Pathogen Dynamics across the Diversity of Aging

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ABSTRACT: Reproduction, mortality, and immune function often change with age but do not invariably deteriorate. Across the tree of life, there is extensive variation in age-specific performance and changes to key life-history traits. These changes occur on a spectrum from classic senescence, where performance declines with age, to juvenescence, where performance improves with age. Reproduction, mortality, and immune function are also important factors influencing the spread of infectious disease, yet there exists no comprehensive investigation into how the aging spectrum of these traits impacts epidemics. We used a model laboratory infection system to compile an aging profile of a single organism, including traits directly linked to pathogen susceptibility and those that should indirectly alter pathogen transmission by influencing demography. We then developed generalizable epidemiological models demonstrating that different patterns of aging produce dramatically different transmission landscapes: in many cases, aging can reduce the probability of epidemics, but it can also promote severity. This work provides context and tools for use across taxa by empiricists, demographers, and epidemiologists, advancing our ability to accurately predict factors contributing to epidemics or the potential repercussions of senescence manipulation.

Keywords: aging populations, transgenerational effects, host heterogeneity, age structure, infectious disease transmission, indirect effects.

Introduction

Population age structure is a dynamic, ubiquitous feature of populations. Within these age-structured populations, individual performance across traits almost invariably changes over the course of an organism's life span. This change can occur on a spectrum, from juvenescence, where performance can improve with age, to senescence, where performance can decline with age (Jones et al. 2014; Hayward et al. 2015), with individual life-history traits often aging asynchronously, such that one trait might decline, while another can remain functional or even improve (Lecomte et al. 2010; Jones et al. 2014; Hayward et al. 2015). This individual-level variation in aging could contribute to population-level dynamics such as pathogen transmission, as aging often impacts key epidemiological parameters including rates of reproduction and mortality as well as susceptibility to infection. However, though age-specific performance in susceptibility is often considered in epidemiology, how age-specific performance in reproduction and mortality can drive pathogen dynamics has received less attention. Additionally, as hosts age, how interactions between these traits can drive pathogen dynamics at the population level has not been explored.

The force of mortality experienced by an infected individual is a determining factor in the life span of infection and the amount of time during which a host can transmit. Additionally, as a rate that shapes population age structure (Goldstein 2009), it will also contribute to shaping the susceptibility profile of a population. This is also the case for reproduction, such that changing rates of reproduction could indirectly influence pathogen transmission through shifts in the supply of susceptible hosts (Clark et al. 2017) and the shaping of a population's susceptibility profile. This is particularly likely in cases where infection is heavily age dependent (e.g., COVID-19, measles, and helminth infections; Anderson and May 1982*b*; Chan et al. 1994; Metcalf et al. 2011; Prada et al. 2018; Davies et al. 2020). Reproduction can have a direct effect on transmission when maternal age has an influence on offspring quality, that is, susceptibility to infectious diseases (Clark et al. 2017).

Indeed, there is considerable evidence that maternal effects, the nongenetic reflection of the maternal environment in the offspring phenotype, can determine offspring susceptibility to infection. For example, mothers experiencing poor environments such as increased temperatures (Garbutt et al. 2014*b*) or poor nutrition availability (Mitchell and Read 2005; Boots and Roberts 2012) can produce more resistant offspring. Similarly, older mothers have been shown to produce more resistant offspring in both

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vertebrate and invertebrate systems (Hansen et al. 2014; Clark et al. 2017). Phenotypic plasticity in response to the maternal environment, including maternal age, has been shown across taxa (Marshall et al. 2010; Clark et al. 2017; Garbutt and Little 2017), suggesting that maternal age effects on offspring susceptibility can drive population and thus—we hypothesize—epidemiological dynamics (Beckerman et al. 2002; Gaillard et al. 2003; Benton et al. 2008).

Age effects on pathogen dynamics may also occur directly from age-specific changes in pathogen defense systems. For example, vertebrates develop an acquired immune system that commonly wains in later life, while many invertebrates become more resistant to infection with an increase in age (Rheins and Karp 1985; Little et al. 2005; Lesser et al. 2006; Wilson-Rich et al. 2008; Piñera et al. 2013; Garbutt et al. 2014*a*; Rimer et al. 2014; Simon et al. 2015). Epidemiological modeling that considers this individual heterogeneity in pathogen susceptibility as a function of host age has provided great insight into pathogen transmission dynamics (Woolhouse 1991; Wallinga et al. 2006), optimal treatment routines (Truscott et al. 2014, 2016), and vaccination strategies (Anderson and May 1982*a*; Metcalf et al. 2011; Worby et al. 2015; Prada et al. 2017). However, how age-specific pathogen defense interacts with other age-specific performance measures to shape pathogen dynamics at the population level has yet to be considered.

To determine the influence of individual aging on pathogen dynamics, we first conducted two experiments, the observations from which then aided the development of a generalizable epidemiological model. Through our experiments, we aimed to characterize within-host aging specifically in individual traits that we hypothesize could have epidemiological consequences. We collected data across two generations using the model laboratory infection system *Daphnia magna* and its bacterial pathogen *Pasteuria ramosa*. We investigated age-specific performance changes in three traits—the force of mortality, fecundity, and offspring quality—and draw from previous observations that *D. magna* become less susceptible to infection with an increase in age (Garbutt et al. 2014*a*; Izhar and Ben-Ami 2015). We then used an epidemiological model to ask, first, how individual aging in these four traits impact pathogen transmission and, second, how aging in these traits interact to shape pathogen dynamics. We also use this model framework to ask how pathogen transmission could be affected by the amelioration of senescence.

Experimental Methods

A single clone of *Daphnia magna* sourced from Kaimes Pond in the south of Scotland (Stjernman and Little 2011) was used. From acclimated females (see the supplemental PDF, available online), two experiments were set up (fig. 1). The aim of these experiments was to identify and characterize in a single organism common life-history traits that change with age and that could alter pathogen dynamics. The first experiment considered age-specific changes in fecundity and offspring quality. The second experiment quantified the force of mortality—a classic metric of senescence—in infected and uninfected hosts. Both experiments utilized dietary restriction (DR) to manipulate the rate of aging.

DR is a nonpharmacological aging intervention that can delay the onset and reduce the rate of individual senescence in exchange for a reduction in reproductive output in a variety of organisms (McCay et al. 1935; Austad 1989; Good and Tatar 2001; Mair et al. 2004, 2005; Colman et al. 2009; Adler and Bonduriansky 2014). Owing to the long history of use and extensive body of work supporting the effects of DR on rates of senescence, it was used in this study to manipulate the rate at which experimental *Daphnia* senesced. In experiment 1, we aimed to delineate the effects of maternal age from maternal senescence on offspring performance by slowing senescence. In experiment 2, we aimed to lower the force of mortality though the use of DR as an example of different environments that produce different forces of mortality.

Experiment 1

Females of the maternal generation were fed daily 8.75×10^6 chlorella cells for normal food intake or 2.2×10^6 chlorella cells for dietary restriction (Stjernman and Little 2011; fig. 1*A*). Subsets of the maternal generation on each diet treatment provided offspring at three time points (fig. 1*A*)—from the first clutch, the second clutch, or the first clutch after 60 days of age—resulting in offspring from primiparous, young or old mothers.

Life-history data were collected from both the maternal (F_1) and offspring (F_2) generations (fig. 1*B*). Fecundity was measured in F_1 and F_2 generations. Offspring longevity was measured only in unexposed offspring and infection status in exposed offspring. Exposed offspring were given 250,000 *Pasteuria ramosa* spores on the day they were born. Body size was measured in all offspring. See the supplemental PDF for further details.

Experiment 2

This was a fully cross-factored experiment where females were allocated to infection or uninfected treatment groups and, within these, to dietary restriction or normal food intake levels (total $N = 97$; fig. 1*C*). They were treated with *P. ramosa* spores, per the above protocol.

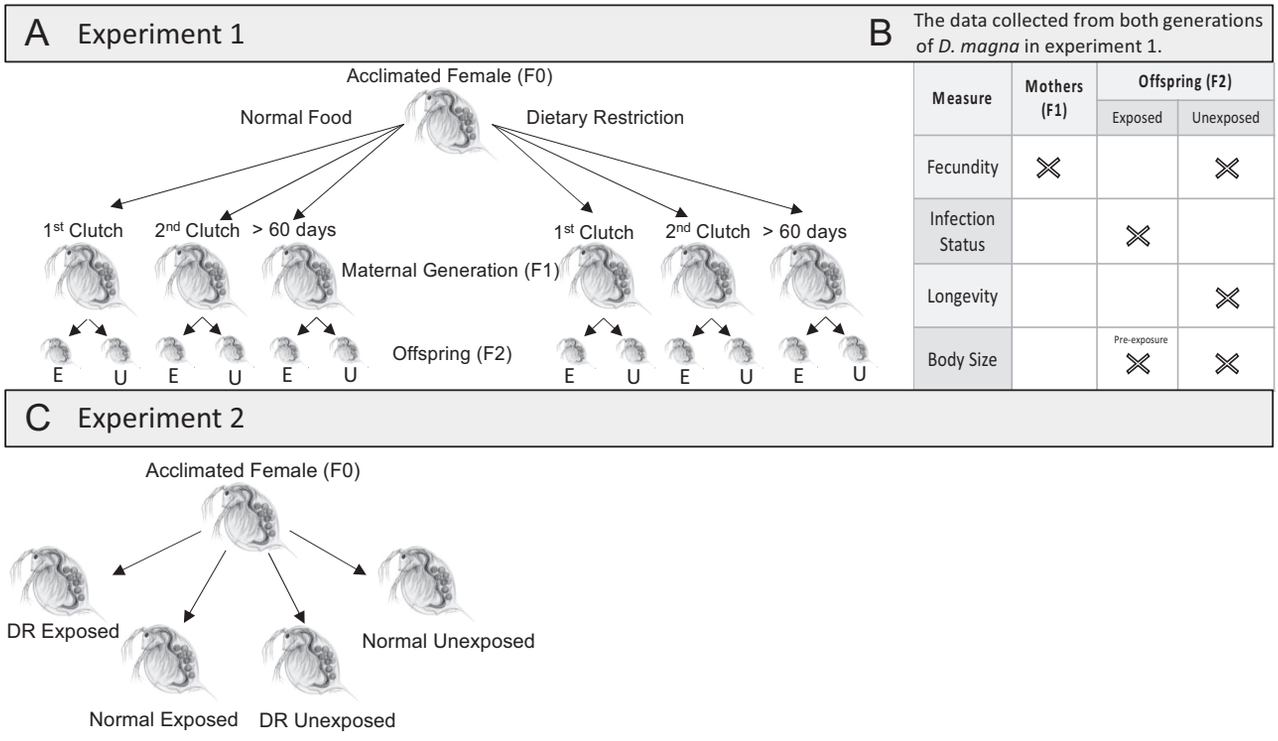


Figure 1: Schematic illustrating the experimental design of experiments 1 and 2. E = exposed; U = unexposed; DR = dietary restriction.

Analysis Methods

All analyses were carried out using R 3.4.3.

Experiment 1

Fecundity. The change in reproductive output with age (reproductive senescence) in the maternal generation (fig. 1, F_1 generation) was analyzed using a polynomial mixed effect model with a normal distribution (R package lme4; Bates et al. 2014). The number of offspring produced at each reproductive event was the response variable with diet (normal: $N = 72$; low: $N = 71$) as an explanatory factor and clutch (reproductive events 1–14) as a continuous variable. Clutch was squared to make the polynomial variable, with clutch and clutch^2 both center scaled using the scale function in R. A unique ID was assigned to each individual for the random effect to account for multiple measures of the same individual (i.e., the number of offspring a female produced at each successive reproductive event).

Mortality. The force of mortality in the offspring generation was analyzed using an accelerated failure time (AFT) model. This parametric analysis specifically allows analysis of factors that increase or decrease life span, that is, the force of mortality. The result of this type of analysis is a percentage increase or decrease in life span as a result of the independent variables. Offspring longevity was analyzed with an AFT model with a Gompertz hazard distribution determined by Akaike information criterion (AIC) comparison. For further details on interpretation, see the supplemental PDF. Maternal age and diet were included as explanatory factors.

Offspring Performance. A generalized linear model with binomial error distribution and a logit link function was used to analyze offspring susceptibility to infection. Analysis of offspring (fig. 1, F_2 generation) fecundity was much like the maternal generation with the number of offspring as the response variable, maternal diet (normal or dietary restriction) and maternal age (primiparous, young or old) as factors, and clutch (1–20) as a continuous scaled variable. Body size at birth was analyzed with an ANOVA with maternal age and diet as explanatory factors.

Experiment 2

Analysis of the force of mortality in infected and uninfected *Daphnia magna* was also conducted with an AFT

model, though with a Weibull hazard distribution, as chosen based on AIC comparison. The response variable was days alive, with diet and infection status as explanatory variables. Further details on interpretation of the Weibull parameters can be found in the supplemental PDF.

Model Methods

Our experimental results show that in *Daphnia magna*, aging differentially impacts life-history traits that could impact pathogen dynamics. Considering these results, while appreciating the vast diversity in aging across taxa, we developed an age-structured epidemiological model (Clark et al. 2017) that is generalizable beyond our experimental model system. We do not include features specifically of the *Daphnia*/*Pasteuria ramosa* system (e.g., host castration, typical of *P. ramosa*). We instead consider the effect of the pathogen as increased mortality when infected. This is in keeping with our results but is also a typical characteristic of many infectious diseases. We also include the full range of aging in the four life-history traits, thereby encompassing the aging profile seen in our results but also allowing for aging profiles seen across taxa, thus resulting in a model framework applicable across host/pathogen systems. We use this model framework to test two hypotheses: (1) Host aging in our four traits can impact pathogen transmission both directly and indirectly. Age-specific pathogen defense systems and transgenerational effects on pathogen defense systems should directly impact infection dynamics through alterations to the occurrence of transmission events. Conversely, changes in rates of mortality or reproduction as a result of age structure will indirectly alter infectious disease burden by altering the density of susceptible hosts and the overall level of susceptibility in the population. (2) The effects of aging in each trait will interact to produce complex patterns of pathogen transmission. This could occur because of dependencies between the traits; for example, the effect of age-specific pathogen defense on transmission depends on population age structure, which is a function of the force of mortality. In addition to testing these hypotheses, we also use the model framework to ask how ameliorating senescence in each trait could impact pathogen transmission.

Aging traits were modeled in line with a pleiotropy model of aging (Williams 1957; Garbutt et al. 2014*a*), where increased performance in a trait at one age results in decreased performance for that same trait in the opposing age class. We investigated the effect of age-specific performance on R_0, a benchmark value that determines epidemic potential within a given population. If a pathogen's R_0 is >1, then its introduction to a given naive population will result in a sustained outbreak (Dietz 1993).

We derived R_0 using the next-generation matrix method. This method allows for a finite number of discrete population categories—in this instance, defined by age and maternal age. A brief overview of the methodology for the derivation of R_0 will be provided here for clarity, and all scripts are publicly available; however, for a detailed protocol, the reader is encouraged to refer to Diekmann and colleagues (2010), Blackwood and Childs (2018), and Bjørnstad (2019). We derive R_0 by splitting equations (1e)–(1h) into two matrices: $\boldsymbol{F}$, which contains all terms for all completely new infections, and $\boldsymbol{V}$, which contains all gains, losses, and transfers between the classes. From these, two Jacobian matrices $\boldsymbol{f}$ and $\boldsymbol{v}$ are developed as the partial derivatives of $\boldsymbol{F}$ and $\boldsymbol{V}$ with respect to the infectious state variables (in this case, the four infected age classes). These are evaluated at the disease-free equilibrium (dfe; suppl. eqq. [3a]–[3d]; suppl. eqq. [1]–[12] are available online)). Then R_0 is given by the dominant eigenvalue of $\boldsymbol{f}\boldsymbol{v}^{-1}\big|_{\text{dfe}}$.

Parameter and state variable descriptions are provided in table 1. Each class is denoted by three characters: infection status (I = inflected; U = uninfected), host age (first subscript; Y = young; O = old), and maternal age (second subscript, Y or O). For example, an uninfected young host from an old mother is denoted $U_{Y,O}$.

The equations describing the dynamics and densities of the susceptible and infected hosts of all age classes are given by

Table 1: Definitions of state variables and model parameters

Variable/parameter	Definition
N	Total population size
U	Uninfected
I	Infected
Y	Young
O	Old
δ	Rate of extrinsic mortality
m	Rate of maturation
k	Carrying capacity
r	Rate of reproduction (fecundity)
v	Pathogen induced mortality
x	Proportional chance in fecundity with age
y	Proportional change in force of mortality with age
A	Proportional change in age-specific pathogen defense with age
M	Proportional change in transgenerational effects on pathogen defense with age
β	Transmission coefficient

$$\frac{dU_{Y,Y}}{dt} = \left((r(1+x)U_{Y,Y} + r(1+x)U_{Y,O})\left(1 - \frac{N_U}{k}\right)\right) - \beta_{Y,Y}U_{Y,Y}N_I - U_{Y,Y}(m + \nu + \delta(1-y)), \quad (1a)$$

$$\frac{dU_{Y,O}}{dt} = \left((r(1-x)U_{O,Y} + r(1-x)U_{O,O})\left(1 - \frac{N_U}{k}\right)\right) - \beta_{Y,O}U_{Y,O}N_I - U_{Y,O}(m + \nu + \delta(1-y)), \quad (1b)$$

$$\frac{dU_{O,Y}}{dt} = mU_{Y,Y} - \beta_{O,Y}U_{O,Y}N_I - U_{O,Y}(\nu + \delta(1+y)), \quad (1c)$$

$$\frac{dU_{O,O}}{dt} = mU_{Y,O} - \beta_{O,O}U_{O,O}N_I - U_{O,O}(\nu + \delta(1+y)), \quad (1d)$$

$$\frac{dI_{Y,Y}}{dt} = \beta_{Y,Y}U_{Y,Y}N_I - I_{Y,Y}(m + \nu + c + \delta(1-y)), \quad (1e)$$

$$\frac{dI_{Y,O}}{dt} = \beta_{Y,O}U_{Y,O}N_I - I_{Y,O}(m + \nu + c + \delta(1-y)), \quad (1f)$$

$$\frac{dI_{O,Y}}{dt} = \beta_{O,Y}U_{O,Y}N_I + mI_{Y,Y} - I_{O,Y}(\nu + c + \delta(1+y)), \quad (1g)$$

$$\frac{dI_{O,O}}{dt} = \beta_{O,O}U_{O,O}N_I + mI_{Y,O} - I_{O,O}(\nu + c + \delta(1+y)), \quad (1h)$$

$$N_I = I_{Y,Y} + I_{Y,O} + I_{O,Y} + I_{O,O}, \quad (1i)$$

$$N_U = U_{Y,Y} + U_{Y,O} + U_{O,Y} + U_{O,O}, \quad (1j)$$

$$N = N_I + N_U. \quad (1k)$$

Equations (1a)–(1d) describe the uninfected population, (1e)–(1h) describe the infected population, and (1i)–(1k) describe the total densities of each and their total. Here, $x \in [-1, 1]$ and $y \in [-1, 1]$ are age-specific changes in fecundity and mortality, respectively, where approaching -1 accounts for juvenescence, and 1 is the extent of senescence.

Assuming that the effects of age and maternal age interact multiplicatively per an earlier model (Clark et al. 2017), the transmission to each host age class is then given by

$$\beta_{Y,Y} = \beta(1-A)(1-M), \quad (2a)$$

$$\beta_{Y,O} = \beta(1-A)(1+M), \quad (2b)$$

$$\beta_{O,Y} = \beta(1+A)(1-M), \quad (2c)$$

$$\beta_{O,O} = \beta(1+A)(1+M), \quad (2d)$$

where the proportional effect of age on pathogen susceptibility $A \in [-1, 1]$ and the effect of maternal age on pathogen susceptibility $M \in [-1, 1]$. The resulting R_0 term is given in supplemental equation (8).

All data, scripts, and notebooks have been deposited in the Dryad Digital Repository (https://doi.org/10.5061/dryad.8cz8w9gnh; Clark et al. 2020).

Experimental Results

Experiment 1

Adult female *Daphnia* on dietary restriction produced fewer offspring in each clutch but did not show fecundity senescence, unlike females on a regular diet, who showed clear signs of fecundity senescence (fig. 2*A*; linear interaction: $f_{1,1,337.1} = 70.73$, $P \leq .0001$; quadratic interaction: $f_{1,1,298.7} = 10.07$, $P = .0015$). Offspring from old mothers were more resistant to infection regardless of maternal food levels (fig. 2*B*; maternal age: $\chi^2_2 = 31.05$, $P \leq .0001$; maternal food: $\chi^2_1 = 0.159$, $P = .7$). Older mothers had larger offspring, with dietary restriction affecting only the size of offspring from primiparous mothers (interaction: $f_{2,553} = 38.369$, $P \leq .0001$; fig. S2; figs. S1–S3 are available online). However, maternal age had no effect on offspring fecundity senescence (fig. S1), but fecundity senescence in offspring of normally fed mothers occurred marginally faster than in offspring of DR mothers (fig. S1). Maternal treatments had no effect on the rate of offspring mortality or longevity (fig. S2).

Experiment 2

The probability of mortality increased with age in *Daphnia magna* (fig. 2*C*; shape (α) = 5.03, lower 95% confidence interval (CI) = 4.52, upper CI = 5.60; scale (μ) = 79.55, lower CI = 79.10, upper CI = 83.16). Dietary restriction in uninfected females increased *D. magna* longevity by 10% (fig. 2*A*; est. = 1.098, lower CI = 1.0404, upper CI = 1.1607). Infected individuals had a 35% reduction in survival (fig. 2*A*; est. = 0.648; lower CI =0.61, upper CI = 0.69).

Modeling Results

We modeled how age-specific changes in fecundity, mortality, susceptibility, and transgenerational effects on pathogen susceptibility may affect R_0. Our analytical results (for specific model details, see the supplemental PDF) show that the effects of aging on pathogen dynamics are largely driven by the relationship between rates of extrinsic mortality (an

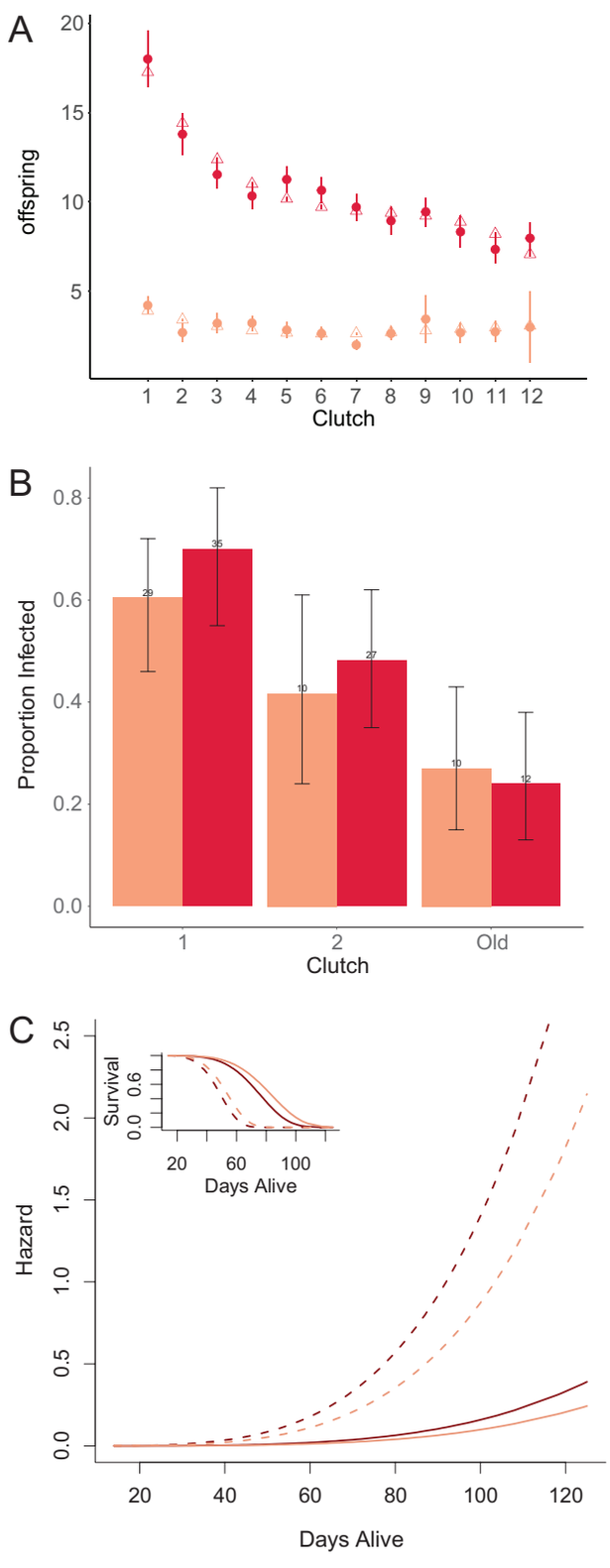


Figure 2: Performance measures across two generations. In all figures, pink represents dietary restriction (DR) and red a normal diet. *A*, Number of offspring produced in clutches 1–13 in the maternal generation from normal diet females and DR females. Data (circle) and model predictions (triangle) are both shown with standard errors. *B*, Proportion of infected offspring from each maternal treatment group with Wilson score binomial confidence intervals. *C*, Force of mortality for four treatments. Solid lines represent uninfected females, and dotted lines show infected females. The inset shows the survival curve of the experimental females.

environmental property) and the rate of maturation (a characteristic of the host). We therefore investigated the effect of aging on pathogen transmission using three levels of extrinsic mortality: low (where the extrinsic mortality rate is less than the maturation rate), medium (where extrinsic mortality rate and maturation rate are equal), and high (where the extrinsic mortality rate exceeds the maturation rate). These can be thought of as simulating mild, moderate, or harsh ecological conditions, respectively.

Aging Has Direct and Indirect Effects on Pathogen Transmission

We first modeled the effect of each aging trait on R_0 in the absence of the other traits. Increasing levels of fecundity and mortality senescence indirectly increase pathogen R_0 under high extrinsic mortality (fig. 3*A*, 3*B*; suppl. eqq. [9], [10]) through their effects on population density and age structure (fig. 3*E*–3*J*; suppl. eqq. [5], [6]). Again, under high extrinsic mortality, old individuals are in lower density, while there are many young hosts. Per the pleiotropic framework of the model, under increasing levels of fecundity senescence, young hosts are producing offspring at an early age. Those young offspring then also reproduce very young and so on, producing a strong supply of hosts. In the case of mortality senescence, the increased intrinsic rate of mortality reduces the number of old hosts further, relieving the carrying capacity pressure. In both cases, this results in an increase in overall population density (fig. 2*I*, 2*J*) and thus an increase in transmission. Conversely, under low extrinsic mortality (mild ecological conditions), increasing levels of senescence in age-specific and transgenerational pathogen defense drove an increase in R_0 (fig. 3*C*, 3*D*; suppl. eqq. [11], [12]). In this low extrinsic mortality scenario, populations consist of many old susceptible hosts, resulting in an increase in transmission. At high extrinsic death rates (harsh ecological conditions), R_0 is decreasing as old, susceptible individuals are more likely to have died, leaving a high density of young resistant hosts.

Interacting Traits Result in Complex Impacts of Aging on Epidemics

The effect of the interactions between aging traits on pathogen R_0 varies greatly under different levels of extrinsic

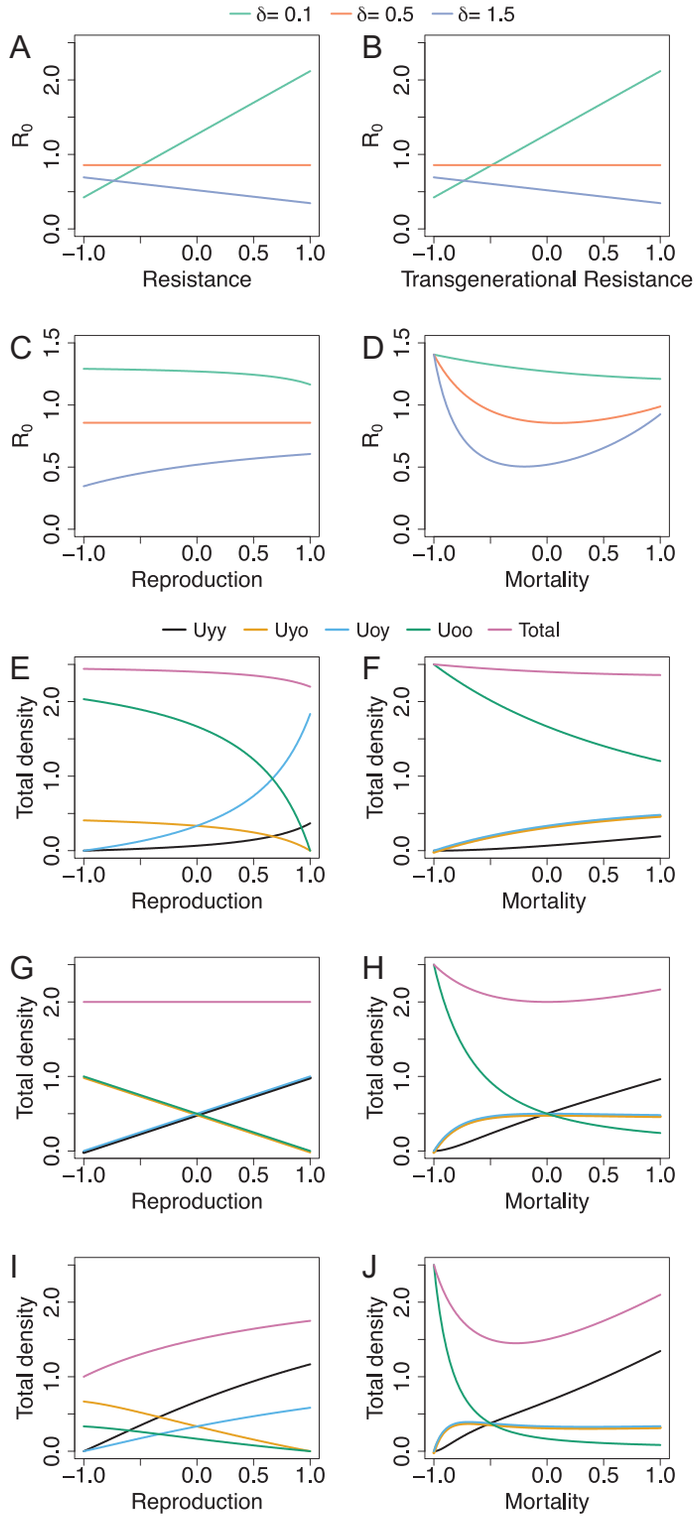
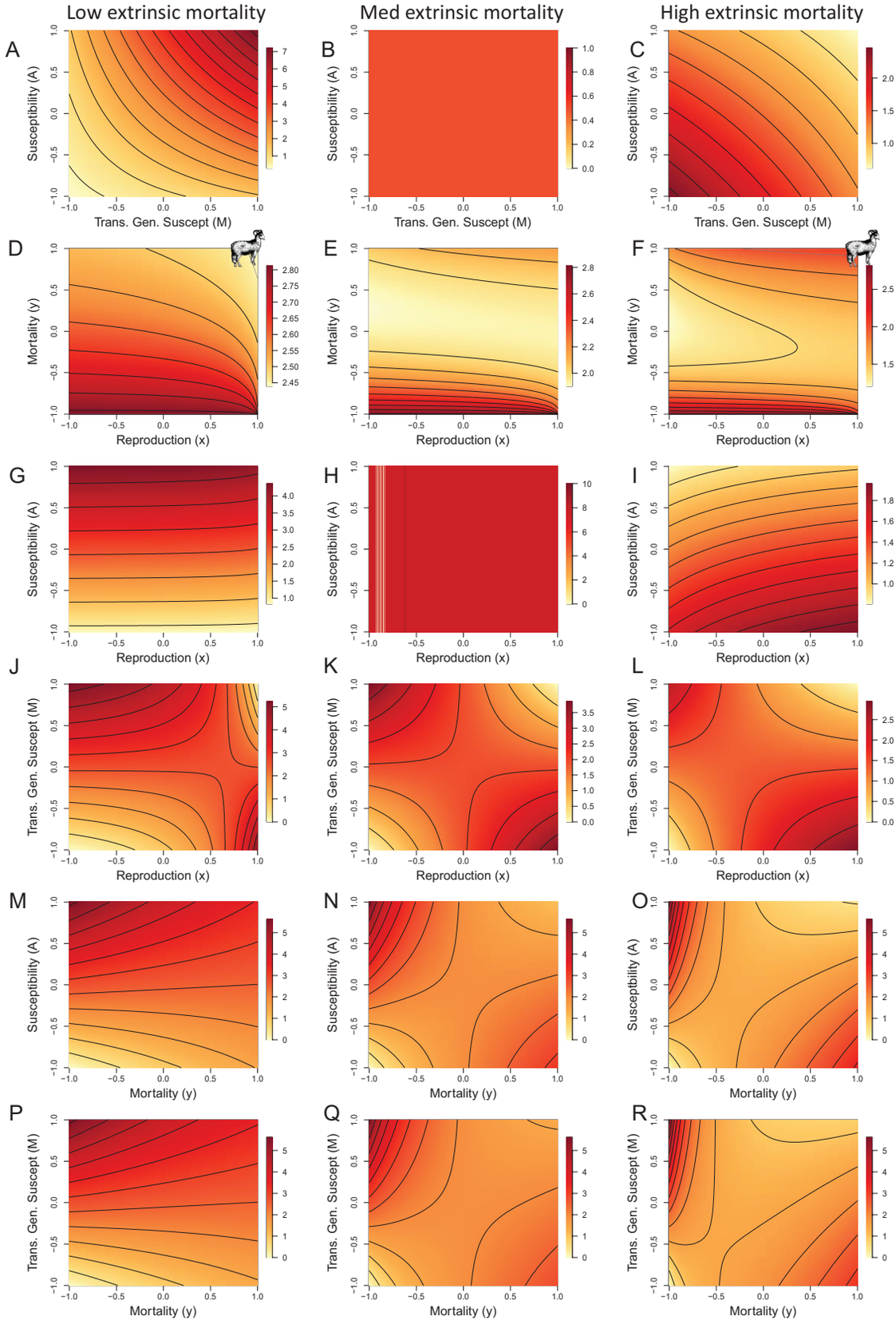


Figure 3: Relationship between aging and R_0 across four traits under variation in extrinsic mortality (δ). Trait aging spans a spectrum from juvenescence (-1) to senescence (1), representing the range of proportional changes in performance with age. *A*, R_0 and fecundity *x*. *B*, R_0 and mortality *y*. *C*, R_0 and transgenerational pathogen defense *M*. *D*, R_0 and age-specific defense *A*. Panels *E–I* display population density with respect to reproductive aging at low mortality ($\delta < m$; $\delta = 0.1$), medium mortality ($\delta = m$; $\delta = 0.5$), and high mortality ($\delta > m$; $\delta = 1$), respectively. Panels *F–J* display population density and age structure with respect to mortality aging at low, medium, and high extrinsic mortality, respectively. Purple = total population density (N_U); red = young individuals from young mothers ($U_{Y,Y}$); blue = young individuals from old mothers ($U_{Y,O}$); yellow = old individuals from young mothers ($U_{O,Y}$); green = old individuals from old mothers ($U_{O,O}$); $r = k = 5$; $c = 0.1$; $m = 0.5$; $\alpha = 1.5$; $\beta = 0.9$.


Low extrinsic mortality
Med extrinsic mortality
High extrinsic mortality
A
B
C
D
E
F
G
H
I
J
K
L
M
N
O
P
Q
R
Susceptibility (A)
Trans. Gen. Suscept (M)
Mortality (y)
Reproduction (x)

mortality, as exemplified in figure 4. We first use the interaction between the two forms of pathogen susceptibility as an example (fig. 4*A*–4*C*). Under low extrinsic mortality (fig. 4*A*), the interaction between pathogen defense and transgenerational pathogen defense has little impact on R_0 when both traits are juvenescent (a plausible biological pattern that we have observed in *Daphnia*; fig. 2; Garbutt et al. 2014*a*). Alternatively, there is a dramatic rise in R_0 when both traits are senescent. In a high-mortality environment, however, the resulting transmission dynamics of this interaction are reversed (fig. 3*C*). As another example, we consider the interaction between reproduction and mortality (fig. 3*D*–3*F*). Under low extrinsic mortality, the pattern of aging that results in the least transmission in this environment is senescence in both traits. This is a typical aging pattern of many mammals, as illustrated by the Soay sheep (Hayward et al. 2015). If we consider this interaction in a high-mortality setting, these interacting traits influence demography sufficiently to produce an environment with higher pathogen transmission than if a different pattern of senescence was observed within the same environment.

Senescence Interventions Can Increase or Mediate Pathogen Transmission

We next considered how senescence interventions that increase the duration of optimal performance could impact pathogen transmission. Such interventions could include nonpharmacological interventions such as dietary restriction and could be applicable to any organism where aging is characterized by a decline in performance in the four modeled traits. However, wild populations are likely to experience higher extrinsic mortality rates, curtailing any benefit to the extension of performance or life span. Alternatively, there is evidence to suggest that actuarial rates of senescence in humans is slowing, driven in part by reductions in extrinsic mortality (Gurven and Fenelon 2009). Furthermore, there is evidence of DR extending human life span, and the use of clinical interventions in humans is gaining momentum (Kennedy and Pennypacker 2015; Most et al. 2017). We therefore model the impact of a senescence intervention in a human population experiencing low extrinsic mortality. This is also more likely to describe a population that would have access to such interventions. We consider the effect of the intervention on one trait at a time while modeling the others at a mild level of senescence (fig. 5).

An intervention that reduces the force of mortality, thus extending life span, can result in an increase in transmission. The more efficacious the intervention, the starker the increase in transmission (fig. 5). This result is intuitive because a reduction in the force of mortality with an increase in age means more individuals in the population reach old age. In the absence of any improvement to pathogen defense with age, old individuals are less resistant to infection, so transmission increases. In contrast, interventions that maintain pathogen defense capability could reduce R_0 by decreasing transmission events (fig. 5). However, aging traits do not occur in isolation, and so the dramatic increase in R_0 as a result of decreased mortality senescence may be tempered by a reduction in immunosenescence (fig. 4*J*).

Discussion

Our experimental and modeling results show that individual aging can drive pathogen dynamics at the population level. In our experiments, we showed that changes in age-specific performance do occur in traits we later link to pathogen transmission but not in a uniform direction. While fecundity and survival declined with age, the transgenerational impact of increased maternal age saw either no effect or improvements in offspring performance. Our modeling results show that when considered independently, each measure of aging can modify pathogen R_0. Our analytical results also provided insight into the environmental conditions (extrinsic mortality pressure) that benefit pathogen transmission in the presence of aging. However, our model results also indicate that considering the effects of aging in single traits is insufficient to understand the relationship between aging and pathogen transmission. Specifically, the three-way interaction (fig. 4) between aging traits and extrinsic mortality clearly show that aging can have complex effects on pathogen dynamics. The predictions we might derive from them are of particular interest for populations subject to rapid ecological change or harvesting, as they may indicate which groups of organisms are at risk of epidemic outbreak within specific ecological conditions.

Figure 4: Landscape of R_0 as a result of interactions between pairs of aging traits under three levels of extrinsic mortality, indicative of three different environmental conditions. Color intensity presents R_0 from darkest red at the highest R_0 to white with the lowest R_0. Numerical R_0 values of each scenario are as shown. Each axis is labeled with the interacting trait, with the spectrum of aging from juvenescence (-1) to senescence (1) representing proportional change in each performance measure with age. *Left column*, low extrinsic mortality ($\delta < m$; $\delta = 0.1$); *center*, medium extrinsic mortality ($\delta = m$; $\delta = 0.5$); *right*, high extrinsic mortality ($\delta > m$; $\delta = 1$). In each plot, the two measures of senescence not considered are set to zero. The Soay sheep in figures D and F highlight a specific aging example given in the text. Other parameters are as follows: $r = k = 5$; $c = 0.1$; $m = 0.5$; $\alpha = 0.9$; $\beta = 0.9$.

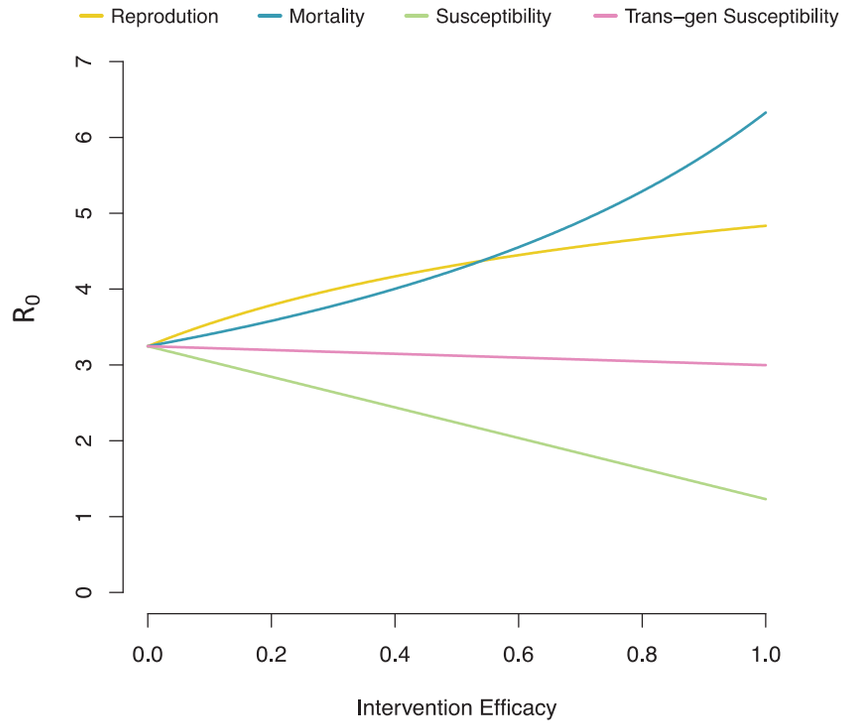


Figure 5: Case where any aging intervention increases physiological performance within a population and the effects on R_0 (Y-axis). Note the different X-axis to previous modeling figures; here, the X-axis is the efficacy of any intervention that slows senescence, maintaining optimal performance for longer. The 0 on the X-axis represents no treatment; values to the right represent the corresponding increase in performance capability of a particular trait. Yellow = reproductive senescence; blue = mortality senescence; green = age-specific pathogen defense; pink = transgenerational effect of age on defense; $\delta = 0.1$; $r = k = 5$; $c = 0.1$; $m = 0.5$; $\alpha = 1.5$; $\beta = 0.9$. Each remaining aging trait is held constant at 0.5.

We also show that the extension of life span in the absence of improved immune function could lead to an increase in pathogen transmission (fig. 5). These results are applicable to any organism that shows senescence, but they are of pressing concern when considering the gathering interest in the development of life-extending treatment for humans (Kennedy and Pennypacker 2015). While global life expectancy increased from 2000 to 2015, it was not matched with an extension in health span, such that individuals now spend, on average, 16%–20% of their lives suffering from morbidity (Jagger et al. 2008; Partridge et al. 2018; but see the WHO Global Health Observatory data repository). It is therefore clear that the extension of health span should take priority over an extension of life span in aging intervention research.

In light of rapid changes to population age structure seen globally, another question is how this will affect the evolution of pathogen virulence. This is relevant to many age-structured host-pathogen systems, not just human infections, for instance, nonhuman animal populations that undergo harvesting or are experiencing rapidly changing mortality pressures. Our experimental results show that individuals of different ages experience the force of mortality differentially. Intrinsic and extrinsic mortality have both been shown independently to be strong selective factors in determining optimal virulence within a population (Ebert and Mangin 1997; Mackinnon and Read 2002; Choo et al. 2003; Yates et al. 2006; Gandon et al. 2007; Alizon 2008; Cousineau and Alizon 2014). Furthermore, heterogeneities in host susceptibility or tolerance to infection can exacerbate the effects of co-occurring population structure on virulence evolution (Cousineau and Alizon 2014). Based on our results that age-specific traits interact to impact pathogen transmission, it is clear that considering the effect of each of our studied traits in tandem could provide insight into the evolution of virulence.

In keeping with numerous studies, dietary restriction reduced the force of mortality in *Daphnia magna*. An interesting result is that this was even the case for infected individuals. This could suggest that DR is in some way encouraging recovery. However, as *Pasteuria ramosa* is a castrating parasite whose virulence can thus be measured as a function of its ability to castrate, we suspect one would see a recovery of reproductive capability if a general recovery were occurring. Alternatively, the reduction in the force of mortality in infected hosts could be because

the parasite is also resource limited. Dietary restriction reduces reproductive output, suggesting that fewer resources are allocated to reproduction and that fewer resources are thus available for exploitation by the parasite. This hypothesis is supported by Vale and colleagues (2013), who showed that the number of spores produced by infected *D. magna* was lower and randomly distributed across hosts when hosts were DR treated.

Increased maternal age did not impact the force of mortality in offspring. In conjunction with the juvenescence of offspring performance, there was no evidence of the Lansing effect, which proposes that old mothers transmit a senesced state to their offspring (Lansing 1947; Comfort 1953; Van Den Heuvel et al. 2016). These results contrast with observations from humans, where congenital disorders are seen more commonly in offspring of older mothers (Kenny et al. 2013), or with other taxa, where negative impacts of advancing parental age on offspring life history have been recorded (Lansing 1947; Comfort 1953; Benton et al. 2005; Hjelmborg et al. 2015; Plaistow et al. 2015). Indeed, the reduction in *Daphnia* susceptibility to infection with age has interesting implications for pathogen transmission. This is highlighted by Ashby and Bruns (2018), who show that juvenile susceptibility to pathogenic infection could evolve from trade-offs between juvenile susceptibility and reproduction later in life and between susceptibility and the probability of maturation under a variety of conditions. Our experimental results and their model results are in agreement when considering their prediction that organisms with short life spans and low probability of maturation are likely to evolve juvenile susceptibility. Our modeling results are also in keeping with Ashby and Bruns's results, as our modeling results highlight the importance of the relationship between host reproduction and maturation in pathogen dynamics.

Despite previous evidence that maternal DR increases offspring body size (Garbutt and Little 2017), DR had no additional effect on offspring body size, after accounting for the effects of maternal age. The superior size and performance of the offspring of older mothers was evident regardless of how much food mothers received (fig. S2). Thus, DR did not impact the changes in offspring quality that accompany the effects of maternal age. Maternal age has previously been shown to impact offspring body size (Priest et al. 2002; Benton et al. 2008); however, where this is the case, mothers often produce fewer offspring, suggesting a size versus number trade-off that we did not explore in these experiments. Furthermore, we were unable to delineate the effects of maternal body size and age on offspring performance, as *D. magna* continuously grow throughout their lifetime. To understand the mechanisms driving transgenerational effects in *D. magna* it would be helpful to know more about changes in egg composition and energy allocation (as in *Drosophila* in O'Brien et al. 2008) or the epigenetic responses resulting from age or food. This could help delineate the effects of size and age. Previous studies show that *D. magna* microRNAs respond to nutritional stress and aging, but these responses are not transgenerational (Hearn et al. 2018). It is of note, however, that our experiments were not designed to probe the mechanisms of DR but instead were used to manipulate aging to inform a mathematical model that we used to explore the epidemiological consequences of individual variation in aging.

In summary, through the use of experiments and mathematical models, we show that aging is indeed a multifaceted architect of pathogen dynamics, requiring far greater consideration in epidemiological studies. By striving to accommodate complex patterns of aging into epidemiological studies, we can move beyond immune systems or contact rates to consider the effects of all aspects of individual aging on infectious disease dynamics.

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Statement of Authorship

Conceptualization, funding acquisition, methods and experimental design, writing (original draft, review, editing), and data analysis: J.C., L.M., T.L. Data collection: J.C. Data visualization, model writing, coding, and analytical assessment: J.C., L.M. Data validation: J.C., T.L. Provision of resources and supervision: L.M., T.L.

Data and Code Availability

All data, R scripts, and Mathematica notebooks are deposited in the Dryad Data Repository (https://doi.org/10.5061/dryad.8cz8w9gnh; Clark et al. 2020).

Literature Cited

Adler, M. I., and R. Bonduriansky. 2014. Why do the well-fed appear to die young? a new evolutionary hypothesis for the effect of dietary restriction on lifespan. BioEssays 36:439–450.

Alizon, S. 2008. Transmission-recovery trade-offs to study parasite evolution. American Naturalist 172:E113–E121.

Anderson, R. M., and R. M. May. 1982*a*. Directly transmitted infectious diseases: control by vaccination. Science 215:1053–1060.

———. 1982*b*. Population dynamics of human helminth infections: control by chemotherapy. Nature 297:557–563.

Ashby, B., and E. Bruns. 2018. The evolution of juvenile susceptibility to infectious disease. Proceedings of the Royal Society B 285:20180844. https://doi.org/10.1098/rspb.2018.0844.

Austad, S. N. 1989. Life extension by dietary restriction in the bowl and doily spider, *Frontinella pyramitela*. Experimental Gerontology 24:83–92.

Bates, D., M. Mächler, B. Bolker, and S. Walker. 2014. Fitting linear mixed-effects models using lme4. Journal of Statistical Software 67. https://doi.org/10.18637/jss.v067.i01.

Beckerman, A. P., T. G. Benton, E. Ranta, V. Kaitala, and P. Lundberg. 2002. Population dynamic consequences of delayed life-history effects. Trends in Ecology and Evolution 17:263–269.

Benton, T. G., S. J. Plaistow, A. P. Beckerman, C. T. Lapsley, and S. Littlejohns. 2005. Changes in maternal investment in eggs can affect population dynamics. Proceedings of the Royal Society B 272:1351–1356.

Benton, T. G., J. J. H. St. Clair, and S. J. Plaistow. 2008. Maternal effects mediated by maternal age: from life histories to population dynamics. Journal of Animal Ecology 77:1038–1046.

Bjørnstad, O. N. 2019. Epidemics: models and data using R. Springer, Cham, Switzerland.

Blackwood, J. C., and L. M. Childs. 2018. An introduction to compartmental modeling for the budding infectious disease modeler. Letters in Biomathematics 5:195–221.

Boots, M., and K. E. Roberts. 2012. Maternal effects in disease resistance: poor maternal environment increases offspring resistance to an insect virus. Proceedings of the Royal Society B 279:4009–4014.

Chan, M. S., H. L. Guyatt, D. A. P. Bundy, and G. F. Medley. 1994. The development and validation of an age-structured model for the evaluation of disease control strategies for intestinal helminths. Parasitology 109:389–396.

Choo, K., P. D. Williams, and T. Day. 2003. Host mortality, predation and the evolution of parasite virulence. Ecology Letters 6:310–315.

Clark, J., J. S. Garbutt, L. McNally, and T. J. Little. 2017. Disease spread in age structured populations with maternal age effects. Ecology Letters 20:445–451.

Clark, J., L. McNally, and T. J. Little. 2020. Data from: Pathogen dynamics across the diversity of aging. American Naturalist, Dryad Digital Repository, https://doi.org/10.5061/dryad.8cz8w9gnh.

Colman, R. J., R. M. Anderson, S. C. Johnson, E. K. Kastman, H. A. Simmons, J. W. Kemnitz, and R. Weindruch. 2009. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science 325:201–204.

Comfort, A. 1953. Absence of a Lansing effect in *Drosophila subobscura*. Nature 171:59.

Cousineau, S. V., and S. Alizon. 2014. Parasite evolution in response to sex-based host heterogeneity in resistance and tolerance. Journal of Evolutionary Biology 27:2753–2766.

Davies, N. G., P. Klepac, Y. Liu, K. Prem, M. Jit, CMMID COVID-19 working group, and R. M. Eggo. 2020. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nature Medicine 26:1205–1211.

Diekmann, O., J. A. Heesterbeek, and M. G. Roberts. 2010. The construction of next-generation matrices for compartmental epidemic models. Journal of the Royal Society Interface 7:873–885.

Dietz, K. 1993. The estimation of the basic reproduction number for infectious diseases. Statistical Methods in Medical Research 2:23–41.

Ebert, D., and K. L. Mangin. 1997. The influence of host demography on the evolution of virulence of a microsporidian gut parasite. Evolution 51:1828–1837.

Gaillard, J.-M., A. Loison, C. Toigo, D. Delorme, and G. Van Laere. 2003. Cohort effects and deer population dynamics. Écoscience 10:412–420.

Gandon, S., V. A. A. Jansen, and M. van Baalen. 2007. Host life history and the evolution of parasite virulence. Evolution 55:1056–1062.

Garbutt, J. S., and T. J. Little. 2017. Bigger is better: changes in body size explain a maternal effect of food on offspring disease resistance. Ecology 7:1403–1409.

Garbutt, J. S., A. J. P. O'Donoghue, S. J. McTaggart, P. J. Wilson, and T. J. Little. 2014*a*. The development of pathogen resistance in *Daphnia magna*: implications for disease spread in age-structured populations. Journal of Experimental Biology 217:3929–3934.

Garbutt, J. S., J. A. Scholefield, P. F. Vale, and T. J. Little. 2014*b*. Elevated maternal temperature enhances offspring disease resistance in *Daphnia magna*. Functional Ecology 28:424–431.

Goldstein, J. R. 2009. How populations age. Pages 7–18 *in* P. Uhlenberg, ed. International handbook of population aging. Springer, Dordrecht, Netherlands.

Good, T. P., and M. Tatar. 2001. Age-specific mortality and reproduction respond to adult dietary restriction in *Drosophila melanogaster*. Journal of Insect Physiology 47:1467–1473.

Gurven, M., and A. Fenelon. 2009. Has actuarial aging "slowed" over the past 250 years? a comparison of small-scale subsistence populations and European cohorts. Evolution 63:1017–1035.

Hansen, Ø. J., V. Puvanendran, and R. Bangera. 2014. Do maternal age and experience contribute to better growth, survival and disease resistance of offspring in Atlantic cod (*Gadus morhua*)? Aquaculture International 23:1157–1164.

Hayward, A. D., J. Moorad, C. E. Regan, C. Berenos, J. G. Pilkington, J. M. Pemberton, and D. H. Nussey. 2015. Asynchrony of senescence among phenotypic traits in a wild mammal population. Experimental Gerontology 71:56–68.

Hearn, J., F. W. Chow, H. Barton, M. Tung, P. J. Wilson, M. Blaxter, A. Buck, et al. 2018. *Daphnia magna* microRNAs respond to nutritional stress and ageing but are not transgenerational. Molecular Ecology 27:1402–1412.

Hjelmborg, J. B., C. Dalgård, M. Mangino, T. D. Spector, U. Halekoh, S. Möller, M. Kimura, et al. 2015. Paternal age and telomere length in twins: the germ stem cell selection paradigm. Aging Cell 14:701–703.

Izhar, R., and F. Ben-Ami. 2015. Host age modulates parasite infectivity, virulence and reproduction. Journal of Animal Ecology 84:1018–1028.

Jagger, C., C. Gillies, F. Moscone, E. Cambois, H. van Oyen, W. Nusselder, J.-M. Robine, et al. 2008. Inequalities in healthy life years in the 25 countries of the European Union in 2005: a cross-national meta-regression analysis. Lancet 372:2124–2131.

Jones, O. R., A. Scheuerlein, R. Salguero-Gómez, C. G. Camarda, R. Schaible, B. B. Casper, J. P. Dahlgren, et al. 2014. Diversity of ageing across the tree of life. Nature 505:169–173.

Kennedy, J. K., and B. K. Pennypacker. 2015. Aging interventions get human. Oncotarget 6:590–591.

Kenny, L. C., T. Lavender, R. McNamee, S. M. O'Neill, T. Mills, and A. S. Khashan. 2013. Advanced maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort. PLoS ONE 8:1–9.

Lansing, A. I. 1947. A transmissible, cumulative, and reversible factor in aging. Journal of Gerontology 2:228–239.

Lecomte, V. J., G. Sorci, S. Cornet, A. Jaeger, B. Faivre, E. Arnoux, M. Gaillard, et al. 2010. Patterns of aging in the long-lived wandering albatross. Proceedings of the National Academy of Sciences of the USA 107:6370–6375.

Lesser, K. J., I. C. Paiusi, and J. Leips. 2006. Naturally occurring genetic variation in the age-specific immune response of *Drosophila melanogaster*. Aging Cell 5:293–295.

Little, T. J., D. Hultmark, and A. F. Read. 2005. Invertebrate immunity and the limits of mechanistic immunology. Nature Immunology 6:651–654.

Mackinnon, M. J., and A. F. Read. 2002. Effects of host immunity on virulence transmissibility relationships in the rodent malaria parasite *Plasmodium chabaudi*. Parasitology 126:103–112.

Mair, W., M. D. W. Piper, and L. Partridge. 2005. Calories do not explain extension of life span by dietary restriction in *Drosophila*. PLoS Biology 3:e223.

Mair, W., C. M. Sgrò, A. P. Johnson, T. Chapman, and L. Partridge. 2004. Lifespan extension by dietary restriction in female *Drosophila melanogaster* is not caused by a reduction in vitellogenesis or ovarian activity. Experimental Gerontology 39:1011–1019.

Marshall, D. J., S. S. Heppell, S. B. Munch, and R. R. Warner. 2010. The relationship between maternal phenotype and offspring quality: do older mothers really produce the best offspring? Ecology 91:2862–2873.

McCay, C. M., M. F. Crowell, and A. L. Maynard. 1935. The effect of retarded growth upon the length of lifespan and upon the ultimate body size. Journal of Nutrition 5:63–79.

Metcalf, C. J., P. Klepac, M. Ferrari, R. F. Grais, A. Djibo, and B. T. Grenfell. 2011. Modelling the first dose of measles vaccination: the role of maternal immunity, demographic factors, and delivery systems. Epidemiology and Infection 139:265–274.

Mitchell, S. E., and A. F. Read. 2005. Poor maternal environment enhances offspring disease resistance in an invertebrate. Proceedings of the Royal Society B 272:2601–2607.

Most, J., V. Tosti, L. M. Redman, and L. Fontana. 2017. Calorie restriction in humans: an update. Ageing Research Reviews 39:36–45.

O'Brien, D. M., K. J. Min, T. Larsen, and M. Tatar. 2008. Use of stable isotopes to examine how dietary restriction extends *Drosophila* lifespan. Current Biology 18:R155–R156.

Partridge, L., J. Deelen, and P. E. Slagboom. 2018. Facing up to the global challenges of ageing. Nature 561:45–56.

Piñera, A. V., H. M. Charles, T. A. Dinh, and K. A. Killian. 2013. Maturation of the immune system of the male house cricket, *Acheta domesticus*. Journal of Insect Physiology 59:752–760.

Plaistow, S. J., C. Shirley, H. Collin, S. J. Cornell, and E. D. Harney. 2015. Offspring provisioning explains clone-specific maternal age effects on life history and life span in the water flea, *Daphnia pulex*. American Naturalist 186:376–389.

Prada, J. M., C. J. E. Metcalf, and M. J. Ferrari. 2018. Improving measles incidence inference using age-structured serological data. Epidemiology and Infection 146:1699–1706.

Prada, J. M., C. J. E. Metcalf, S. Takahashi, J. Lessler, A. J. Tatem, and M. Ferrari. 2017. Demographics, epidemiology and the impact of vaccination campaigns in a measles-free world—can elimination be maintained? Vaccine 35:1488–1493.

Priest, N. K., B. Mackowiak, and D. E. L. Promislow. 2002. The role of parental age effects on the evolution of aging. Evolution 56:927–935.

Rheins, L. A., and R. D. Karp. 1985. Ontogeny of the invertebrate humoral immune response: studies on various developmental states of the American cockroach. Developmental and Comparative Immunology 9:395–406.

Rimer, J., I. R. Cohen, and N. Friedman. 2014. Do all creatures possess an acquired immune system of some sort? BioEssays 36:273–281.

Simon, A. K., G. A. Hollander, and A. McMichael. 2015. Evolution of the immune system in humans from infancy to old age. Proceedings of the Royal Society B 282.

Stjernman, M., and T. J. Little. 2011. Genetic variation for maternal effects on parasite susceptibility. Journal of Evolutionary Biology 24:2357–2363.

Truscott, J., T. D. Hollingsworth, S. J. Brooker, and R. M. Anderson. 2014. Can chemotherapy alone eliminate the transmission of soil transmitted helminths? Parasites and Vectors 7:266.

Truscott, J. E., H. C. Turner, S. H. Farrell, and R. M. Anderson. 2016. Soil-transmitted helminths: mathematical models of transmission, the impact of mass drug administration and transmission elimination criteria. Advances in Parasitology 94:133–198.

Vale, P. F., M. Choisy, and T. J. Little. 2013. Host nutrition alters the variance in parasite transmission potential. Biology Letters 9:20121145.

Van Den Heuvel, J., S. English, and T. Uller. 2016. Disposable soma theory and the evolution of maternal effects on ageing. PLoS ONE 11:1–17.

Wallinga, J., P. Teunis, and M. Kretzschmar. 2006. Using data on social contacts to estimate age-specific transmission parameters for respiratory-spread infectious agents. American Journal of Epidemiology 164:936–944.

Williams, G. C. 1957. Pleiotropy, natural selection, and the evolution of senescence. Evolution 11:398–411.

Wilson-Rich, N., S. T. Dres, and P. T. Starks. 2008. The ontogeny of immunity: development of innate immune strength in the honey bee (*Apis mellifera*). Journal of Insect Physiology 54:1392–1399.

Woolhouse, M. E. 1991. On the application of mathematical models of schistosome transmission dynamics. I. Natural transmission. Acta Tropica 49:241–270.

Worby, C. J., S. S. Chaves, J. Wallinga, M. Lipsitch, L. Finelli, and E. Goldstein. 2015. On the relative role of different age groups in influenza epidemics. Epidemics 13:10–16.

Yates, A., R. Antia, and R. R. Regoes. 2006. How do pathogen evolution and host heterogeneity interact in disease emergence? Proceedings of the Royal Society B 273:3075–3083.

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