The evolution of age-specific resistance to infectious disease

Lydia J. Buckingham[1,2,*], Emily L. Bruns[3] and Ben Ashby[1,2,4]

1. Department of Mathematical Sciences, University of Bath, Bath, UK
2. Milner Centre for Evolution, University of Bath, Bath, UK
3. Department of Biology, University of Maryland, College Park, MD 20742, USA
4. Department of Mathematics, Simon Fraser University, Burnaby, BC, Canada

*Corresponding author: ljb74@bath.ac.uk

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

ABSTRACT

Innate, infection-preventing resistance often varies between host life-stages. Juveniles are more resistant than adults in some species, whereas the converse pattern is true in others. This variation cannot always be explained by prior exposure or physiological constraints and so it has been hypothesised that trade-offs with other life-history traits may be involved. However, little is known about how trade-offs between various life-history traits and resistance at different life-stages affect the evolution of age-specific resistance. Here, we use a mathematical model to explore how trade-offs with natural mortality, reproduction and maturation combine to affect the evolution of resistance at different life-stages. Our results show that certain combinations of trade-offs have substantial effects on whether adults or juveniles are more resistant, with trade-offs between juvenile resistance and adult reproduction inherently more costly than trade-offs involving maturation or mortality (all else being equal), resulting in consistent evolution of lower resistance at the juvenile stage even when infection causes a lifelong fecundity reduction. Our model demonstrates how the differences between patterns of age-structured resistance seen in nature may be explained by variation in the trade-offs involved and our results suggest conditions under which trade-offs tend to select for lower resistance in juveniles than adults.

INTRODUCTION

Immunity to infectious diseases typically varies across the lifespan of the host, which has significant consequences for host health and disease transmission [1–3]. Variation in different types of immunity (e.g. innate, adaptive, infection-preventing resistance, tolerance) with host age has been observed in many taxa, including plants [4–7], invertebrates [8–12] and vertebrates [13–15], including humans [16–18]. Yet the nature of age-specific immunity varies widely, with adults better protected than juveniles in many [5–10,12–17] but not all cases [4,11,12,18]. Differences in age-related patterns of host immunity exist both within and between species [19–22], but the reasons behind these diverse patterns are not always well understood. In particular, we lack a detailed understanding of how age-specific host defences against infectious disease can evolve.

Variation in host immunity with age may occur due to a variety of mechanisms, including immune priming [23,24]; adaptive immunity [25,26]; the loss of maternal antibodies in mammals [27,28]; senescence [29,30]; the accumulation of pathogenesis-related (PR) proteins and activation of the salicylic acid pathway in plants [6]; dilution of pathogen effects due to changes in body size in insects [8]; differences in transcriptional responses to infection in molluscs [12] and changes in the ratio of naïve to memory T-cells in humans [16]. However, in many cases, the mechanisms which cause differences in juvenile and adult immunity are unknown or poorly understood [4,5,7,9–11,13–15,17,18]. When immunity depends on prior exposure, juveniles may be less resistant to infection simply because they have yet to experience pathogens that adults have previously encountered (although juveniles may be more resistant to infection than adults if immunity wanes over time). Whilst variation in prior exposure can contribute to patterns of age-specific immunity, especially in vertebrates, it

cannot fully explain observed differences in juvenile and adult immunity. Such differences also exist, for instance, in species which rely solely or primarily on innate, rather than acquired, immunity [5–10,12] and when a population encounters a novel pathogen to which neither adults nor juveniles have acquired immunity [31].

From an evolutionary perspective, one might expect that innate (non-adaptive) defences against infectious diseases should always be greater in juveniles than in adults, since infection at a young age could lead to death or sterilisation before reproduction can occur [32]. However, this is not always the case. Trivially, physiological constraints may constrain juvenile defences in some species, preventing juveniles from evolving stronger protection against parasitism or herbivory [33,34]. However, artificial selection for increased innate immunity [35–37] and evidence of polymorphism in the level of immunity in natural populations [19–22,38–40] have shown that many hosts do not possess the maximum possible level of juvenile immunity. Hence physiological constraints on juvenile defences do not provide a full explanation. Differences in disease outcomes may also drive selection for age-specific immunity, for example, if a disease causes higher virulence in adults than in juveniles (see appendix D of [41]). However, adult immunity has been found to be higher than juvenile immunity in systems in which the disease has the same effect on susceptible hosts of all life stages [7] and so this cannot provide a complete explanation either.

An alternative evolutionary explanation for differences in juvenile and adult immunity is that host defences trade off with other life-history traits. For example, increased juvenile immunity may require resource allocation away from growth and development, resulting in a negative relationship between juvenile immunity and maturation, mortality or future

reproduction. Similarly, adult immunity may require resources to be diverted away from reproduction or may be associated with higher mortality from other causes. There is empirical evidence for trade-offs between reproduction [42,43] or growth [42–45] and host immunity in plants and invertebrates, though little data is available on age-specific effects. The impact of different trade-offs on the evolution of immunity across the host lifespan has yet to be determined theoretically.

To date, theoretical models have explored the spread of disease in age-structured populations [3] or the evolution of immunity in populations with no age structure [46–50]. However, the evolution of innate, infection-preventing resistance at different life stages has received little attention. As an exception, Ashby & Bruns [51] explored the evolution of (innate) juvenile susceptibility to infection in a population with fixed adult susceptibility, under the assumption that juveniles are always at least as susceptible as adults. They found that juveniles may evolve higher susceptibility than adults under a wide range of conditions, but the difference was most extreme when hosts had very long or very short lifespans. Here, we build on these findings by allowing juvenile and adult resistance to evolve simultaneously and independently and by exploring how a range of trade-offs with different life-history traits affect the evolution of resistance across the host lifespan. As in Ashby & Bruns' paper [51], we consider the specific case where resistance prevents the onset of infection (as opposed to resistance which limits or eliminates infection). We focus our analysis on trade-offs with maturation, mortality and reproduction, along with variation in pathogen traits, specifically the strength and type of virulence, and transmissibility. We show that juvenile resistance is most costly when it trades off with reproduction later in life, resulting in lower juvenile resistance than evolves under other trade-offs and also lower juvenile than adult resistance

100 (assuming equal strength of trade-offs). Furthermore, we show that a trade-off between
101 juvenile resistance and reproduction can cause juvenile resistance to be lower than adult
102 resistance even when infection causes a permanent reduction in fecundity.
103
104 **METHODS**
105 *MODEL DESCRIPTION*
106 We expand the model described by Ashby and Bruns [51] to explore the evolution of innate,
107 infection-preventing resistance at juvenile (J) and adult (A) stages, in a well-mixed, asexual
108 host population (see Fig. 1a for a model schematic and Table 1 for a full list of parameters and
109 variables). Let S_i and I_i be the densities of susceptible and infected hosts respectively at life
110 stage $i \in \{J, A\}$, giving a total host population density of $N = S_J + S_A + I_J + I_A$. Juveniles
111 mature into adults at rate $g > 0$ and adults reproduce at a maximum rate $a > 0$ (juveniles
112 do not reproduce) subject to density-dependent competition given by $q > 0$. Juvenile and
113 adult hosts die naturally at rates b_J and b_A. Disease transmission is assumed to be density-
114 dependent, with stage-dependent transmission rates, $\beta_i(r_i) = \beta_0(1 - r_i)$, where $\beta_0 > 0$ is
115 the baseline transmission rate and r_i is host resistance at life stage i (hence a host's level of
116 resistance determines the rate at which it becomes infected). Hosts are fully susceptible to
117 infection when $r_i = 0$ and fully resistant when $r_i = 1$. The force of infection (rate at which
118 susceptible hosts become infected) experienced at life stage i is $\lambda_i(r_i) = \beta_i(r_i)(I_J + I_A)$. We
119 consider two types of virulence; infected hosts may either experience sterility virulence equal
120 to $1 - f$, where $0 \leq f \leq 1$ is the reduction in fecundity when infected, or mortality virulence
121 given by $\alpha > 0$, the disease-associated mortality rate. We seek to compare the effects of
122 mortality and sterility virulence and so we only allow the pathogen to exhibit one type of

123 virulence at a time. We also assume that there is no recovery from infection, so that we can
124 explore the effects of a lifelong reduction in fecundity on the evolution of juvenile resistance.
125
126 In a monomorphic population, the population dynamics are described by the following set of
127 ordinary differential equations:

$$\frac{dS_J}{dt} = a(1-qN)(S_A + fI_A) - \left(b_J + g + \lambda_J(r_J)\right)S_J \quad (1a)$$

$$\frac{dS_A}{dt} = gS_J - \left(b_A + \lambda_A(r_A)\right)S_A \quad (1b)$$

$$\frac{dI_J}{dt} = \lambda_J(r_J)S_J - (b_J + g + \alpha)I_J \quad (1c)$$

$$\frac{dI_A}{dt} = gI_J + \lambda_A(r_A)S_A - (b_A + \alpha)I_A \quad (1d)$$

128 The disease-free equilibrium is given by:

$$S_J^* = \frac{b_A\left(ag - b_A(b_J + g)\right)}{ag(b_J + g)} \quad (2a)$$

$$S_A^* = \frac{ag - b_A(b_J + g)}{a(b_J + g)} \quad (2b)$$

129 and is stable provided $ag > b_A(b_J + g)$ and

$$R_0 = \beta_0\left(ag - b_A(b_J + g)\right)\frac{(1-r_J)(b_A + \alpha + g)b_A + (1-r_A)g(b_J + \alpha + g)}{ag(b_A + \alpha)(b_J + g)(b_J + g + \alpha)} < 1 \quad (3)$$

130 where R_0 is the basic reproductive ratio of the pathogen (see *Supplementary Materials* for
131 derivation). The disease can spread when $R_0 > 1$, in which case there is a stable, endemic
132 (non-trivial) equilibrium for the parameters used in our analysis (this can be shown
133 numerically, but there is no analytic expression for the endemic equilibrium; see
134 *Supplementary Materials*).
135

In the absence of trade-offs, both juvenile and adult resistance will evolve to their maximum possible values $(r_J, r_A = 1)$. We therefore assume that resistance at each life stage trades off with another life-history trait. We consider a variety of trade-offs, with juvenile resistance either trading off with the maturation rate (g), reproduction rate (a) or juvenile mortality rate (b_J) and adult resistance with either the reproduction rate (a) or adult mortality rate (b_A). Biologically, these trade-offs assume that resistance requires hosts to divert resources from growth (slower maturation), reproduction (fewer offspring) or survival-related traits (higher mortality). We assume that resistance at each life history stage only trades off with one other life-history trait. Specifically, we define the following trade-offs (when present) for the maturation rate,

$$g(r_J) = g_0\left(1 - \frac{c_1^{\mathrm{J}}\left(1 - e^{c_2^{\mathrm{J}} r_J}\right)}{1 - e^{c_2^{\mathrm{J}}}}\right) \tag{4a}$$

the reproduction rate, when it trades off with either juvenile $(\mathrm{i} = \mathrm{J})$ or adult $(\mathrm{i} = \mathrm{A})$ resistance

$$a(r_i) = a_0\left(1 - \frac{c_1^{\mathrm{i}}\left(1 - e^{c_2^{\mathrm{i}} r_i}\right)}{1 - e^{c_2^{\mathrm{i}}}}\right) \tag{4b}$$

or with both juvenile and adult resistance,

$$a(r_J, r_A) = a_0\left(1 - \frac{c_1^{\mathrm{J}}\left(1 - e^{c_2^{\mathrm{J}} r_J}\right)}{1 - e^{c_2^{\mathrm{J}}}}\right)\left(1 - \frac{c_1^{\mathrm{A}}\left(1 - e^{c_2^{\mathrm{A}} r_A}\right)}{1 - e^{c_2^{\mathrm{A}}}}\right) \tag{4c}$$

and the mortality rate

$$b_i(r_i) = b_0\left(1 + \frac{c_1^{\mathrm{i}}\left(1 - e^{c_2^{\mathrm{i}} r_i}\right)}{1 - e^{c_2^{\mathrm{i}}}}\right) \tag{4d}$$

where g_0, a_0, and b_0 are baseline maturation, reproduction and mortality rates (assuming equal baseline juvenile and adult mortality rates), $c_1^{\mathrm{i}} > 0$ 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 curvature of the trade-off (larger absolute values correspond to greater deviations from linearity; Fig. 1b).

Intuitively, if the costs of resistance are sufficiently low at one life stage relative to the other (e.g. $c_1^{\mathrm{J}} \ll c_1^{\mathrm{A}}$) then resistance will always evolve to be higher at the life stage with much lower costs. Hence one can easily choose trade-offs such that juvenile resistance is always greater than adult resistance, or vice versa. We therefore focus our analysis on how certain combinations of trade-offs promote higher juvenile or adult resistance, all else being equal, by keeping the proportional impact of all trade-offs the same $\left(c_1^{\mathrm{J}} = c_1^{\mathrm{A}}, c_2^{\mathrm{J}} = c_2^{\mathrm{A}}\right)$, so that we can make fair comparisons across trade-offs. For example, if maximum juvenile resistance is associated with a 50% increase in juvenile mortality $\left(c_1^{\mathrm{J}} = 0.5\right)$, then we assume that maximum adult resistance is associated with either a 50% increase in adult mortality or a 50% decrease in reproduction $\left(c_1^{\mathrm{A}} = 0.5\right)$. We only consider accelerating fitness costs $(c_2^{\mathrm{i}} > 0)$, so that higher levels of resistance have diminishing returns, leading to evolutionarily stable strategies (decelerating fitness costs typically generate evolutionary repellers, but we restrict our attention to evolutionary attractors). We also fix the strength and curvature of the trade-offs such that $c_1^{\mathrm{i}} = 0.5$ and $c_2^{\mathrm{i}} = 3$, as our preliminary analysis revealed that variation in these parameters does not appear to cause qualitative changes to our key results (e.g., see Fig. S7, S8, S12, S13). It is also possible to rescale the system of equations (1a) to (1d) so that we can set $q = 1$ and $b_0 = 1$ without loss of generality (see *Supplementary Materials*).

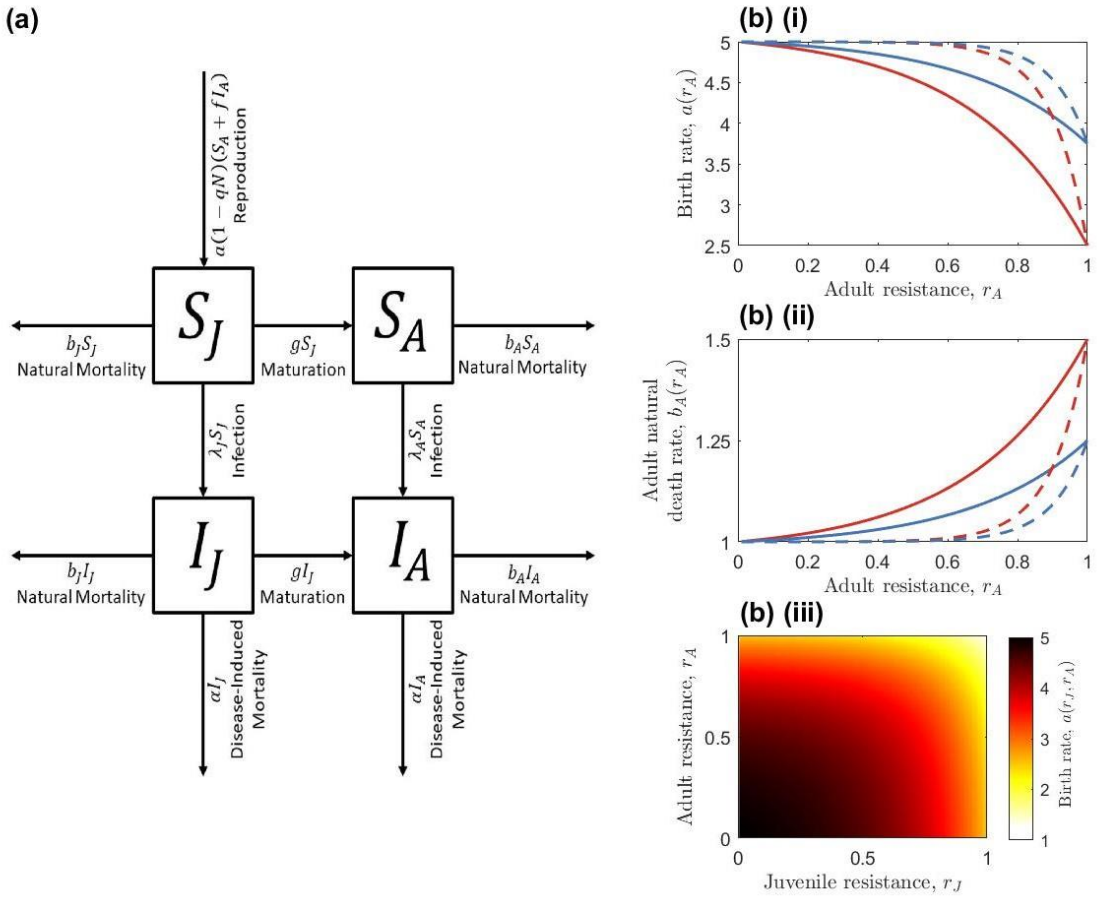


Fig. 1: (a) Model schematic for the ecological model. (b) Examples of trade-off functions. Trade-offs are shown between: (i) adult resistance and birth rate (with $a_0 = 5$), (ii) adult resistance and adult mortality (with $b_0 = 1$) and (iii) both juvenile and adult resistance and the birth rate (with $a_0 = 5$). Trade-offs between juvenile resistance and the maturation or birth rate take the same form as (i) and the trade-off between juvenile resistance and juvenile mortality takes the same form as (ii). Trade-off strength is controlled by the parameter c_1^{i}; a relatively strong trade-off ($c_1^{\mathrm{A}} = 0.5$, red curve) results in a much larger reduction in the birth rate for a given level of adult resistance than a relatively weak trade-off does ($c_1^{\mathrm{A}} = 0.25$, blue curve). Trade-off curvature is controlled by the parameter c_2^{i}; a relatively high curvature ($c_2^{\mathrm{A}} = 10$, dashed line) means that there is initially a low cost of increasing resistance but the cost eventually increases rapidly compared to a trade-off with lower curvature ($c_2^{\mathrm{A}} = 3$, solid line). Figure (iii) is shown only in the strong, low curvature case.

185 *EVOLUTIONARY INVASION ANALYSIS*

186 We use evolutionary invasion analysis (adaptive dynamics) to determine the coevolutionary
187 dynamics of juvenile and adult resistance [52,53]. Specifically, we assume that mutations are
188 sufficiently rare that there is a separation of ecological and evolutionary timescales (the
189 ecological dynamics of the resident population reach equilibrium before the next mutation
190 occurs) and that the mutations have small phenotypic effects. The invasion dynamics of rare
191 host mutants are given in the *Supplementary Materials*. Using the next generation method
192 [54], we derive the following expressions for the invasion fitness in the juvenile trait

$$w_J(r_J^{\mathrm{m}}) = \frac{g(r_J^{\mathrm{m}})a(r_J^{\mathrm{m}}, r_A)(1-N^*)A_J^{\mathrm{m}}}{(b_A(r_A)+\alpha)\big(b_J(r_J^{\mathrm{m}})+g(r_J^{\mathrm{m}})+\alpha\big)\big(b_A(r_A)+\lambda_A^*(r_A)\big)\Big(b_J(r_J^{\mathrm{m}})+g(r_J^{\mathrm{m}})+\lambda_J^*(r_J^{\mathrm{m}})\Big)} - 1 \qquad (5a)$$

193 and in the adult trait

$$w_A(r_A^{\mathrm{m}}) = \frac{g(r_J)a(r_J, r_A^{\mathrm{m}})(1-N^*)A_A^{\mathrm{m}}}{(b_A(r_A^{\mathrm{m}})+\alpha)\big(b_J(r_J)+g(r_J)+\alpha\big)\big(b_A(r_A^{\mathrm{m}})+\lambda_A^*(r_A^{\mathrm{m}})\big)\Big(b_J(r_J)+g(r_J)+\lambda_J^*(r_J)\Big)} - 1 \qquad (5b)$$

194 where asterisks denote the endemic equilibrium of the resident population. For notational
195 convenience we set:

$$A_J^{\mathrm{m}} = (b_A(r_A)+\alpha)\big(b_J(r_J^{\mathrm{m}})+g(r_J^{\mathrm{m}})+\alpha\big) + f\big(b_J(r_J^{\mathrm{m}})+g(r_J^{\mathrm{m}})+\alpha\big)\lambda_A^*(r_A) + f\lambda_J^*(r_J^{\mathrm{m}})\big(b_A(r_A)+\lambda_A^*(r_A)\big) \qquad (5c)$$

$$A_A^{\mathrm{m}} = (b_A(r_A^{\mathrm{m}})+\alpha)\big(b_J(r_J)+g(r_J)+\alpha\big) + f\big(b_J(r_J)+g(r_J)+\alpha\big)\lambda_A^*(r_A^{\mathrm{m}}) + f\lambda_J^*(r_J)\big(b_A(r_A^{\mathrm{m}})+\lambda_A^*(r_A^{\mathrm{m}})\big) \qquad (5d)$$

196 A mutant with juvenile resistance r_J^{m} can invade a resident population (with resistance traits
197 r_J and r_A) if and only if $w_J(r_J^{\mathrm{m}}) > 0$, and similarly for a mutant with adult resistance r_A^{m}. We
198 assume equal mutation rates in juveniles and adults. There is no analytic expression for the
199 endemic equilibrium of our model, so we cannot determine the singular strategies
200 analytically. We therefore use numerical methods to calculate pairs of co-singular strategies

(values of r_J and r_A that simultaneously maximise/minimise w_J and w_A) and to determine their evolutionary and strong convergence stability (see *Supplementary Materials*) [55,56]. Specifically, we calculate the fitness gradients ($\frac{\partial w_J}{\partial r_J^{\mathrm{m}}}$ and $\frac{\partial w_A}{\partial r_A^{\mathrm{m}}}$ evaluated at $r_J^{\mathrm{m}} = r_J$ and $r_A^{\mathrm{m}} = r_A$) and solve simultaneously when both are equal to zero using numerical methods to give the co-singular strategies. We determine evolutionary stability by considering the signs of the second derivatives ($\frac{\partial^2 w_J}{\partial r_j^{\mathrm{m}^2}}$ and $\frac{\partial^2 w_A}{\partial r_A^{\mathrm{m}^2}}$ evaluated at the co-singular strategy). We determine strong convergence stability using other conditions on the second derivatives which tell us the signs of the real parts of the eigenvalues of the Jacobian matrix of the system (see *Supplementary Materials* for more details on the stability conditions). Evolutionary invasion analysis relies on the assumptions that mutations are rare and have small phenotypic effects. Also, strong convergence stability only guarantees that the co-singular strategy is an attractor of the evolutionary dynamics if the mutations have sufficiently small effects. We relax these assumptions by using evolutionary simulations to verify our results (see *Supplementary Materials* for a description of the simulations and for the source code).

Parameter/ variable	Description	Default value or range
a	Reproduction rate of adult hosts	5
b_J, b_A	Natural mortality rate of juvenile/adult hosts	1
$c_1^{\mathrm{J}}, c_1^{\mathrm{A}}$	Strength of juvenile/adult trade-offs	0.5
$c_2^{\mathrm{J}}, c_2^{\mathrm{A}}$	Curvature of juvenile/adult trade-offs	3
$1 - f$	Sterility virulence	$0 \leq f \leq 1$
g	Host maturation rate	1
I_J, I_A	Density of infected juveniles/adults	n/a
N	Host population density	n/a
q	Strength of host density-dependence	1
r_J, r_A	Juvenile/adult resistance	$0 \leq r_J, r_A \leq 1$
S_J, S_A	Density of susceptible juveniles/adults	n/a
t	Time, measured in arbitrary units	n/a
α	Mortality virulence	$0 \leq \alpha$
β_0	Baseline transmission rate	$0 \leq \beta_0$
λ_J, λ_A	Force of infection on juveniles/adults	n/a

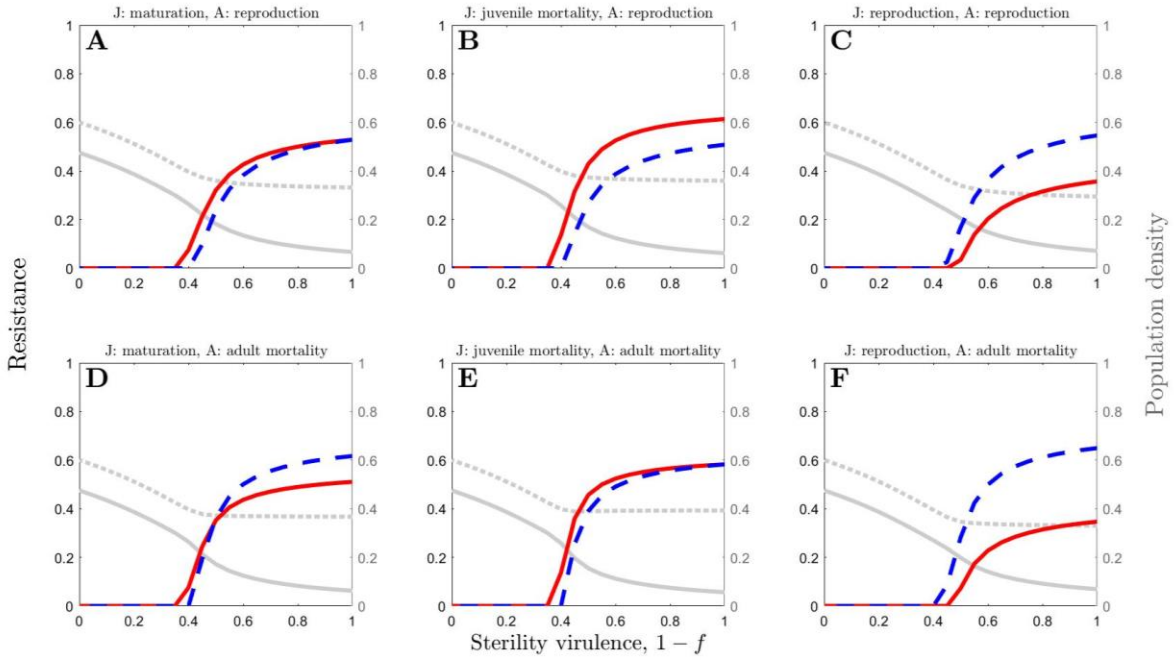
Table 1 – Model parameters and variables.

RESULTS

STERILITY VIRULENCE

First, we consider the case where infection causes a reduction in the fecundity of the host ($f < 1$) but has no effect on host mortality ($\alpha = 0$). Unsurprisingly, neither adult nor juvenile resistance evolve for sufficiently low levels of sterility virulence but resistance at both life stages may evolve when sterility virulence is sufficiently high (Fig. 2). Typically, juvenile and adult resistance both evolve towards a continuously stable strategy, although bistability is also possible for more extreme parameters (e.g., high transmissibility as shown in Fig. 4). We focus here on continuously stable strategies. If both juvenile and adult resistance are initially low then disease prevalence is likely to be relatively high and hence there may be selection for resistance at both life stages. As both resistance traits increase, disease prevalence (and hence the risk of infection) falls, acting as a negative feedback on selection until both juvenile and adult resistance reach stable values (Fig. 3A). The stable levels of juvenile and adult resistance will clearly depend on the nature of the trade-offs involved, as equal levels of resistance will generally not incur the same cost to the host. However, regardless of which life-history traits trade-off with resistance and at which life stage resistance acts, the general shape of the resistance curve in response to variation in sterility virulence is consistent. Specifically, at moderate levels of sterility virulence there is a sharp increase in resistance but this plateaus when sterility virulence is high. This suggests that when sterility virulence is at moderate levels, a relatively small increase in virulence can lead to a marked increase in selection for resistance at both juvenile and adult stages, regardless of the underlying trade-offs.

All else being equal (i.e. trade-offs have the same proportional effect on life-history traits for a given level of resistance), juvenile and adult resistance are typically similar if juvenile resistance trades off with maturation (Fig. 2A, D) or if resistance is associated with an increase in mortality (Fig. 2E). If, however, juvenile resistance is associated with higher juvenile mortality and adult resistance is associated with lower reproduction, our model predicts that juvenile resistance is consistently higher than adult resistance (Fig. 2B). Conversely, if juvenile resistance trades off with adult reproduction, then adult resistance is consistently higher than juvenile resistance regardless of whether adult resistance trades off with reproduction (Fig. 2C) or mortality (Fig. 2F), and we also see lower levels of juvenile resistance than we do when other trade-offs are present (Fig. 2, S1). Since there is no recovery in our model, becoming infected as a juvenile leads to a permanent reduction in fecundity, yet our model suggests that risking infection as a juvenile is generally a better strategy than investing in resistance if this incurs a reproduction cost.



254 Fig. 2: The effects of varying sterility virulence, $1-f$, on juvenile resistance (solid red) and
255 adult resistance (dashed blue), for six different combinations of trade-offs: (A)-(C) adult
256 resistance with reproduction, (D)-(F) adult resistance with adult mortality, (A) & (D) juvenile
257 resistance with maturation, (B) & (D) juvenile resistance with juvenile mortality and (C) & (F)
258 juvenile resistance with reproduction. The dotted, grey line shows total population density
259 and the solid, grey line shows the density of infected hosts (both are non-dimensionalised).
260 Parameters as in Table 1 with $\beta_0 = 8$ and $\alpha = 0$.
261

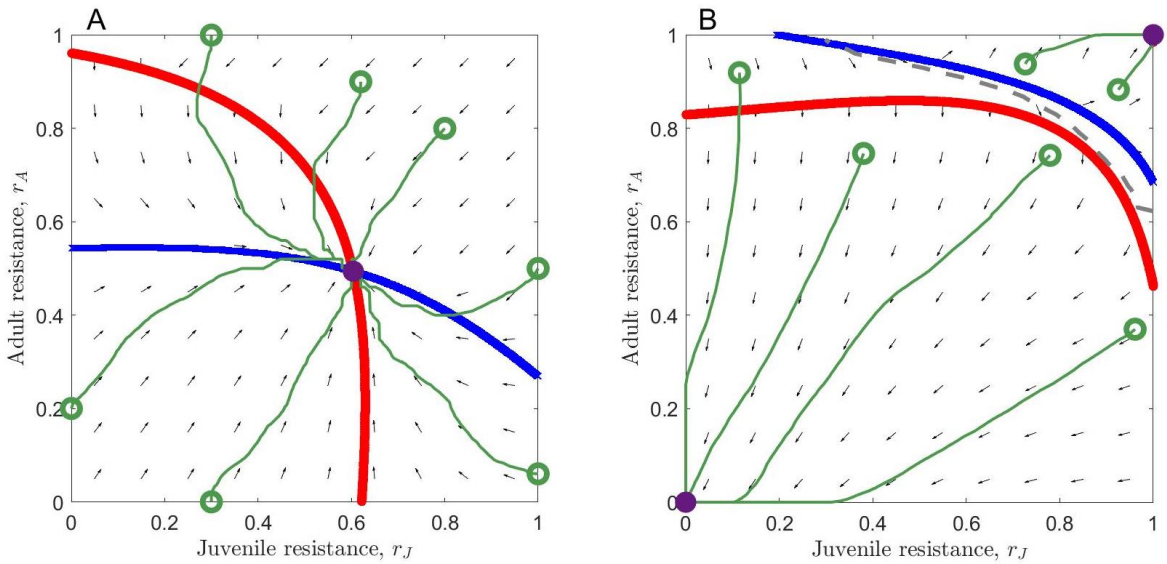
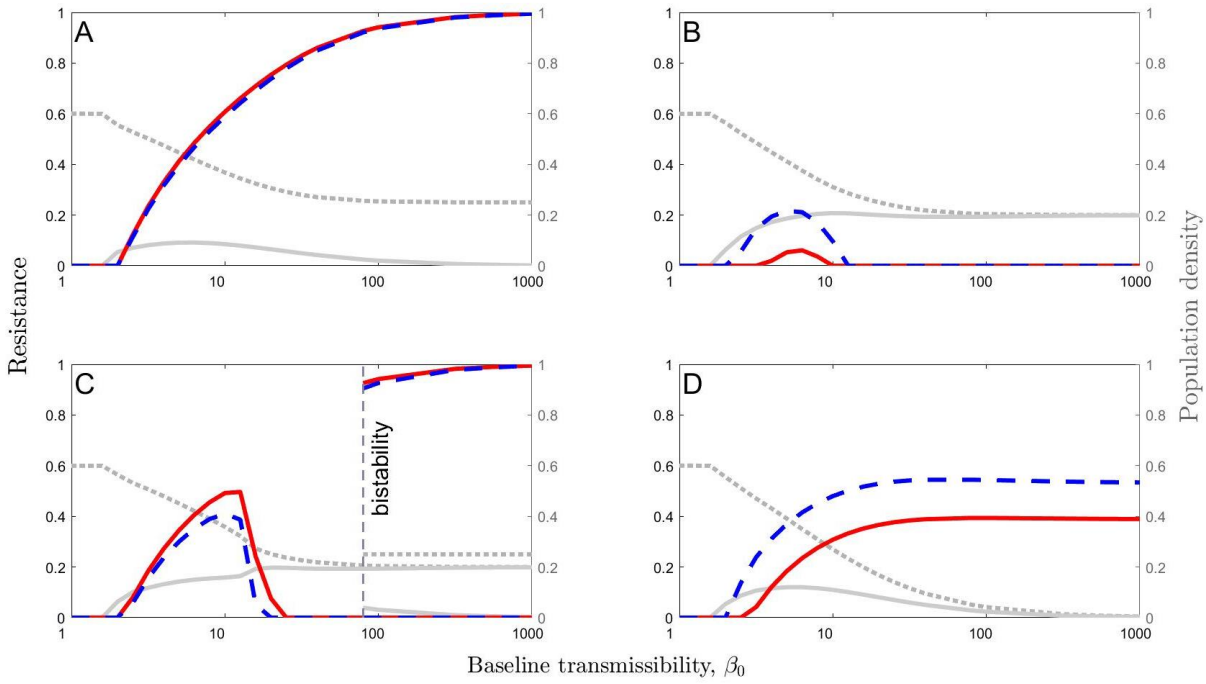


Fig. 3: Phase planes showing (A) a continuously stable strategy and (B) bistability, with the juvenile nullcline in red and the adult nullcline in blue. In (A), the host population will always evolve towards the CSS (purple circle), no matter what the starting values of the juvenile and adult resistance traits. In (B), the host population will evolve towards one of the attractors (purple circles), depending on the starting values of the juvenile and adult resistance traits (basins of attraction are separated by the dashed line). Example trajectories are shown in green. In (A), juvenile resistance trades off with juvenile mortality, adult resistance trades off with reproduction and parameter values are as in Table 1 with $\beta_0 = 8$, $\alpha = 0$ and $f = 0.1$. In (B), juvenile resistance trades off with juvenile mortality, adult resistance trades off with adult mortality and parameter values are as in Table 1 with $\beta_0 = 1000$, $\alpha = 0$ and $f = 0.5$.

These results are qualitatively consistent for variation in the baseline reproduction (a_0) and maturation (g_0) rates and trade-off parameters (c_1^{i} and c_2^{i}) (Fig. S9-S13), with adult resistance exceeding juvenile resistance most markedly when maturation is fast and when juvenile resistance trades off with reproduction (Fig. S10C and S10F).

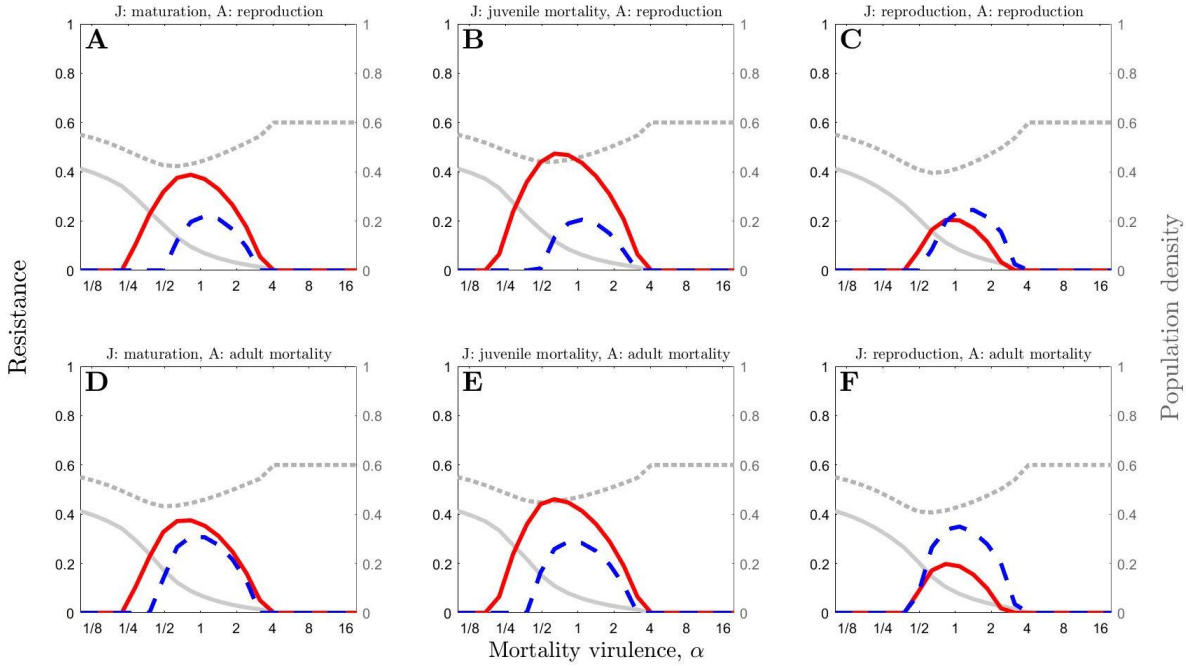
Similarly, variation in baseline transmissibility (β_0) affects the risk of infection for adults and juveniles equally and so has a similar effect on resistance evolution at both life stages (Fig. 4). When β_0 is very low, the risk of infection is low and hence resistance does not evolve at either life stage. As β_0 increases, disease becomes more common, causing both juvenile and adult resistance to rise (Fig. 4), with similar differences between trade-offs as described above (Fig. S2 and Fig. S3). For sufficiently high values of β_0, the outcome depends on whether the host population remains viable (see *Supplementary Materials*), in which case resistance may tend towards either a high value if the pathogen is sufficiently virulent (Fig. 4A) or else a low value if disease prevalence approaches 100% with most individuals infected very shortly after birth (with selection against ineffective resistance; Fig. 4B). Alternatively, for some parameter and trade-off combinations, the population may enter a region of bistability for extremely high values of β_0 (Fig. 4C), where hosts either evolve to high or zero levels of resistance at both life stages, depending on the initial levels of resistance in the population (Fig. 3B). This bistability suggests that, in principle, initially similar populations could experience very different evolutionary outcomes, although such high levels of transmissibility are unlikely to be biologically realistic. Finally, if the host population size tends towards zero as β_0 increases, then resistance tends towards an intermediate level (e.g. Fig. 4D), although the level of resistance is inconsequential as the host population crashes.



297 Fig. 4: The effect of varying baseline transmissibility, β_0, on juvenile resistance (solid red) and
298 adult resistance (dashed blue), in the cases where juvenile resistance trades off with juvenile
299 mortality and adult resistance trades off with adult mortality (A and C) and where both
300 juvenile and adult resistance trade off with reproduction (B and D). The dotted, grey line
301 shows total population density and the solid, grey line shows the density of infected hosts
302 (both are non-dimensionalised). In the bistability region in panel C, the higher total population
303 density and the lower infected density correspond to the higher levels of resistance.
304 Parameters used as in Table 1, with $\alpha = 0$ and $f = 0.5$ (B and C) or $f = 0.3$ (A and D).

Mortality Virulence

We now consider the case where infection increases the mortality rate ($\alpha > 0$) but has no effect on host fecundity ($f = 1$). Juvenile and adult resistance follow the same qualitative patterns as mortality virulence varies. As in non-age-structured models, hosts do not evolve resistance when α is sufficiently low because the costs of infection are low, or when α is sufficiently high because this reduces the infectious period and hence disease prevalence. Resistance therefore peaks at intermediate values of α, although both the extent of resistance and when it peaks may differ between life stages (Fig. 5). Moreover, certain combinations of trade-offs consistently favour higher juvenile resistance and others higher adult resistance, all else being equal (Fig. 5). Specifically, juvenile resistance tends to be markedly lower than adult resistance when the former trades off with maturation or natural mortality rate (Fig. 5A-B, D-E) but the converse is true when juvenile resistance trades off with adult reproduction (Fig. 5C, F). We can see that juvenile resistance is significantly lower in the latter case (Fig. 5C, F) than in the former cases (Fig. 5A-B, D-E). These patterns are consistent as other model parameters are varied (Fig. S4-S8) and largely mirror those for sterility virulence (Fig. 2).



321 Fig. 5: The effect of varying mortality virulence, α, on juvenile resistance (solid red) and adult
322 resistance (dashed blue), for six different combinations of trade-offs: (A)-(C) adult resistance
323 with reproduction, (D)-(F) adult resistance with adult mortality, (A) & (D) juvenile resistance
324 with maturation, (B) & (D) juvenile resistance with juvenile mortality and (C) & (F) juvenile
325 resistance with reproduction. The dotted, grey line shows total population density and the
326 solid, grey line shows the density of infected hosts (both are non-dimensionalised).
327 Parameters as in Table 1 with $\beta_0 = 8$ and $f = 1$.

DISCUSSION

Significant differences in innate, infection-preventing resistance have been observed between juveniles and adults across many taxa and yet the evolutionary drivers of these differences are not well understood [51]. Here, we theoretically explored how trade-offs between age-specific resistance and various life-history traits combine to affect selection for resistance at different life stages and investigated whether selection typically favours higher juvenile or adult resistance, all else being equal. Overall, our analysis suggests that trade-offs between juvenile resistance and adult reproduction are inherently more costly than other trade-offs, regardless of whether virulence affects mortality or fecundity. These particular trade-offs may lead to the evolution of relatively low resistance as a juvenile (compared with adult resistance and with juvenile resistance when other trade-offs are present), even when infection as a juvenile causes lifelong reductions in fecundity. The latter result may appear counter-intuitive at first, but if the lifelong reduction in fecundity due to infection and the risk of infection as a juvenile are both sufficiently low, then it is better for the host to risk infection as a juvenile rather than always to suffer from a reduced reproduction rate as an adult.

We fixed the strength and shape of the trade-offs in our model to be the same for all trade-off functions so that we could make fair comparisons between different combinations of trade-offs. Hence, our key finding that adult resistance tends to be relatively higher when juvenile resistance trades off with reproduction suggests that this is because it is inherently costlier – compared to trade-offs with maturation or mortality – for hosts to evolve juvenile resistance if it results in decreased reproduction as an adult. This also suggests that costs of juvenile resistance associated with reproduction may have a disproportionately greater effect on host fitness than costs associated with maturation or mortality. Whether juvenile

resistance is higher than adult resistance, or vice versa, in a particular host-pathogen system will also depend on the strength and shape of the trade-offs. For example, if a given level of adult resistance is proportionately much more costly than a given level of juvenile resistance, then we should expect juvenile resistance to be higher. However, we predict that when the strength and shape of the trade-offs are similar, adult resistance will tend to be higher than juvenile resistance if the latter trades off with reproduction. This result may also provide clues as to where trade-offs may exist if empirical observations reveal that juveniles are intrinsically less resistant than adults.

Our study examined the effect of trade-offs with different life history traits: mortality, maturation and fecundity. In plants, where costs of resistance have been relatively well-studied, trade-offs between innate, infection-preventing resistance and fecundity are well supported [42–44,57–60]. In many crop plants, resistance is typically measured at the seedling (juvenile) stage whereas costs may be measured in growing or mature (adult) plants. For example, in oats, seedling resistance to infection by rust fungi has been linked to substantial (9%) reductions in yield [58]. In tobacco, resistance to infection by tobacco mosaic virus, measured at 4 weeks post planting, led to reduced growth [60]. In *Arabidopsis*, a resistance gene that affects the ability of a bacterial pathogen to invade at 3 weeks of age (when plants are in the young rosette stage), has been associated with up to 9% reductions in seed set [59]. There is also some evidence of costs associated with maturation rate. For example, Barlett *et al.* found a negative correlation between maturation rate and resistance to infection by a baculovirus at the third-instar larval stage in the moth *Plodia interpunctella* [45]. Survival is less commonly investigated as a potential trade-off mechanism and there is currently little evidence for trade-offs between survival and innate resistance (although see

376 [61] for a review of immunopathology). Our study shows that when costs are paid through
377 reductions in fecundity, adult resistance is favoured over juvenile resistance in most cases.
378
379 It is critical to note that whilst trade-offs have been documented for both juvenile and adult
380 resistance, we can find no study that directly quantifies the magnitude of these costs within
381 a single host. This is largely because resistance phenotyping is typically done at a single age,
382 or in the case of crop studies, seedling and adult resistance are measured in completely
383 different settings with different inoculum sources and so are difficult to compare [62–64].
384 One study by Biere & Antonovics found a negative correlation between flower production
385 and resistance of adult *Silene latifolia* plants to anther-smut infection in a field setting, but no
386 apparent correlation between flower production and family-level resistance measured in the
387 lab at the seedling stage [42]. It is, however, reasonable to expect (from a resource allocation
388 perspective) that diversion of resources to resistance during development could negatively
389 impact on adult fecundity, for instance by restricting growth (body size or secondary sex
390 traits) which could make individuals less competitive for mates or less able to support a larger
391 number of offspring. Our results demonstrate that quantifying the magnitude and form of
392 such trade-offs at juvenile and adult stages is critically important for determining the
393 evolutionary outcomes of age-specific resistance. We tentatively predict that, in systems
394 where juveniles are less resistant to infection than adults, trade-offs between juvenile
395 resistance and reproduction may be more likely than trade-offs between other life-history
396 traits.
397
398 This prediction could be tested using a host species which is naturally polymorphic in
399 resistance to a particular pathogen. Having bred separate families of hosts, the juvenile and

adult resistance of each family could be estimated by exposing hosts of different ages to the pathogen and calculating the proportion of each age-group within each family which becomes infected. Other individuals from each family could be used to measure possible trade-off traits at different life stages (for instance growth or reproduction). A negative correlation between resistance at any life-stage and any other beneficial trait would suggest a trade-off.

Our results are broadly consistent as our model parameters are varied, although when the pathogen is highly transmissible it is possible for the host to experience bistability, with selection either favouring high juvenile and adult resistance or no resistance across the life span, depending on the initial conditions. This suggests that founder effects, or drift reinforced by selection, could drive initially similar populations to contrasting evolutionary outcomes. However, we found no evidence of bistability causing levels of resistance to diverge substantially at different life-stages (i.e. high juvenile resistance and no adult resistance, or vice versa). Bistability is therefore not likely to be the cause of contrasting levels of resistance in juveniles and adults.

Previous theory has almost entirely focused on the evolution of resistance in populations without age-structure [46–50]. Our model was an extension of the one explored by Ashby & Bruns, which considered the evolution of juvenile susceptibility (the inverse of resistance) subject to trade-offs with reproduction or maturation [51]. However, Ashby & Bruns assumed that hosts were always more resistant as adults than as juveniles [51], whereas here we have relaxed these assumptions to consider how juvenile and adult resistance evolve simultaneously subject to a wider range of trade-offs.

We made several simplifying assumptions in the process of modelling this evolutionary process. Firstly, we assumed that juvenile and adult resistance evolve independently, which is reasonable if different mechanisms are responsible for resistance at different life stages [65], but instead juvenile and adult resistance may be correlated if the mechanism is the same. Secondly, we assumed that each resistance trait only incurred one type of cost rather than trading off with multiple life-history traits, which is reasonable from a general modelling perspective, but may not hold true in certain systems where, for example, juvenile resistance may trade-off against multiple life-history traits such as maturation, reproduction and mortality. Thirdly, we assumed that disease effects on juveniles and adults were identical, but the severity of disease may differ depending on the age of the host. For example, age is a strong predictor of the risk of mortality from COVID-19 in humans [66]. Including age-related disease effects in our model would have greatly complicated our analysis, but this should be considered in future theoretical work. Similarly, we assumed that juveniles and adults mixed randomly, but the effects of biased (assortative) transmission between individuals at the same life-stage should also be considered in future work.

Fourthly, we assumed that there was no recovery from infection, as our model was loosely inspired by the sterilising anther-smut pathogen (*Microbotryum*) in carnations (*Caryophyllaceae*), which rarely recover from infection but exhibit substantial variation in resistance between seedling and mature plants [67]. Preliminary analysis revealed that recovery from infection does not change our key results, but by assuming that there was no recovery we were readily able to explore the effects of lifelong reductions in fecundity arising from infection as a juvenile. Finally, we assumed that the pathogen was monomorphic and evolutionarily static. Clearly, in a real-world scenario the pathogen would be expected to

448 evolve in response to changes in the host and so future models should consider the effects of
449 host-pathogen coevolution in age-structured populations. This could include the evolution of
450 either parasite infectivity or virulence, which would also extend previous theoretical work on
451 the evolution of stage-specific virulence [41]. Host-pathogen coevolution with age-specific
452 resistance has yet to be explored theoretically [68].
453
454 In our model, we focused on the evolution of innate, infection-preventing resistance, as
455 opposed to other forms of host defence such as tolerance. Both forms of defence against
456 pathogens are common in nature, with resistance and tolerance strategies operating
457 concurrently in many cases. However, age-structured tolerance is not well-understood and
458 would therefore be difficult to model. For instance, how would the host's level of tolerance
459 change as it aged from a juvenile to an adult whilst infected? Combining the two types of
460 defence might also complicate matters if resistance and tolerance had significant effects on
461 one another. Future work should consider how tolerance may evolve across the lifespan of
462 the host.
463
464 Overall, our model shows that trade-offs between juvenile resistance and reproduction
465 during adulthood are intrinsically more costly than trade-offs between other traits, even
466 when infection leads to permanent reductions in fecundity. Such trade-offs could therefore
467 explain why adults are sometimes more resistant to disease than juveniles.
468

469 **ACKNOWLEDGEMENTS**

470 We thank Nick Priest for helpful discussions about the manuscript.
471

Data Accessibility Statement

Source code is available in the *Supplementary Materials* and at https://github.com/ecoevotheory/Buckingham_and_Ashby_2022.

Funding

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.

References

1. Altizer S, Davis AK, Cook KC, Cherry JJ. 2004 Age, sex, and season affect the risk of mycoplasmal conjunctivitis in a southeastern house finch population. *Can J Zool* **82**, 755–763. (doi:10.1139/Z04-050)
2. Apolloni A, Poletto C, Colizza V. 2013 Age-specific contacts and travel patterns in the spatial spread of 2009 H1N1 influenza pandemic. *BMC Infect Dis* **13**.
3. Clark J, Garbutt JS, McNally L, Little TJ. 2017 Disease spread in age structured populations with maternal age effects. *Ecol Lett* **20**, 445–451. (doi:10.1111/ele.12745)
4. Miller ME. 1983 Relationships between onion leaf age and susceptibility to Alternaria porri. *Plant Dis* **67**.
5. Panter SN, Jones DA. 2002 Age-related resistance to plant pathogens. *Adv Bot Res* **38**, 251–280.
6. Develey-Rivière MP, Galiana E. 2007 Resistance to pathogens and host developmental stage: A multifaceted relationship within the plant kingdom. *New Phytologist* **175**, 405–416. (doi:10.1111/j.1469-8137.2007.02130.x)

7. Bruns EL, Antonovics J, Carasso V, Hood M. 2017 Transmission and temporal dynamics of anther-smut disease (Microbotryum) on alpine carnation (Dianthus pavonius). *Journal of Ecology* **105**, 1413–1424. (doi:10.1111/1365-2745.12751)

8. Sait SM, Begon M, Thompson DJ. 1994 The influence of larval age on the response of Plodia interpunctella to a Granulosis virus. *J Invertebr Pathol* **63**, 107–110.

9. Kubi C, van den Abbeele J, de Deken R, Marcotty T, Dorny P, van den Bossche P. 2006 The effect of starvation on the susceptibility of teneral and non-teneral tsetse flies to trypanosome infection. *Med Vet Entomol* **20**, 388–392. (doi:10.1111/j.1365-2915.2006.00644.x)

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

11. Garbutt JS, O'Donoghue AJP, McTaggart SJ, Wilson PJ, Little TJ. 2014 The development of pathogen resistance in Daphnia magna: Implications for disease spread in age-structured populations. *Journal of Experimental Biology* **217**, 3929–3934. (doi:10.1242/jeb.111260)

12. Green TJ, Vergnes A, Montagnani C, de Lorgeril J. 2016 Distinct immune responses of juvenile and adult oysters (Crassostrea gigas) to viral and bacterial infections. *Vet Res* **47**. (doi:10.1186/s13567-016-0356-7)

13. Duca CJ. 1948 Age specific susceptibility to tuberculosis; experiments on guinea pigs and rats. *Am Rev Tuberc* **57**, 389–399.

14. Zuckerman A, Yoeli M. 1954 Age and sex as factors influencing Plasmodium berghei infections in intact and splenectomized rats. *J Infect Dis* **94**, 225–236.

15. Francis J. 1961 The effect of age on the susceptibility of guinea pigs to tuberculosis. *Tubercle* **42**, 333–336.

16. Baird JK. 1998 Age-dependent characteristics of protection v. susceptibility to Plasmodium falciparum. *Ann Trop Med Parasitol* **92**, 367–390.

17. Kurtis JD, Mtalib R, Onyango FK, Duffy PE. 2001 Human resistance to Plasmodium falciparum increases during puberty and is predicted by dehydroepiandrosterone sulfate levels. *Infect Immun* **69**, 123–128. (doi:10.1128/IAI.69.1.123-128.2001)

18. Glynn JR, Moss PAH. 2020 Systematic analysis of infectious disease outcomes by age shows lowest severity in school-age children. *Sci Data* **7**. (doi:10.1038/s41597-020-00668-y)

19. Parker MA. 1988 Polymorphism for disease resistance in the annual legume Amphicarpaea bracteata. *Heredity (Edinb)* **60**, 27–31.

20. Jarosz AM, Burdon JJ. 1990 Predominance of a single major gene for resistance to Phakopsora pachyrhizi in a population of Glycine argyrea. *Heredity (Edinb)* **64**, 347–353.

21. Chung E, Petit E, Antonovics J, Pedersen AB, Hood ME. 2012 Variation in resistance to multiple pathogen species: Anther smuts of Silene uniflora. *Ecol Evol* **2**, 2304–2314. (doi:10.1002/ece3.346)

22. Bruns E. 2016 Fitness costs of plant disease resistance. *eLS* , 1–11. (doi:10.1002/9780470015902.a0020094.pub2)

23. Milutinovic B, Peuß R, Ferro K, Kurtz J. 2016 Immune priming in arthropods: an update focusing on the red flour beetle. *Zoology* **119**, 254–261. (doi:10.1016/j.zool.2016.03.006)

24. Sheehan G, Farrell G, Kavanagh K. 2020 Immune priming: the secret weapon of the insect world. *Virulence* **11**, 238–246. (doi:10.1080/21505594.2020.1731137)
25. Flajnik MF. 2018 A cold-blooded view of adaptive immunity. *Nature Reviews* **18**, 438–453. (doi:10.1038/s41577)
26. Yan AWC, Zaloumis SG, Simpson JA, McCaw JM. 2019 Sequential infection experiments for quantifying innate and adaptive immunity during influenza infection. *PLoS Comput Biol* **15**. (doi:10.1371/journal.pcbi.1006568)
27. Leuridan E, van Damme P. 2007 Passive transmission and persistence of naturally acquired or vaccine-induced maternal antibodies against measles in newborns. *Vaccine* **25**, 6296–6304. (doi:10.1016/j.vaccine.2007.06.020)
28. Edwards KM. 2015 Maternal antibodies and infant immune responses to vaccines. *Vaccine* **33**, 6469–6472. (doi:10.1016/j.vaccine.2015.07.085)
29. Maue AC, Yager EJ, Swain SL, Woodland DL, Blackman MA, Haynes L. 2009 T-cell immunosenescence: lessons learned from mouse models of aging. *Trends Immunol* **30**, 301–305. (doi:10.1016/j.it.2009.04.007)
30. Lian J, Yue Y, Yu W, Zhang Y. 2020 Immunosenescence: a key player in cancer development. *J Hematol Oncol* **13**. (doi:10.1186/s13045-020-00986-z)
31. Baird JK, Basri H, Weina P, Maguire JD, Barcus MJ, Picarema H, Elyazar IRF, Ayomi E, Sekartuti A. 2003 Adult Javanese migrants to Indonesian Papua at high risk of severe disease caused by malaria. *Epidemiol Infect* **131**, 791–797. (doi:10.1017/S0950268803008422)
32. Hamilton W. 1996 *Narrow roads of gene land: The collected papers of W D Hamilton*. Oxford: Oxford University Press.

33. McDade TW. 2003 Life History Theory and the Immune System: Steps Toward a Human Ecological Immunology. *Am J Phys Anthropol* **122**, 100–125. (doi:10.1002/ajpa.10398)
34. Boege K, Marquis RJ. 2005 Facing herbivory as you grow up: The ontogeny of resistance in plants. *Trends Ecol Evol* **20**, 441–448. (doi:10.1016/j.tree.2005.05.001)
35. Dyck PL, Kerber ER. 1985 Resistance of the race-specific type. In *The cereal rust vol. 2: Disease, distribution, epidemiology, and control*, Orlando.
36. Line RF, Chen X. 1995 Sucesses in breeding for and managing durable resistance to wheat rusts. *Plant Dis* **79**.
37. Bovill W, Horne M, Herde D, Davis M, Wildermuth G, Sutherland M. 2010 Pyramiding QTL increases seedling resistance to crown rot (Fusarium pseudograminearum) of wheat (Triticum aestivum). *Theoretical and Applied Genetics* **121**, 127–136.
38. Burdon JJ, Oates JD, Marshall DR. 1983 Interactions between Avena and Puccinia species. I. The Wild Hosts. *Journal of Applied Ecology* **20**, 571–584.
39. Hill AVS *et al.* 1991 Common West African HLA antigens are associated with protection from severe malaria. *Nature* **352**.
40. Mockenhaupt FP *et al.* 2006 Toll-like receptor (TLR) polymorphisms in African children: Common TLR-4 variants predispose to severe malaria. *PNAS* **103**, 177–182.
41. Iritani R, Visher E, Boots M. 2019 The evolution of stage-specific virulence: Differential selection of parasites in juveniles. *Evol Lett* **3**, 162–172. (doi:10.1002/evl3.105)
42. Biere A, Antonovics J. 1996 Sex-specific costs of resistance to the fungal pathogen ustilago violacea (microbotryum violaceum) in silene alba. *Evolution (N Y)* **50**, 1098–1110.
43. Karasov TL, Chae E, Herman JJ, Bergelson J. 2017 Mechanisms to mitigate the trade-off between growth and defense. *Plant Cell* **29**, 666–680. (doi:10.1105/tpc.16.00931)

588 44. Susi H, Laine AL. 2015 The effectiveness and costs of pathogen resistance strategies in
589 a perennial plant. *Journal of Ecology* **103**, 303–315. (doi:10.1111/1365-2745.12373)
590 45. Bartlett LJ, Wilfert L, Boots M. 2018 A genotypic trade-off between constitutive
591 resistance to viral infection and host growth rate. *Evolution (N Y)* **72**, 2749–2757.
592 (doi:10.1111/evo.13623)
593 46. Antonovics J, Thrall PH. 1994 The cost of resistance and the maintenance of genetic
594 polymorphism in host-pathogen systems. *Proceedings of the Royal Society B* **257**, 105–
595 110.
596 47. Boots M, Haraguchi Y. 1999 The evolution of costly resistance in host-parasite systems.
597 *Am Nat* **153**.
598 48. Carlsson-Graner U, Thrall PH. 2006 The impact of host longevity on disease
599 transmission: host-pathogen dynamics and the evolution of resistance. *Evol Ecol Res* **8**,
600 659–675.
601 49. Miller MR, White A, Boots M. 2007 Host life span and the evolution of resistance
602 characteristics. *Evolution (N Y)* **61**, 2–14. (doi:10.1111/j.1558-5646.2007.00001.x)
603 50. Donnelly R, White A, Boots M. 2015 The epidemiological feedbacks critical to the
604 evolution of host immunity. *J Evol Biol* **28**, 2042–2053. (doi:10.1111/jeb.12719)
605 51. Ashby B, Bruns E. 2018 The evolution of juvenile susceptibility to infectious disease.
606 *Proceedings of the Royal Society B* **285**. (doi:10.1098/rspb.2018.0844)
607 52. Hofbauer J, Sigmund K. 1990 Adaptive Dynamics and Evolutionary Stability. *Appl. Math.*
608 *Lett* **3**, 75–79.
609 53. Dieckmann U, Law R. 1996 The dynamical theory of coevolution: a derivation from
610 stochastic ecological processes. *J. Math. Biol* **34**, 579–612.

611 54. Hurford A, Cownden D, Day T. 2010 Next-generation tools for evolutionary invasion
612 analyses. *J R Soc Interface* **7**, 561–571. (doi:10.1098/rsif.2009.0448)
613 55. Kisdi É. 2006 Trade-off geometries and the adaptive dynamics of two co-evolving
614 species. *Evol Ecol Res* **8**, 959–973.
615 56. Leimar O. 2009 Multidimensional convergence stability. *Evol Ecol Res* **11**, 191–208.
616 57. Gwynn DM, Callaghan A, Gorham J, Walters KFA, Fellowes MDE. 2005 Resistance is
617 costly: Trade-offs between immunity, fecundity and survival in the pea aphid.
618 *Proceedings of the Royal Society B: Biological Sciences* **272**, 1803–1808.
619 (doi:10.1098/rspb.2005.3089)
620 58. Simons MD. 1979 Influence of Genes for Resistance to Puccinia coronata from Avena
621 sterilis on Yield and Rust Reaction of Cultivated Oats. *Phytopathology* **69**, 450–452.
622 59. Tian D, Traw MB, Chen JQ, Kreitman M, Bergelson J. 2003 Fitness Costs of R-Gene-
623 Mediated Resistance in Arabidopsis thaliana. *Nature* **423**, 74–77.
624 (doi:10.1038/nature01575)
625 60. Chaplin JF, Mann TJ. 1978 Evaluation of tobacco mosaic resistance factor transferred
626 from burley to flue-cured tobacco. *Journal of Heredity* **69**, 175–178.
627 61. Lochmiller RL, Deerenberg C. 2000 Trade-offs in evolutionary immunology: just what is
628 the cost of immunity? *Oikos* **88**, 87–98.
629 62. Zegeye H, Rasheed A, Makdis F, Badebo A, Ogbonnaya FC. 2014 Genome-wide
630 association mapping for seedling and adult plant resistance to stripe rust in synthetic
631 hexaploid wheat. *PLoS One* **9**. (doi:10.1371/journal.pone.0105593)
632 63. Gao L, Kathryn Turner M, Chao S, Kolmer J, Anderson JA. 2016 Genome wide
633 association study of seedling and adult plant leaf rust resistance in elite spring wheat
634 breeding lines. *PLoS One* **11**. (doi:10.1371/journal.pone.0148671)

64. Liu W, Maccaferri M, Rynearson S, Letta T, Zegeye H, Tuberosa R, Chen X, Pumphrey M. 2017 Novel sources of stripe rust resistance identified by genome-wide association mapping in Ethiopian durum wheat. *Front Plant Sci* **8**. (doi:10.3389/fpls.2017.00774)

65. Bruns EB, Hood ME, Antonovics J, Ballister IH, Troy SE, Cho J -H. 2022 Can disease resistance evolve independently at different ages? Genetic variation in age-dependent resistance to disease in three wild plant species. *Journal of Ecology* (doi:10.1111/1365-2745.13966)

66. Yang W *et al.* 2021 Estimating the infection-fatality risk of SARS-CoV-2 in New York City during the spring 2020 pandemic wave: a model-based analysis. *Lancet Infect Dis* **21**, 203–212. (doi:10.1016/S1473-3099(20)30769-6)

67. Hood ME *et al.* 2010 Distribution of the anther-smut pathogen Microbotryum on species of the Caryophyllaceae. *New Phytologist* **187**, 217–229. (doi:10.1111/j.1469-8137.2010.03268.x)

68. Buckingham LJ, Ashby B. 2022 Coevolutionary theory of hosts and parasites. *J Evol Biol* **35**, 205–224. (doi:10.1111/jeb.13981)