or
77 maintaining resistance is costly. In some cases, however, age-related changes in resistance
78 have been observed towards pathogens which have similar effects on hosts of all ages (Bruns
79 et al. 2017), suggesting that the timing of the onset of resistance is also affected by other
80 factors. Hence, none of these mechanisms can provide a full explanation for variation in the
81 age of onset of disease resistance.
82
83 An alternative evolutionary explanation for increases in resistance with age is that heightened
84 resistance incurs costs to host life-history traits. For instance, hosts which invest in developing
85 resistance quickly may allocate resources away from growth or development which may in
86 turn impact on future reproduction or survival. In principle, these reductions in fecundity or
87 survival may only be experienced while resistance is developing but such costs may also have

88 long-term consequences which affect the reproduction or survival of the host later in life
89 (Chaplin and Mann 1978; Simons 1979; Tian et al. 2003). Evolutionary trade-offs may
90 therefore provide an explanation as to why hosts might develop resistance later in life rather
91 than being resistant from birth or from a very early age. Empirical studies reveal trade-offs
92 between reproduction (Biere and Antonovics 1996; Karasov et al. 2017) or growth (Biere and
93 Antonovics 1996; Susi and Laine 2015; Karasov et al. 2017; Bartlett et al. 2018) and disease
94 resistance in plants and insects, but little data is available on age-specific costs (Izhar and Ben-
95 Ami 2015).
96
97 Epidemiological models have considered disease spread in age-structured populations (e.g.
98 (Clark et al. 2017)) and evolutionary models have considered the evolution of resistance in
99 populations with no age structure (e.g. (Antonovics and Thrall 1994; Boots and Haraguchi
100 1999; Carlsson-Graner and Thrall 2006; Miller et al. 2007; Donnelly et al. 2015)). In contrast,
101 the evolution of age-structured resistance has received relatively little attention. However,
102 recent theory has explored the evolution of age-specific resistance in juveniles and adults,
103 showing that differences in resistance between life-stages are most pronounced for
104 particularly long- or short-lived hosts (Ashby and Bruns 2018) and that adult resistance often
105 evolves to exceed juvenile resistance, depending on which traits trade off with resistance
106 (Buckingham et al. 2023). Here, we investigate a different characteristic of age-specific
107 resistance, namely the timing of the onset of resistance. We focus our analysis on trade-offs
108 with mortality and reproduction, which may affect the host during development of resistance,
109 during the resistant stage or throughout the lifetime of the host. We also consider variation
110 in pathogen traits, specifically transmissibility and the strength and type of virulence. We find
111 that the timing of the trade-offs (costs paid before or after the onset of resistance or

throughout the host's lifetime) has a significant effect on evolutionary outcomes, often determining whether the host becomes resistant very early or very late in life. We also find that evolutionary branching of the age of onset of resistance can generate a dimorphic population where some hosts are resistant throughout their lives and others never develop resistance.

METHODS

MODEL DESCRIPTION

We consider a well-mixed, asexual host population in which hosts are born fully susceptible to an infectious disease but develop full innate resistance to infection at a constant (but evolvable) rate $\zeta > 0$ (see Fig. 1A for a model schematic and Table 1 for a full list of parameters and variables). The length of time before an individual becomes resistant is therefore exponentially distributed (with parameter $\frac{1}{\zeta}$) and so $\frac{1}{\zeta}$ gives the average age of onset of resistance. Let S, I and R be the densities of susceptible, infected and resistant hosts respectively, giving a total host population density of $N = S + I + R$. Non-resistant hosts reproduce at a maximum rate $a > 0$, subject to density-dependent competition given by $q > 0$, and die naturally at rate $b > 0$. Similarly, resistant hosts reproduce at rate a_R and die naturally at rate b_R. Pathogen transmission is assumed to be density-dependent, with transmission rate β, and infected hosts may either experience sterility virulence equal to $1 - f$, where $0 \leq f \leq 1$ is the reduction in fecundity when infected, or mortality virulence given by $\alpha > 0$, the relative increase in the mortality rate. We assume that hosts do not recover from infection, as recovery would complicate the timing of the onset of resistance (it is not

clear how infected individuals would transition to the innately resistant stage in this case) and would also require us to account for potential long-term effects of sterility virulence.

In a monomorphic population and in the absence of any costs of resistance, the population dynamics are described by the following set of ordinary differential equations:

$$\frac{dS}{dt} = a(1 - qN)(S + fI) + a_R(1 - qN)R - \beta SI - bS - \zeta S \qquad (1a)$$

$$\frac{dI}{dt} = \beta SI - b(1 + \alpha)I \qquad (1b)$$

$$\frac{dR}{dt} = -b_R R + \zeta S \qquad (1c)$$

Intuitively, in the absence of any costs of resistance, selection will favour ever larger rate of onset of resistance (ζ) so that there is an immediate onset of resistance at the start of the host lifespan, which will in turn drive the pathogen extinct. We therefore consider cases where being resistant or developing resistance incurs a cost to the host, either through higher mortality or lower fecundity (e.g., due to resource allocation). Such costs might be paid only when the host is resistant (i.e., in the R class), or prior to the onset of resistance (i.e., during development in classes S and I), or throughout the lifetime of the host. The magnitude of any costs may therefore be constant, or depend on the rate of onset of resistance, ζ. To account for costs of resistance, we modify equation (1) so that the reproduction rates, $a(\zeta)$ and $a_R(\zeta)$, and mortality rates, $b(\zeta)$ and $b_R(\zeta)$, may depend on the rate of onset of resistance.

We consider six possible scenarios:

(1) A constant fecundity cost, paid only when the host is resistant ($a_R(\zeta) = ah$, where $1 - h$ is the relative reduction in fecundity when resistant, with $b_R(\zeta) = b$, $a = a_0$ and $b = b_0$)

(2) A constant mortality cost, paid only when the host is resistant ($b_R(\zeta) = b(1+\delta)$, where δ is the relative increase in mortality when resistant, with $a_R(\zeta) = a$, $a = a_0$ and $b = b_0$)

(3) A whole-life fecundity cost ($a_R(\zeta) = a(\zeta)$ as defined in equation (2a), with $b_R(\zeta) = b$ and $b = b_0$)

(4) A whole-life mortality cost ($b_R(\zeta) = b(\zeta)$ as defined in equation (2b), with $a_R(\zeta) = a$ and $a = a_0$)

(5) A developmental fecundity cost ($a(\zeta)$ as defined in equation (2a), with $a_R(\zeta) = a_0, b_R(\zeta) = b$ and $b = b_0$)

(6) A developmental mortality cost ($b(\zeta)$ as defined in equation (2b), with $a_R(\zeta) = a$, $b_R(\zeta) = b_0$ and $a = a_0$).

where a_0 and b_0 are baseline reproduction and mortality rates and we use the following trade-offs for the reproduction rate:

$$a(\zeta) = a_0\left(1 - \frac{c_1^a\left(1 - e^{-c_2^a\zeta}\right)}{1 - e^{-c_2^a}}\right) \tag{2a}$$

and the mortality rate:

$$b(\zeta) = b_0\left(1 + \frac{c_1^b\left(1 - e^{-c_2^b\zeta}\right)}{1 - e^{-c_2^b}}\right) \tag{2b}$$

where $c_1^i > 0$ determines the maximum strength of the trade-off (i.e. the maximum proportional reduction or increase in the associated life-history trait) and c_2^i determines the shape of the trade-off (larger absolute values correspond to greater deviations from linearity; Fig. 1B & Fig. 1C). Note that it is possible to rescale the system of equations (1a) to (1c) so that we can set $q = 1$ and $b_0 = 1$ without loss of generality (see *Supplementary Materials*).

EPIDEMIOLOGICAL DYNAMICS

The disease-free equilibrium of system (1) is given by:

$$S^* = \frac{b_R(ab_R + a_R\zeta - bb_R - b_R\zeta)}{q(b_R + \zeta)(ab_R + a_R\zeta)} \tag{3a}$$

$$R^* = \frac{\zeta(ab_R + a_R\zeta - bb_R - b_R\zeta)}{q(b_R + \zeta)(ab_R + a_R\zeta)} \tag{3b}$$

and is stable provided that $ab_R + a_R\zeta > bb_R + b_R\zeta$ and

$$R_0 = \frac{\beta b_R(ab_R + a_R\zeta - bb_R - b_R\zeta)}{q(b_R + \zeta)(ab_R + a_R\zeta)b(1+\alpha)} < 1 \tag{4}$$

where R_0 is the basic reproductive ratio of the pathogen (see *Supplementary Materials* for derivation). The pathogen can spread when $R_0 > 1$, in which case there is a stable, endemic (non-trivial) equilibrium (see *Supplementary Materials*).

EVOLUTIONARY INVASION ANALYSIS

We use evolutionary invasion analysis (adaptive dynamics) to determine the evolutionary dynamics of the rate of onset of resistance, ζ (Geritz et al. 1998). Specifically, we assume that mutations are sufficiently rare that there is a separation of ecological and evolutionary timescales (the ecological dynamics of the resident population reach equilibrium before the next mutation occurs) and are sufficiently small that $\zeta_m \approx \zeta$, where ζ_m is the mutant trait and ζ is the resident trait. The invasion dynamics of rare host mutants in a resident population at its endemic equilibrium are given by:

$$\frac{\mathrm{d}S_m}{\mathrm{d}t} = a(1 - qN^*)(S_m + fI_m) + a_R(1 - qN^*)R_m - \beta S_m I^* - bS_m - \zeta_m S_m \tag{S5a}$$

$$\frac{\mathrm{d}I_m}{\mathrm{d}t} = \beta S_m I^* - b(1+\alpha)I_m \tag{S5b}$$

$$\frac{\mathrm{d}R_m}{\mathrm{d}t} = -b_R R_m + \zeta_m S_m \qquad (S5c)$$

where asterisks denote the endemic equilibrium of the resident population and a, a_R, b and b_R may be functions of ζ_m, depending on the nature of the costs of resistance.

Using the next generation method (Hurford et al. 2010), one can derive the following expression for the invasion fitness of a rare mutant in a resident population (see *Supplementary Materials*):

$$w(\zeta_m, \zeta) = \frac{a(\zeta_m)(1-qN^*)b(\zeta_m)(1+\alpha)b_R(\zeta_m) + a(\zeta_m)(1-qN^*)f\beta I^* b_R(\zeta_m) + a_R(\zeta_m)(1-qN^*)b(\zeta_m)(1+\alpha)\zeta_m}{(\beta I^* + b(\zeta_m) + \zeta_m)b(\zeta_m)(1+\alpha)b_R(\zeta_m)} - 1 \qquad (6)$$

In the general case, the lengthy expression for the endemic equilibrium limits analytical progress. However, in cases (1) and (2), where the costs of resistance are constant, we can proceed to determine an expression for the singular value (value which maximises or minimises the invasion fitness) of the rate of onset of resistance.

SIMULATIONS

We can also use simulations to investigate the evolution of ζ (the rate of onset of resistance). To simulate an evolutionary trajectory of the evolving trait (ζ), we first choose a resident value for ζ and an initial composition for the host population. We then run the ecological dynamics for a fixed length of time, T. At this stage, we introduce a small, second sub-population with a different value of ζ (chosen at random to be either slightly higher or lower than the resident value) to model the introduction of a rare mutant into the population. The ecological dynamics (given for an arbitrary number of phenotypes in the *Supplementary Materials*) are then run again for this new population for a fixed length of time, T. If the size of the sub-

population with a particular value of ζ falls below a threshold, then that sub-population is removed (it has gone extinct). An additional, small sub-population with a new value of ζ (chosen at random to be slightly higher or lower than one of the existing trait values in the population) is introduced at each evolutionary timestep, the ecological dynamics are run and sub-populations that fall below the extinction threshold are removed. This process is repeated for many evolutionary timesteps to simulate the evolution of ζ.

Parameter/ variable	Description	Default value or range
a, b	Reproduction rate/natural mortality rate of non-resistant hosts	n/a
a_R, b_R	Reproduction rate/natural mortality rate of resistant hosts	n/a
a_0	Baseline value of the reproduction rate	5
b_0	Baseline value of the natural mortality rate	0.1
c_1^a, c_1^b	Strength of reproduction/mortality trade-offs	0.1
c_2^a, c_2^b	Shape of reproduction/mortality trade-offs	± 2
$1 - f$	Sterility virulence	$0 \leq f \leq 1$
ζ	Rate of onset of resistance	$0 \leq \zeta$
S, I, R	Density of susceptible/infected/resistant hosts	n/a
N	Total host population density	n/a
q	Strength of host density dependence	1
t	Time, measured in arbitrary units	n/a
α	Mortality virulence (proportional increase in mortality rate)	$0 \leq \alpha$
β	Pathogen transmission rate	0.5
$1 - h$	Relative reduction in fecundity when resistant	$0 \leq h \leq 1$
δ	Relative increase in mortality when resistant	$0 \leq \delta$

Table 1 Descriptions and default values or ranges of model parameters and variables.

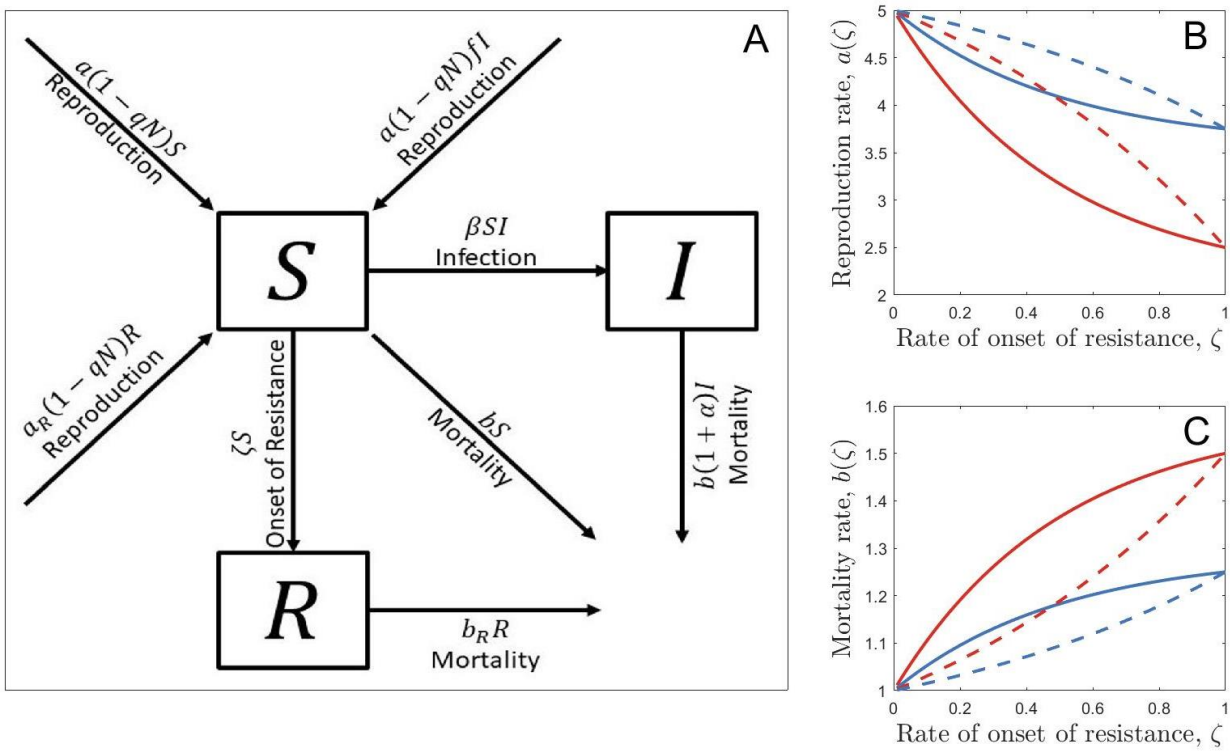

Fig. 1 (A) Model schematic for a monomorphic population. (B) Examples of reproduction trade-off functions (with $a_0 = 5$). (C) Examples of mortality trade-off functions (with $b_0 = 1$). Trade-off strength is controlled by the parameter c_1^i; a relatively strong trade-off ($c_1^i = 0.5$, red) results in a much larger reduction in the birth rate for a given level of adult resistance than a relatively weak trade-off does ($c_1^i = 0.25$, blue). Trade-off shape is controlled by the parameter c_2^i; a positive value ($c_2^i = 2$, solid) means that the costs of resistance decelerate (increasing returns) as the rate of onset gets faster whereas a negative value ($c_2^i = -1$, dashed) leads to accelerating costs (diminishing returns).

227 **RESULTS**

228 *CONSTANT COSTS*

229 We begin by considering the effects of constant fecundity and mortality costs (cases 1 and 2
230 described in the methods) on the evolution of the onset of resistance, ζ. This means that we
231 have a constant fecundity cost when resistant $a_R = ah$, where the reproduction rate when
232 susceptible is $a = a_0$, and a constant mortality cost when resistant, $b_R = b(1+\delta)$, where
233 the mortality rate when susceptible is $b = b_0$. In this case, we can differentiate the invasion
234 fitness with respect to the mutant trait ζ_m to calculate the fitness gradient (see
235 *Supplementary Materials*) and then find the root of the fitness gradient to give us the singular
236 strategy for the rate of onset of resistance:

$$\zeta^* = b_0(1+\delta)\left(\frac{p-1}{fp-(1+\alpha)} + \frac{\beta(a_0 - b_0 p)}{a_0 q\, b_0(1+\alpha)} - 1\right) \qquad (7)$$

237 where $p = \frac{1+\delta}{h}$ for notational convenience. Note that this expression can take a negative
238 value, in which case the singular strategy is effectively at $\zeta^* = 0$ (no onset of resistance).

239

240 We can see from this expression that the rate of onset of resistance rises linearly as the
241 pathogen transmissibility increases. This is because a more transmissible parasite will have a
242 higher disease prevalence and so will exert stronger selection for fast onset of resistance. The
243 singular strategy also rises as sterility virulence increases because more virulent pathogens
244 impose stronger selection for resistance (Fig. 2D). This pattern is also seen as mortality
245 virulence rises but only as long as mortality virulence is not too high. When mortality virulence
246 is high, infected hosts die quickly, reducing the infectious period and so the potential for
247 disease transmission. This reduces the pathogen density and so weakens selection for fast
248 onset of resistance, leading to a fall in the rate of onset of resistance (Fig. 2B).

We might also expect that the rate of onset of resistance would fall as the costs of being resistant rise. This is indeed true when the costs of fast onset of resistance are fecundity costs or when they are relatively large mortality costs (Fig. 2A, C). However, when low mortality costs are paid, it is possible for the rate of onset to rise as the costs of being resistant increase (Fig. 2A). This is because raising the mortality costs causes a significant increase in the density of the pathogen; resistant individuals die faster and so there are fewer of them in the population, yet reproduction is still high enough to maintain the population near to its density-dependent limit, meaning that the density of non-resistant individuals rises. This leads to a population with a reduced proportion of resistant individuals and an increased proportion of infected individuals. This heightened pathogen density then imposes greater selection for fast onset of resistance.

Analytical calculations reveal the invasion fitness of any mutant in a resident population at the singular strategy is zero: $w(\zeta_m, \zeta^*) = 0$ (see *Supplementary Materials*). Hence $\frac{\partial^2 w}{\partial \zeta_m^2}|_{\zeta_m=\zeta=\zeta^*} = 0$ always and so the singular strategy is not strictly evolutionarily stable. The expression which determines convergence stability $\left(\frac{\partial^2 w}{\partial \zeta_m \partial \zeta}|_{\zeta_m=\zeta=\zeta^*}\right)$ is intractable and so it is not possible to determine conditions for convergence stability analytically. However, extensive numerical calculations suggest that the singular strategy is always convergence stable (see *Supplementary Materials*). In order to classify the stability of the singular strategy fully however, we also need to determine whether it appears to be evolutionarily stable or unstable in practice. To do this, we use simulations. Evolutionary simulations (see *Supplementary Materials* for description) reveal that the singular strategies behave like

continuously stable strategies (CSS's), for a wide range of parameter sets. Fig. 3 depicts graphically the simulated changes in the rate of onset of resistance over evolutionary time, showing how it tends towards the analytically determined singular strategy and then remains there.

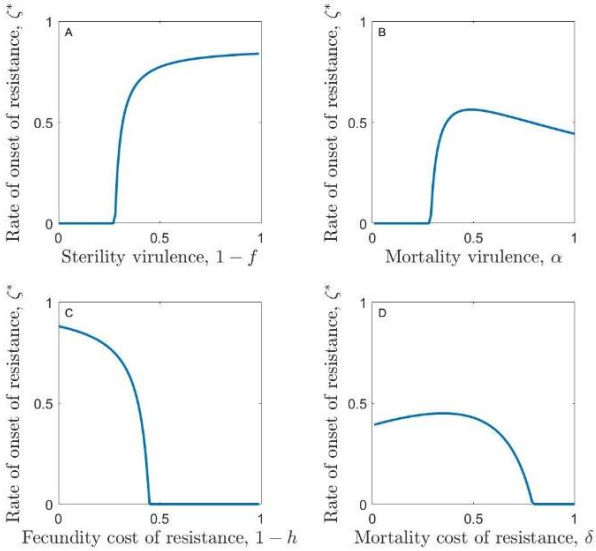

Fig. 2 Evolution of the rate of onset of resistance, ζ^*, in the case of constant costs of resistance. Parameters used are as in Table 1 except for $\beta = 1$, with (A) $1 - f = 0$, $1 - h = 0$ and $\alpha = 1$, (B) $1 - f = 0$, $1 - h = 0$ and $\delta = 0.25$, (C) $1 - f = 0.5$, $\alpha = 0$ and $\delta = 0$ and (D) $1 - h = 0.25$, $\alpha = 0$ and $\delta = 0$.

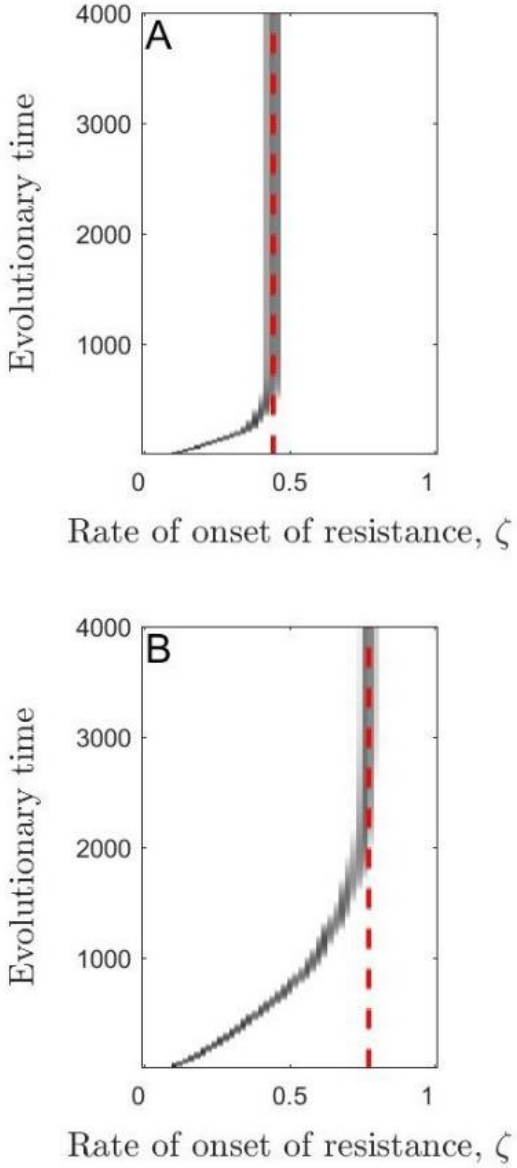

Fig. 3 Simulated trajectories of the evolution of the rate of onset of resistance over time. The red, dashed lines show the analytically determined values of the singular strategies. Parameters used are as in Table 1 except for $\beta = 1$, with (A) $1 - f = 0$, $\alpha = 1$, $1 - h = 0$ and $\delta = 0.25$ in the case of scenario (2) where the host pays a constant mortality cost when resistant and with (B) $1 - f = 0.5$, $\alpha = 0$, $1 - h = 0.25$ and $\delta = 0$ in the case of scenario (1) where the host pays a constant fecundity cost when resistant.

288 *NON-CONSTANT COSTS*

289 We now consider non-constant costs for the onset of resistance (cases 3-6 described in the
290 methods). When costs to reproduction or mortality accelerate (c_2^a,$c_2^b < 0$), the rate of onset
291 of resistance always evolves to a single, continuously stable strategy (CSS). When the costs
292 decelerate, there are more possible evolutionary outcomes; a single CSS (the trait evolves
293 towards this value and then remains there), repeller (the trait evolves away from this value,
294 tending towards zero, another singular strategy, or increasing indefinitely) or branching point
295 (the trait evolves towards this value but then undergoes disruptive selection and splits into
296 two sub-populations) may be observed, as well as a repeller above a branching point, a
297 branching point above a repeller or two repellers with a branching point in between
298 (parameter values for which these occur are shown in Fig. S1 and Fig. S2).

299

300 When the costs of having a faster onset of resistance are paid throughout the host's lifetime
301 (cases 3 & 4), we can show analytically that the singular strategy (or the uppermost singular
302 strategy if there is more than one) is always convergence stable (see *Supplementary*
303 *Materials*). When the costs of having a faster onset of resistance are only paid before the
304 onset of resistance (cases 5 & 6), this singular strategy is never convergence stable (see
305 *Supplementary Materials*). This means that, if the rate of onset of resistance is initially
306 sufficiently high, then it will increase indefinitely, in effect causing new-born hosts to become
307 resistant immediately. This is because the host is already paying a significant cost for a
308 reasonably fast onset of resistance. It is more beneficial for hosts to pay a slightly higher cost

309 for a shorter time (before it becomes resistant and stops paying the cost) than to pay a slightly
310 lower cost for a longer time.
311
312 Many factors influence whether the onset of resistance is fast or slow. However, certain
313 parameters have especially strong effects. We can see these effects most clearly if we
314 consider accelerating costs (c_2^a,$c_2^b < 0$), as each set of parameters produces a single
315 evolutionary endpoint which does not depend on the initial conditions. We find that the
316 virulence of the pathogen plays a particularly important role, with the fastest onset of
317 resistance evolving when the pathogen exerts weak mortality virulence and strong sterility
318 virulence (see Fig. 4; note that contours show the proportion of the host population which is
319 resistant to the pathogen). This is because strong mortality virulence reduces disease
320 prevalence by reducing the average duration of infection and so weakens selection for
321 resistance. Sterility virulence, in contrast, does not affect the average duration of infection
322 and so does not reduce disease prevalence but does greatly reduce host fitness. The fastest
323 onset of resistance therefore evolves when disease prevalence is high (low mortality
324 virulence) and when there is strong sterility virulence. Conversely, the rate of onset of
325 resistance tends to zero when both sterility and mortality virulence are negligible (because
326 the cost of infection is minimal) or when mortality virulence is very high (because disease
327 prevalence is so low that the host is unlikely to be exposed to the pathogen). The results
328 described above are qualitatively similar for decelerating trade-offs when the costs of
329 resistance are paid throughout the lifetime of the hosts and there is a single CSS.
330

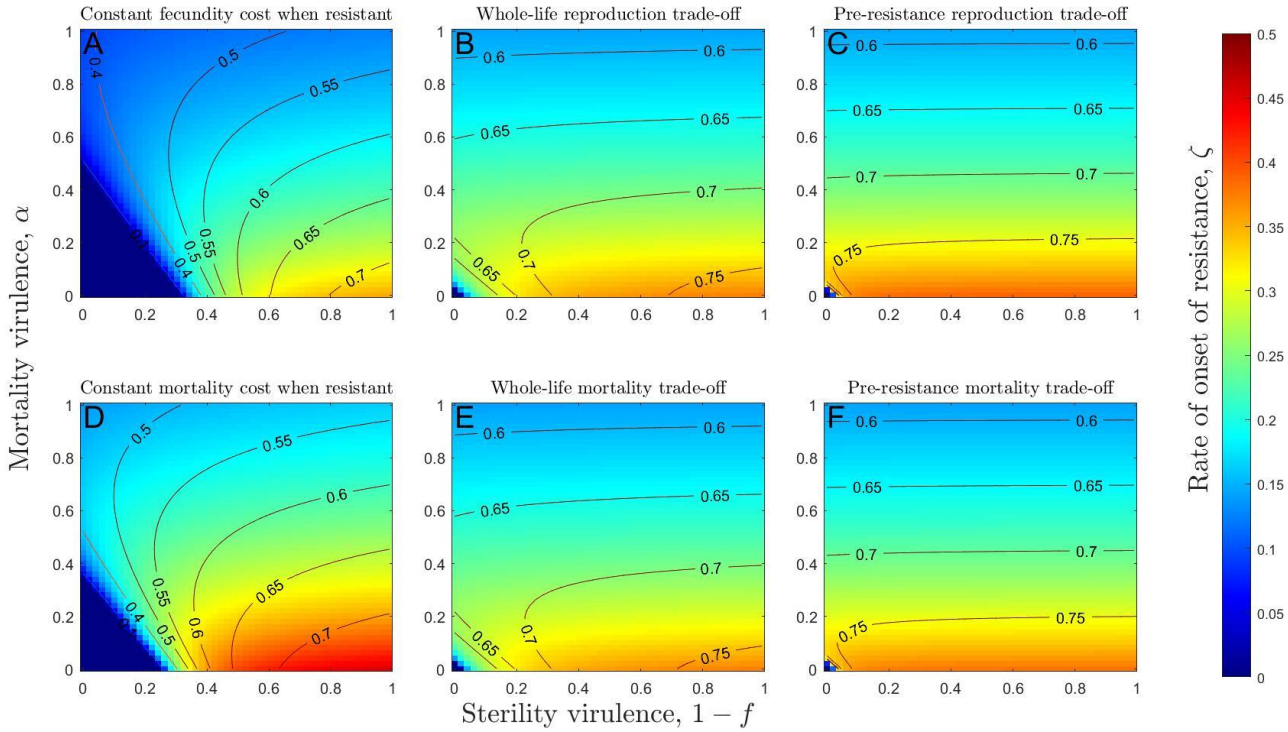

Fig. 4 Heatmaps showing the evolved rate of onset of resistance as mortality and sterility virulence vary and for qualitatively different trade-offs. Contours show the proportion of the host population that is resistant to the disease and so do not correspond to heatmap colours. The rate of onset of resistance is highest (red) when mortality virulence is low and sterility virulence is high (bottom right of each panel). Increasing sterility virulence (left to right within each panel) always causes the rate of onset of resistance to increase. Increasing mortality virulence (bottom to top within each panel) may also cause the rate of onset of resistance to rise and then fall for sufficiently low values of sterility virulence. These patterns are broadly consistent across all six trade-off scenarios (A-F). Parameters used are as in Table 1, except $c_2^a = c_2^b = -2$ (accelerating costs), $h = 0.75$ and $\delta = 0.25$, where applicable.

In general, greater pathogen transmissibility leads to the evolution of faster onset of resistance. However, as pathogen transmissibility gets very high, the rate of onset of resistance begins to fall (Fig. 5). This is because higher transmissibility corresponds to a lower average age on infection, and so it is more costly for a host to invest in a rapid onset of resistance (which will have to be very fast to take effect before the host becomes infected by a highly transmissible pathogen) than it is for the host to become infected with the pathogen (having not paid the costs of fast onset of resistance). This is consistent for both fecundity and mortality trade-offs (Fig. 5) of a variety of different strengths (values of c_1^a and c_1^b). As expected, greater costs (higher values of c_1^a and c_1^b) lead to the evolution of slower onset of resistance. Fecundity and mortality costs with the same proportional effects (e.g., a 50% increase in mortality or a 50% decrease in reproduction) have similar quantitative impacts on the rate of onset of resistance (Fig. 5).

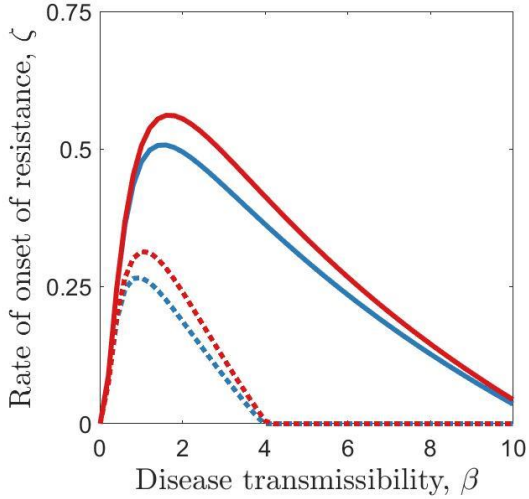

Fig. 5 The effect of disease transmissibility (β) on the rate of onset of resistance, when either a fecundity cost (blue curves) or a mortality cost (red curves) is paid throughout the lifetime of the host (scenarios 3 and 4). The qualitative effects of transmissibility are the same whether the costs of fast onset of resistance are low (c_1^a or $c_1^b = 0.3$; solid) or high (c_1^a or $c_1^b = 0.8$; dotted). Parameters used are as in Table 1 with $c_2^a = -2$, $c_2^b = -2$, $f = 0.5$ and $\alpha = 0$.

DIVERSIFICATION

The host population may diversify through evolutionary branching when the costs are decelerating (c_2^a,$c_2^b > 0$; see Fig. 6). Evolutionary branching leads to one sub-population with a very high rate of onset of resistance (ζ large) that increases indefinitely (see *Supplementary Materials)*, until these individuals effectively develop resistance immediately after birth, and another sub-population with a very low rate of onset of resistance ($\zeta \approx 0$), with these individuals unlikely ever to become resistant given the typical lifespan of the host. When costs are paid throughout the lifetime of the host, these costs must be strongly decelerating ($c_2^{\mathrm{i}} \gg 0$) for branching to occur (Fig. 7A). When costs are paid before the onset of resistance, branching only occurs for weakly decelerating costs (c_2^i small but positive). The latter branching points always sit below repellers and so the population will only branch if the initial rate of onset of resistance is sufficiently low (otherwise, the rate of onset of resistance will increase indefinitely; Fig. 7B).

When costs of having a faster onset of resistance are paid throughout the lifetime of the host, branching is most commonly observed when the baseline reproduction rate (a_0), disease transmissibility (β) and sterility virulence ($1 - f$) are high, baseline mortality (b_0) and the strength of trade-offs (c_1^a or c_1^b) are low and mortality virulence (α) is intermediate (Fig. S1). When costs of fast onset of resistance are paid only before the onset of resistance, branching is most common when the baseline reproduction rate (a_0), disease transmissibility (β), mortality virulence (α), baseline mortality rate (b_0) and strength of the mortality trade-off (c_1^b) take intermediate values, when sterility virulence ($1 - f$) is high and when the strength of the reproduction trade-off (c_1^a) is low (Fig. S2).

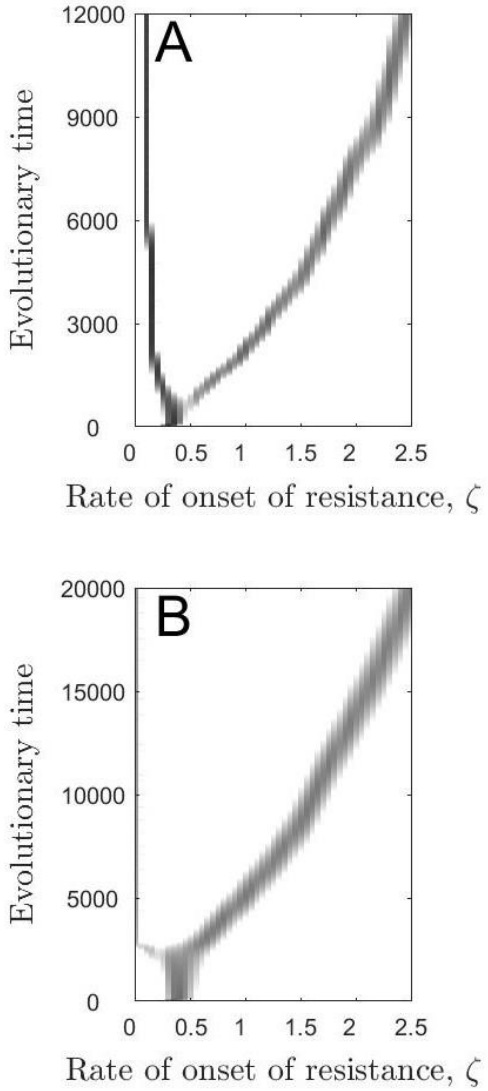

Fig. 6 Simulated trajectories of the evolution of the rate of onset of resistance over time. (A) When costs of fast onset of resistance are paid throughout the lifetime of the host, the lower branch often tends towards a low, non-zero value whereas the upper branch goes to infinity. (B) When costs are paid only before the onset of resistance, the lower branch goes to zero whereas the upper branch goes to infinity. Parameters used are as in Table 1 with $1 - f = 0.5$ and $\alpha = 0$. We also use (a) $c_2^a = 5$ and (b) $c_2^a = 1$ to generate branching points.

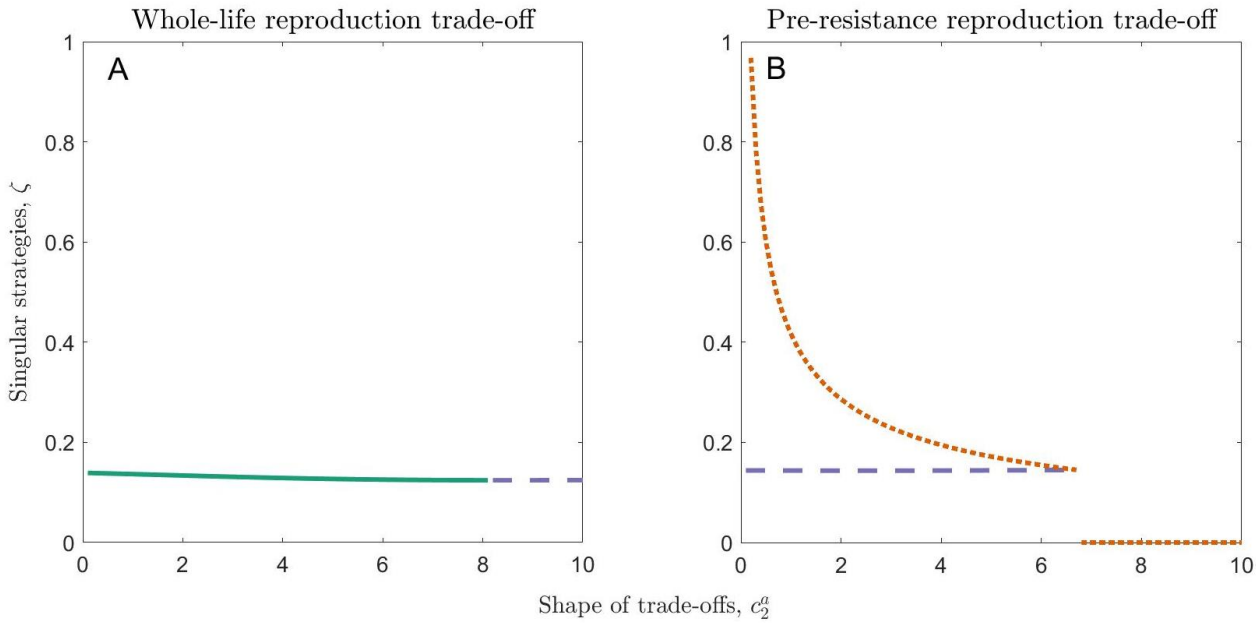

Fig. 7 The effect of the shape of trade-offs on the incidence of branching points for different timings of costs. Continuously stable strategies are shown in green (solid), repellers are shown in orange (dotted) and branching points are shown in purple (dashed). (A) When costs of fast onset of resistance are paid throughout the host's lifetime, costs must be strongly decelerating (high c_2^a) for branching to occur. (B) When costs are paid only before the onset of resistance, they must be weakly decelerating for branching to occur. Parameters used are as in Table 1 with $1 - f = 0$ and $\alpha = 1$.

396 **DISCUSSION**

397 Recent theory has shown how trade-offs and life-history traits combine to shape the
398 evolution of age-specific resistance (Ashby and Bruns 2018; Buckingham et al. 2023). Here,
399 we have shown how the average age at which hosts become resistant $(1/\zeta)$ evolves,
400 depending on how and when costs of resistance are paid (costs only paid before or after the
401 onset of resistance, or throughout the host's lifetime). Our key findings are that (1) the rate
402 of onset of resistance peaks for low mortality virulence, high sterility virulence and
403 intermediate pathogen transmissibility; (2) when costs of resistance are paid throughout the
404 lifetime of the host (or only after the onset of resistance) the onset of resistance typically
405 evolves to a stable, intermediate rate whereas when costs are paid only before the onset of
406 resistance, hosts are more likely to evolve no onset of resistance or an extremely fast onset
407 of resistance (depending on parameters and initial conditions); and (3) pathogens may drive
408 host diversification in the rate of onset of resistance.

409

410 Hosts evolve the fastest onset of resistance when pathogens cause high sterility virulence,
411 low mortality virulence and intermediate transmissibility. Such pathogens induce the highest
412 selection for resistance because they are able to maintain a significant density within the host
413 population but also cause a large fitness cost to their hosts. Given a fixed, low-to-intermediate
414 level of sterility virulence, an intermediate level of mortality virulence leads to the fastest rate
415 of onset of resistance, but we have found that the combination of high sterility virulence and
416 low mortality virulence leads to the fastest rate of onset overall in our model. This could be
417 tested by determining the level of sterility or mortality inflicted by pathogens against which
418 hosts experience a particularly early onset of resistance. We tentatively hypothesise that such

419 pathogens would be more likely to inflict high levels of sterility virulence than high levels of
420 mortality virulence.
421
422 The life-stage at which trade-offs occur has a significant effect on the evolution of the rate of
423 onset of resistance. It is well established that the magnitude and shape of trade-offs, as well
424 as the life-history traits involved, are critical to the evolution of various traits, including
425 resistance (Kisdi 2006; Ashby and Bruns 2018; Buckingham et al. 2023). We have shown that
426 the life-stage at which trade-offs act also drastically alters the evolutionary outcome for the
427 rate of onset of resistance. An intermediate rate of onset of resistance is most likely to evolve
428 when costs are paid throughout the host's lifetime whereas very fast or very slow rates of
429 onset, or dimorphism, are more likely if the costs are paid predominantly during the
430 development of resistance. Very little empirical work has considered age-specific costs of
431 resistance. However, we tentatively predict that organisms with very fast, very slow or
432 polymorphic onset of resistance are most likely to experience costs which only act early in
433 life.
434
435 When the rate of onset of resistance diversifies, it results in a fully (or almost fully) susceptible
436 subpopulation coexisting with a fully resistant subpopulation. Such dimorphic populations,
437 where some individuals are effectively resistant throughout their lives and others are always
438 (or almost always) susceptible, are often seen in real, biological systems (Parker 1988; Jarosz
439 and Burdon 1990; Wayne et al. 1996; Turkington et al. 2019). This evolutionary endpoint is
440 very similar to classical models of host resistance evolution which result in dimorphic host
441 populations with resistant and susceptible phenotypes (Antonovics and Thrall 1994; Boots
442 and Haraguchi 1999). However, the mechanism for arriving at this endpoint is very different

443 in our model. We have shown that this evolutionary endpoint can also arise through evolution
444 of the rate of onset of resistance, where all hosts may transition from being susceptible to
445 resistant as they age, rather than resistance/susceptibility being fixed before birth. This
446 suggests that there may be an alternative evolutionary history of populations which are
447 dimorphic in disease resistance, with the rate of onset of resistance diverging rather than the
448 level of resistance. If this is indeed the case in some species, then one would expect
449 "susceptible" hosts typically to have resistance genes that are suppressed rather than absent.
450 However, it is possible that once the rate of onset of resistance approaches zero, resistance
451 genes are lost rather than remaining suppressed. Experimental evolution may offer another
452 path to testing this result by always selecting for hosts that have an earlier or later onset of
453 resistance, thus validating whether a similar evolutionary endpoint can be achieved through
454 the evolution of the timing of onset of resistance.
455
456 This paper constitutes an initial investigation into the theoretical consequences of the
457 evolution of the age of onset of disease resistance. As such, we have considered a simple
458 model which allows us to determine some possible outcomes of this evolutionary process.
459 There are many additions and adjustments which could make this a more realistic model for
460 specific biological systems. For example, we only focus on host evolution, but changes in
461 patterns of host resistance are likely to affect pathogen evolution as well (Buckingham and
462 Ashby 2022). We have also only considered the case of a disease with no recovery, as recovery
463 would require differential handling of infection-acquired immunity or individuals who
464 experience the onset of resistance while infected. Although this is a reasonable assumption
465 for some host-pathogen interactions where recovery is negligible, such as systemic infections
466 in plants, invertebrates, and bacteria (Ebert 2008; Abatángelo et al. 2017; Bruns et al. 2017),

467 a more general development of the theory here would require careful consideration of how
468 recovery affects immunity and post-infection sequelae. Recovery could be incorporated into
469 our model in several different ways, depending on the mechanisms underlying recovery and
470 the onset of resistance. For example, one could allow infected individuals to return to the
471 susceptible class, but then the rate of onset of resistance takes on a different interpretation,
472 as the process of becoming resistant is effectively turned off and on again as the host becomes
473 infected and then later recovers. Alternatively, one could allow infected individuals to move
474 into the resistant class if the onset of resistance occurred while they were infected, but would
475 this process cause the host to clear the infection or just become resistant to re-infection?
476 These scenarios cover rather different biological scenarios and so deserve careful
477 consideration in future work.
478
479 For simplicity, we assumed that hosts experience a rapid onset of disease resistance (i.e.
480 transitioning from susceptible to resistant in a short space of time). Rapid changes from low
481 to high levels of resistance have been observed to occur in a number of biological systems.
482 For example, Kurtis *et al.* showed that malaria (*Plasmodium falciparum*) resistance increases
483 significantly in boys during puberty (between ages 15 and 20) which is relatively quick in
484 relation to their lifespan (Kurtis et al. 2001). Critchlow *et al.* found that flour beetles (*Tribolium*
485 *castaneum*) express more antimicrobial proteins as pupae than as larvae, resulting in a
486 sudden increase in resistance during metamorphosis (Critchlow et al. 2019). Bruns *et al.*
487 showed that alpine carnations (*Dianthus pavonius*) are far more resistant to anther-smut
488 disease (*Microbotryum*) as adults than during the seedling stage, suggesting a rapid onset of
489 resistance at maturation (Bruns et al. 2017). Farber & Mundt found that wheat plants
490 (*Triticum aestivum*) significantly increase their resistance to stripe rust (*Puccinia striiformis*)

491 between the ages of 3 and 5 weeks (with an average lifespan of 20 to 25 weeks) (Farber and
492 Mundt 2017). As none of these changes in resistance occur instantaneously, however, our
493 model could be extended to include not just completely susceptible and completely resistant
494 stages, but also an additional stage in which resistance is intermediate, to represent the
495 period during which these organisms are developing resistance. In cases where this stage is
496 very short, our model should provide a good approximation.
497
498 However, some species do experience a very rapid onset of complete resistance, as in our
499 model. For example, nucleopolyhedrovirus can only infect gypsy moths at the larval stage,
500 with moths becoming fully resistant to the virus at the point of maturation (Elderd et al. 2008).
501 This system closely mirrors our model and so may be a good candidate for empirical testing
502 of the predictions made in this paper. Alternatively, anther-smut infections of Alpine
503 carnations have previously been used as a model system for investigating age-specific
504 differences in resistance (Bruns 2019). Seedlings are often significantly more susceptible to
505 infection than adult plants and so this may provide an alternative system for testing our
506 predictions empirically. To our knowledge, no empirical papers have sought to quantify the
507 precise timing of the onset of resistance, or how this relates to characteristics of the disease.
508
509 Our model also assumes that hosts are born completely susceptible and later in life become
510 fully resistant. Although large increases in the level of disease resistance may occur during a
511 host's lifetime, in many cases the host may shift between quantitative levels of resistance
512 rather than qualitative resistance (Kurtis et al. 2001; Farber and Mundt 2017; Bruns et al.
513 2017; Critchlow et al. 2019). In future, our model should be extended to explore the timing
514 of shifts between different levels of partial resistance. There are also empirical examples of

515 reductions in resistance with host age and so the timing of the loss of resistance could be
516 considered. For instance, Klemme *et al.* found that Atlantic salmon (*Salmo salar*) experience
517 a reduction in resistance to a trematode (*Diplostomum pseudospathaceum*) when they
518 mature from resident to migrant life-stages (Klemme et al. 2022). Similarly, species can also
519 experience multiple changes in resistance during their lifetime. For instance, Garbutt *et al.*
520 found that disease resistance in *Daphnia magna* increases as hosts mature into adults but
521 subsequently decreases after their reproductive prime (Garbutt et al. 2014). A second change
522 in resistance could be incorporated into our model by allowing resistant individuals to move
523 into an older-age susceptible class, from which they could again become infected. This might
524 reduce selection for a fast onset of resistance as the benefits of being resistant would be felt
525 for a shorter time.
526
527 Overall, we have shown how the rate of onset of resistance evolves in response to variation
528 in the nature of associated trade-offs and disease characteristics, potentially leading to host
529 diversification and the same evolutionary endpoint as classical models of resistance
530 evolution. Our model therefore provides an alternative explanation for the origin of
531 dimorphism in host resistance.
532

533 **DATA AVAILABILITY**

534 The source code generated and analysed during the current study is available in the GitHub
535 repository at: github.com/ecoevotheory/Buckingham_and_Ashby_2022b
536

537 **REFERENCES**

538 Abatángelo V, Peressutti Bacci N, Boncompain CA, et al (2017) Broad-range lytic
539 bacteriophages that kill Staphylococcus aureus local field strains. PLoS One 12:.
540 https://doi.org/10.1371/journal.pone.0181671

541 Altizer S, Davis AK, Cook KC, Cherry JJ (2004) Age, sex, and season affect the risk of
542 mycoplasmal conjunctivitis in a southeastern house finch population. Can J Zool 82:755–
543 763. https://doi.org/10.1139/Z04-050

544 Antonovics J, Thrall PH (1994) The cost of resistance and the maintenance of genetic
545 polymorphism in host-pathogen systems. Proceedings of the Royal Society B 257:105–
546 110

547 Apolloni A, Poletto C, Colizza V (2013) Age-specific contacts and travel patterns in the spatial
548 spread of 2009 H1N1 influenza pandemic. BMC Infect Dis 13:

549 Armitage SAO, Boomsma JJ (2010) The effects of age and social interactions on innate
550 immunity in a leaf-cutting ant. J Insect Physiol 56:780–787.
551 https://doi.org/10.1016/j.jinsphys.2010.01.009

552 Ashby B, Bruns E (2018) The evolution of juvenile susceptibility to infectious disease.
553 Proceedings of the Royal Society B 285:. https://doi.org/10.1098/rspb.2018.0844

554 Baird JK (1998) Age-dependent characteristics of protection v. susceptibility to Plasmodium
555 falciparum. Ann Trop Med Parasitol 92:367–390

556 Bartlett LJ, Wilfert L, Boots M (2018) A genotypic trade-off between constitutive resistance to
557 viral infection and host growth rate. Evolution (N Y) 72:2749–2757.
558 https://doi.org/10.1111/evo.13623

559 Biere A, Antonovics J (1996) Sex-specific costs of resistance to the fungal pathogen ustilago
560 violacea (microbotryum violaceum) in silene alba. Evolution (N Y) 50:1098–1110

561 Boots M, Haraguchi Y (1999) The evolution of costly resistance in host-parasite systems.
562 American Naturalist 153:
563 Bruns E (2019) Effects of host lifespan on the evolution of age-specific resistance: a case study
564 of anther-smut disease on wild carnations. In: Wilson K, Fenton A, Tompkins D (eds)
565 Wildlife Disease Ecology. Cambridge University Press, Cambridge, pp 161–186
566 Bruns EL, Antonovics J, Carasso V, Hood M (2017) Transmission and temporal dynamics of
567 anther-smut disease (Microbotryum) on alpine carnation (Dianthus pavonius). Journal of
568 Ecology 105:1413–1424. https://doi.org/10.1111/1365-2745.12751
569 Buckingham LJ, Ashby B (2022) Coevolutionary theory of hosts and parasites. J Evol Biol
570 35:205–224. https://doi.org/10.1111/jeb.13981
571 Buckingham LJ, Bruns EL, Ashby B (2023) The evolution of age-specific resistance to infectious
572 disease. Proceedings of the Royal Society B 290:.
573 https://doi.org/10.1098/rspb.2022.2000
574 Carlsson-Graner U, Thrall PH (2006) The impact of host longevity on disease transmission:
575 host-pathogen dynamics and the evolution of resistance. Evol Ecol Res 8:659–675
576 Chaplin JF, Mann TJ (1978) Evaluation of tobacco mosaic resistance factor transferred from
577 burley to flue-cured tobacco. Journal of Heredity 69:175–178
578 Clark J, Garbutt JS, McNally L, Little TJ (2017) Disease spread in age structured populations
579 with maternal age effects. Ecol Lett 20:445–451. https://doi.org/10.1111/ele.12745
580 Critchlow JT, Norris A, Tate AT (2019) The legacy of larval infection on immunological
581 dynamics over metamorphosis. Philosophical Transactions of the Royal Society B 374:.
582 https://doi.org/10.1098/rstb.2019.0066

583 Develey-Rivière MP, Galiana E (2007) Resistance to pathogens and host developmental stage:
584 A multifaceted relationship within the plant kingdom. New Phytologist 175:405–416.
585 https://doi.org/10.1111/j.1469-8137.2007.02130.x
586 Donnelly R, White A, Boots M (2015) The epidemiological feedbacks critical to the evolution
587 of host immunity. J Evol Biol 28:2042–2053. https://doi.org/10.1111/jeb.12719
588 Duca CJ (1948) Age specific susceptibility to tuberculosis; experiments on guinea pigs and rats.
589 Am Rev Tuberc 57:389–399
590 Ebert D (2008) Host-parasite coevolution: Insights from the Daphnia-parasite model system.
591 Curr Opin Microbiol 11:290–301. https://doi.org/10.1016/j.mib.2008.05.012
592 Elderd BD, Dushoff J, Dwyer G (2008) Host-pathogen interactions, insect outbreaks, and
593 natural selection for disease Resistance. American Naturalist 172:829–842.
594 https://doi.org/10.1086/592403
595 Farber DH, Mundt CC (2017) Effect of plant age and leaf position on susceptibility to wheat
596 stripe rust. Phytopathology 107:412–417. https://doi.org/10.1094/PHYTO-07-16-0284-
597 R
598 Francis J (1961) The effect of age on the susceptibility of guinea pigs to tuberculosis. Tubercle
599 42:333–336
600 Garbutt JS, O'Donoghue AJP, McTaggart SJ, et al (2014) The development of pathogen
601 resistance in Daphnia magna: Implications for disease spread in age-structured
602 populations. Journal of Experimental Biology 217:3929–3934.
603 https://doi.org/10.1242/jeb.111260
604 Geritz SAH, Kisdi É, Meszéna G, Metz JAJ (1998) Evolutionarily singular strategies and the
605 adaptive growth and branching of the evolutionary tree. Evol Ecol 12:35–57

606 Glynn JR, Moss PAH (2020) Systematic analysis of infectious disease outcomes by age shows
607 lowest severity in school-age children. Sci Data 7:. https://doi.org/10.1038/s41597-020-
608 00668-y
609 Green TJ, Vergnes A, Montagnani C, de Lorgeril J (2016) Distinct immune responses of juvenile
610 and adult oysters (Crassostrea gigas) to viral and bacterial infections. Vet Res 47:.
611 https://doi.org/10.1186/s13567-016-0356-7
612 Hurford A, Cownden D, Day T (2010) Next-generation tools for evolutionary invasion analyses.
613 J R Soc Interface 7:561–571. https://doi.org/10.1098/rsif.2009.0448
614 Izhar R, Ben-Ami F (2015) Host age modulates parasite infectivity, virulence and reproduction.
615 Journal of Animal Ecology 84:1018–1028. https://doi.org/10.1111/1365-2656.12352
616 Jarosz AM, Burdon JJ (1990) Predominance of a single major gene for resistance to
617 Phakopsora pachyrhizi in a population of Glycine argyrea. Heredity (Edinb) 64:347–353
618 Karasov TL, Chae E, Herman JJ, Bergelson J (2017) Mechanisms to mitigate the trade-off
619 between growth and defense. Plant Cell 29:666–680.
620 https://doi.org/10.1105/tpc.16.00931
621 Kisdi É (2006) Trade-off geometries and the adaptive dynamics of two co-evolving species.
622 Evol Ecol Res 8:959–973
623 Klemme I, Debes PV, Primmer CR, et al (2022) Host developmental stage effects on parasite
624 resistance and tolerance. American Naturalist. https://doi.org/10.1086/721159
625 Kubi C, van den Abbeele J, de Deken R, et al (2006) The effect of starvation on the
626 susceptibility of teneral and non-teneral tsetse flies to trypanosome infection. Med Vet
627 Entomol 20:388–392. https://doi.org/10.1111/j.1365-2915.2006.00644.x

628 Kurtis JD, Mtalib R, Onyango FK, Duffy PE (2001) Human resistance to Plasmodium falciparum
629 increases during puberty and is predicted by dehydroepiandrosterone sulfate levels.
630 Infect Immun 69:123–128. https://doi.org/10.1128/IAI.69.1.123-128.2001
631 Miller ME (1983) Relationships between onion leaf age and susceptibility to Alternaria porri.
632 Plant Dis 67:
633 Miller MR, White A, Boots M (2007) Host life span and the evolution of resistance
634 characteristics. Evolution (N Y) 61:2–14. https://doi.org/10.1111/j.1558-
635 5646.2007.00001.x
636 Panter SN, Jones DA (2002) Age-related resistance to plant pathogens. Adv Bot Res 38:251–
637 280
638 Parker MA (1988) Polymorphism for disease resistance in the annual legume Amphicarpaea
639 bracteata. Heredity (Edinb) 60:27–31
640 Sait SM, Begon M, Thompson DJ (1994) The influence of larval age on the response of Plodia
641 interpunctella to a Granulosis virus. J Invertebr Pathol 63:107–110
642 Simons MD (1979) Influence of genes for resistance to Puccinia coronata from Avena sterilis
643 on yield and rust reaction of cultivated oats. Phytopathology 69:450–452
644 Susi H, Laine AL (2015) The effectiveness and costs of pathogen resistance strategies in a
645 perennial plant. Journal of Ecology 103:303–315. https://doi.org/10.1111/1365-
646 2745.12373
647 Tian D, Traw MB, Chen JQ, et al (2003) Fitness costs of R-gene-mediated resistance in
648 Arabidopsis thaliana. Nature 423:74–77. https://doi.org/10.1038/nature01575
649 Turkington CJR, Morozov A, Clokie MRJ, Bayliss CD (2019) Phage-resistant phase-variant sub-
650 populations mediate herd immunity against bacteriophage invasion of bacterial meta-
651 populations. Front Microbiol 10:. https://doi.org/10.3389/fmicb.2019.01473

652 Wayne ML, Contamine D, Kreitman M (1996) Molecular population genetics of ref(2)P, a locus
653 which confers viral resistance in Drosophila. Mol Biol Evol 13:191–199
654 Zuckerman A, Yoeli M (1954) Age and sex as factors influencing Plasmodium berghei
655 infections in intact and splenectomized rats. Journal of Infectious Diseases 94:225–236
656