THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Pathogen dynamics across the diversity of ageing

Citation for published version:

Clark, J, McNally, L & Little, TJ 2021, 'Pathogen dynamics across the diversity of ageing', *The American Naturalist*. <https://doi.org/10.1086/712380>

Digital Object Identifier (DOI):

[10.1086/712380](https://doi.org/10.1086/712380)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

The American Naturalist

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Pathogen Dynamics Across the Diversity of Ageing.

Jessica Clark ^{1,2}, Luke McNally ²⁻⁴, Tom Little ²

1. Institute of Biodiversity, Animal Health and Comparative Medicine, University of Glasgow, Glasgow, UK.
2. Institute of Evolutionary Biology, University of Edinburgh, Edinburgh, UK
3. Centre for Immunity, Infection and Evolution, University of Edinburgh, Edinburgh, UK
4. Centre for Synthetic and Systems Biology, University of Edinburgh, Edinburgh, UK

jessica.clark@glasgow.ac.uk

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 ageing spectrum of these traits impacts epidemics. We used a model laboratory infection system to compile an ageing 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 generalisable epidemiological models demonstrating that different patterns of ageing produce dramatically different transmission landscapes: in many cases ageing 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.

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 lifespan. This change can occur on a spectrum, from juvenescence where performance can improve with age, to senesce where performance can decline with age (Hayward et al. 2015; Jones et al. 2014), with individual life history traits often ageing asynchronously, such that whilst one trait might decline another can remain functional, or even improve (Hayward et al. 2015; Jones et al. 2014; Lecomte et al. 2010). This individual level variation in ageing could contribute to population level dynamics

like pathogen transmission, as ageing 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 lifespan of infection and the amount of time a host can transmit for. 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 (Covid-19, measles and helminth infections to name a few (Anderson and May 1982b; Chan et al. 1994; Davies et al. 2020; Metcalf et al. 2011; Prada et al. 2018)). Reproduction can have a direct effect on transmission when maternal age has an influence on offspring quality i.e. susceptibility to infectious diseases (Clark et al. 2017).

Indeed, there is considerable evidence that maternal effects, the non-genetic reflection of the maternal environment in the offspring phenotype, can determine offspring susceptibility to infection. For example, mothers experiencing poor environments like increased temperatures (Garbutt et al. 2014b) or poor nutrition availability (Boots and Roberts 2012; Mitchell and Read 2005) can produce more resistant offspring. Similarly, older mothers have been shown to produce more resistant offspring in both vertebrate and invertebrate systems (Clark et al. 2017; Hansen et al. 2014). Phenotypic plasticity in response to the maternal environment, including maternal age, has been shown across taxa (Clark et al.

2017; Garbutt and Little 2017; Marshall et al. 2010) suggesting that maternal age effects on offspring susceptibility can drive population and thus we hypothesise, epidemiological dynamics (Beckerman et al. 2002; Benton et al. 2008; Gaillard et al. 2003).

Age effects on pathogen dynamics may also occur directly from age specific changes in pathogen defence systems. For example, vertebrates develop an acquired immune system that commonly wains in later life, whilst many invertebrates become more resistant to infection with an increase in age (Garbutt et al. 2014a; Lesser et al. 2006; Little et al. 2005; Piñera et al. 2013; Rheins and Karp 1985; Rimer et al. 2014; Simon et al. 2015; Wilson-Rich et al. 2008). Epidemiological modelling that considers this individual heterogeneity in pathogen susceptibility as a function of host age, has provided great insight into pathogen transmission dynamics (Wallinga et al. 2006; Woolhouse 1991), optimal treatment routines (Truscott et al. 2014; Truscott et al. 2016) and vaccination strategies (Anderson and May 1982a; Metcalf et al. 2011; Prada et al. 2017; Worby et al. 2015). However, how age-specific pathogen defence 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 ageing on pathogen dynamics we first conducted two experiments, the observations from which then aided the development of a generalisable epidemiological model. Through our experiments we aimed to characterise within-host ageing specifically in individual traits we hypothesise 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. 2014a; Izhar and Ben-Ami 2015). We then used an epidemiological model to ask first, how individual ageing in these four traits impact pathogen transmission, and secondly how ageing 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

All data, scripts and notebooks are available in the cited Dryad Digital Repository <https://doi.org/10.5061/dryad.8cz8w9gnh>.

A single clone of *D. magna* sourced from Kaimes Pond in the south of Scotland (Stjernman and Little 2011) was used. From acclimated females (SM methods) two experiments were set up (Fig. 1). The aim of these experiments was to identify and characterise in a single organism, common life history traits that change with age, 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 utilised Dietary Restriction to manipulate the rate of ageing.

Dietary restriction (DR) is a non-pharmacological ageing 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 (Adler and Bonduriansky 2014; Austad 1989; Colman et al. 2009; Good and Tatar 2001; Mair et al. 2005; Mair et al. 2004; McCay et al. 1935). 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 through 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 on 8.75×10^6 chlorella cells for normal food or 2.2×10^6 chlorella cells for dietary restriction (Stjernman and Little 2011) (Fig. 1A). Subsets of the maternal generation on each diet treatment provided offspring at three time points (Fig. 1A) - 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 (F1) and offspring (F2) generations (Table 1). Fecundity was measured in F1 and F2 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 SM 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 dietary restriction or normal food levels (Total N = 97) (Fig. 1B). They were treated with *P. ramosa* spores as per above protocol.

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 - F1 generation) was analysed 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; or 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 clutch² both centre 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 analysed using an Accelerated Failure Time (AFT) model. This parametric analysis specifically allows analysis of factors that increase or decrease lifespan – i.e. the force of mortality. The result of this type of analysis is a percentage increase or decrease in lifespan as a result of the independent variables. Offspring longevity was analysed with an AFT model with a Gompertz hazard distribution determined by AIC comparison. For further details on interpretation see SM methods. Maternal age and diet were included as explanatory factors.

Offspring Performance

A generalised linear model with binomial error distribution and a logit link function was used to analyse offspring susceptibility to infection. Analysis of offspring (Fig. 1 – F2 generation) fecundity was much like the maternal generation with the number of offspring as the

response variable and 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 analysed with an ANOVA with maternal age and diet as explanatory factors.

Experiment 2

Analysis of the force of mortality in infected and uninfected *D. 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 supplementary methods.

Model Methods

Our experimental results show that in *D. magna* ageing differentially impacts life history traits that could impact pathogen dynamics. Considering these results, whilst appreciating the vast diversity in ageing across taxa, we developed an age-structured epidemiological model (Clark et al. 2017), that is generalisable beyond our experimental model system. We do not include features specifically of the *Daphnia* / *P. ramosa* system (such as host castration, typical of *P. ramosa*). Instead we 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 ageing in the four life history traits, therefore encompassing the ageing profile seen in our results, but also allowing for ageing 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. That host ageing in our four traits can impact pathogen transmission both directly and indirectly. Age-specific pathogen defence systems and trans-generational effects on pathogen defence 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. That the effects on ageing 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 defence 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.

Ageing traits were modelled in line with a pleiotropy model of ageing (Garbutt et al. 2014a; Williams 1957), 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 naïve population will result in a sustained outbreak (Dietz 1993).

We derived R_0 using the next generation matrix (NGM) 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 the following references (Bjørnstad 2019; Blackwood and Childs 2018; Diekmann et al. 2010). R_0 is derived by splitting equations 1e-h into two matrices; $\mathbf{F}$ which contains all terms for all completely new infections and $\mathbf{V}$ which contains all gains, losses and transfers between the classes. From these, two Jacobian matrices $\mathbf{f}$ and $\mathbf{v}$ are developed as the partial derivatives of $\mathbf{F}$ and $\mathbf{V}$ with respect to the infectious state variables (in this case the four infected age classes). These are evaluated at the disease-

free equilibrium (dfe) (eq. SM 3a-d). R_0 is then given by the dominant eigenvalue of $f\mathbf{v}^{-1}|_{dfe}$.

Parameter and state variable descriptions are provided in Table 2. Each class is denoted by three characters; infection status (I or U), host age (Y or O in first subscript), and maternal age (Y or O in second subscript). For example, an uninfected young host from an old mother is denoted $U_{Y,O}$.

Table 2. All model parameters and state variables with their definitions.

State Variables & Parameters	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 change in fecundity with age
y	Proportional change in the force of mortality with age
A	Proportional change in age-specific pathogen defence with age
M	Proportional change in transgenerational effects on pathogen defence with age
β	Transmission coefficient

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

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

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

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

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

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

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

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

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

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

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

$$N = N_I + N_U \quad 1k$$

Equations 1a-d describe the uninfected population and equations 1e-h are the infected population, and 1i-k describe the total densities of each and total. $x \in [-1,1]$ 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 the effects of age and maternal age interact multiplicatively as 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 SM eq. 8.

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. 2A; linear interaction $f_{1, 1337.1} = 70.73$, $p = <0.0001$, quadratic interaction $f_{1, 1298.7} = 10.07$, $p = 0.0015$). Offspring from old mothers were more resistant to infection regardless of maternal food levels (Fig. 2B; Maternal age; $\chi^2_2 = 31.05$, $p = <.0001$ and maternal food; $\chi^2_1 = 0.159$, $p = 0.7$). Older mothers had larger offspring, with dietary restriction only affecting the size of offspring from primiparous mothers (Fig. S2; interaction $f_{2, 553} = 38.369$, $p = <.0001$). 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 *D. magna* (Fig. 2C; shape (α) = 5.03, 95% CI lower = 4.52, upper = 5.60; scale (μ) = 79.55% CI lower = 79.10, upper = 83.16). Dietary restriction in uninfected females increased *D. magna* longevity by 10% (Fig. 2A; estimate = 1.098, 95% CI lower = 1.0404, upper = 1.1607). Infected individuals had a 35% reduction in survival (Fig. 2A; estimate = 0.648; 95% CI lower = 0.61, upper = 0.69).

Modelling Results

We modelled how age-specific changes in fecundity, mortality, susceptibility, and trans-generational effects on pathogen susceptibility may affect R_0 . Our analytical results (see supplementary materials for specific model details) show the effects of ageing on pathogen dynamics are largely driven by the relationship between rates of extrinsic mortality (an environmental property) and the rate of maturation (a characteristic of the host). We therefore investigated the effect of ageing 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 to harsh ecological conditions respectively.

Ageing Has Direct and Indirect Effects on Pathogen Transmission.

We first modelled the effect of each ageing 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-B; eq. 9 & 10 SM), through their effects on population density and age structure (Fig. 3 E-J, eq. 5 & 6 SM). Again, under high extrinsic mortality old individuals are in lower density, whilst there are many young hosts. As 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. 2I-J) and thus an increase in transmission. Conversely, under low extrinsic mortality (mild ecological conditions) increasing levels of senescence in age-specific and trans-generational pathogen defence drove an increase in R_0 (Fig 3 C-D; eq. 11 & 12 SM). 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 ageing on epidemics.

The effect of the interactions between ageing traits on pathogen R_0 varies greatly under different levels of extrinsic mortality, as exemplified in Figure 4. We first use the interaction between the two forms of pathogen susceptibility as an example (Fig. 4A-C). Under low extrinsic mortality (Fig. 4A), the interaction between pathogen defence and transgenerational pathogen defence has little impact on R_0 when both traits are juvenescent (a plausible biological pattern that we have observed in *Daphnia*, Fig 2 and Garbutt et al (2014a)). 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. 3C). As another example we consider the interaction between reproduction and mortality (Fig. 3D-F). Under low extrinsic mortality, the pattern of

ageing that results in the least transmission in this environment is senescence in both traits. This is a typical ageing 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 non-

pharmacological interventions like dietary restriction and could be applicable to any organism where ageing is characterised by a decline in performance in the four modelled traits. However, wild populations are likely to experience higher extrinsic mortality rates, curtailing any benefit to the extension of performance or lifespan. 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 lifespan, 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 whilst modelling the others at a mild level of senescence (Fig 5).

An intervention that reduces the force of mortality, thus extending lifespan 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 defence with age, old individuals are less resistant to infection, so transmission increases. In contrast, interventions that maintain pathogen defence capability could reduce R_0 by decreasing transmission events (Fig 5). However, ageing 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 4J).

Discussion

Our experimental and modelling results show that individual ageing 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. Whilst fecundity and survival declined with age, the transgenerational impact of increased maternal age saw either no effect, or improvements in offspring performance. Our modelling results show that when considered independently, each measure of ageing 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 ageing. However, our model results also indicate that considering the effects of ageing in single traits is insufficient to understand the relationship between ageing and pathogen transmission. Specifically, the three-way (Figure 4)

interaction between ageing traits and the extrinsic mortality clearly show that ageing 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.

We also show that the extension of lifespan 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 however, they are of pressing concern when considering the gathering interest in the development of life extending treatment for humans (Kennedy and Pennypacker 2015). Whilst global life expectancy increased from 2000 to 2015, it was not matched with an extension in healthspan, such that individuals now spend on average 16-20% of their lives suffering from morbidity (Jagger et al. 2008; Partridge et al. 2018 though 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 lifespan in ageing 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 non-human 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 a strong selective factor in determining optimal virulence within a population (Alizon 2008; Choo et al. 2003; Cousineau and Alizon 2014; Ebert and Mangin 1997; Gandon et al. 2007; Mackinnon and Read 2002; Yates et al. 2006). 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 *D. 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 *P. ramosa* is a castrating parasite and thus its virulence can be measured as a function of its ability to castrate, we suspect one would see a recovery of reproductive capability if 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 fewer resources are allocated to reproduction and thus fewer resources are available for exploitation by the parasite. This hypothesis is supported by Vale et al (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 (Comfort 1953; Lansing 1947; 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 (Benton et al. 2005; Comfort 1953; Hjelmborg et al. 2015; Lansing 1947; 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 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 lifespans and low probability of maturation are likely to evolve juvenile susceptibility. Our modelling results are also in keeping with Ashby & Bruns' results, as our modelling 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 (Figure 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 (Benton et al. 2008; Priest et al. 2002), 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 (*similar to O'Brien et al. 2008 in Drosophila*), 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 ageing however, 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 ageing, to inform a mathematical model that we used to explore the epidemiological consequences of individual variation in ageing.

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

Acknowledgements

We would like to thank Phil Wilson for his help carrying out the experiments. We also thank the editors and reviewers for their time and thoughtful comments. JC was funded by a NERC E3 DTP studentship award.

Contribution Statement

Conceptualization: JC, LM, TL. Funding acquisition: JC, LM, TL. Methods and experimental design: JC, LM, TL. Data Collection: JC. Data analysis: JC, LM. Data validation: JC, TL. Data visualisation: JC, LM. Provided resources: LM, TL. Data analysis: JC, TL. Model writing, coding and analytical assessment: JC, LM. Supervision: LM, TL. Writing - original draft – JC, LM, TL. Writing – review and editing: JC, LM, TL.

Data Availability

All data, R scripts and Mathematica note books are available from the Dryad Data Repository <https://doi.org/10.5061/dryad.8cz8w9gnh>

- 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 : news and reviews in molecular, cellular and developmental biology* 36:439-450.
- Alizon, S. 2008. Transmission-recovery trade-offs to study parasite evolution. *The American Naturalist* 172:E113-121.
- Anderson, R. M., and R. M. May. 1982a. Directly Transmitted Infectious Diseases: Control By Vaccination. *Science* 215:1053-1060.
- . 1982b. 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: Biological Sciences* 285.
- 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.
- 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: Biological Sciences* 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. : Use R!* Switzerland, Springer.
- 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: Biological Sciences* 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.
- 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. Pathogen dynamics across the diversity of ageing *in Dryad*, ed.
- 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, C. C.-w. 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. *Ecoscience* 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. 2014a. 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. 2014b. 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 Ageing. IHOP*. Dordrecht, Springer 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.
- Hjelmberg, 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. *The 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* 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. *The Journal of Nutrition*:63-79.
- Metcalfe, 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: Biological Sciences* 272:2601-2607.
- Most, J., V. Tosti, L. M. Redman, and L. Fontana. 2017. Calorie restriction in humans: An update. *Ageing Res Rev* 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:R155-156.
- 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*. *The 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. Cambridge University Press:1-8.
- 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; international journal of organic 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: Biological Sciences* 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 & Vectors* 7.
- 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. *Adv Parasitol* 94:133-198.
- Vale, P. F., M. Choisy, and T. J. Little. 2013. Host nutrition alters the variance in parasite transmission potential. *Biology Letters* 9:20121145-20121145.
- 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: Biological Sciences* 273:3075-3083.

Figure 1. A schematic illustrating the experimental design of experiments 1 and 2. E = exposed. U = unexposed. DR = dietary restriction.

Figure 2. Performance measures across two generations. In all figures, salmon represents DR and dark red for normal diet. A. The number of offspring produced in clutches 1-13 in the maternal generation from normal diet females and DR females. Circle – data & Triangle – model predictions both with standard error. B. The proportion of infected offspring from each maternal treatment group with Wilson Score binomial confidence intervals. C. Force of mortality for four treatments. Uninfected females - solid lines. Infected females - dotted lines. Inset: The survival curve of the experimental females.

Figure 3. The relationship between ageing and R_0 across four traits under variation in extrinsic mortality (δ). Trait ageing spans a spectrum from juvenescence (-1) to senescence (1), representing the range of proportional changes in performance with age. The relationship between A. R_0 and fecundity x . B. R_0 and Mortality y , C. R_0 and transgenerational pathogen defence M and D. R_0 and age-specific defence A . Panels E, G, & I display population density with respect to reproductive ageing 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, H & J display population density and age structure with respect to mortality ageing at low, medium and high extrinsic mortality respectively. Purple represents 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 ($U_{O,O}$). Other parameters; $r = k = 5$; $c = 0.1$; $m = 0.5$; $\alpha = 1.5$; $\beta = 0.9$

Figure 4. The R_0 landscape as a result of interactions between pairs of ageing traits under three levels of extrinsic mortality, indicative of three different environmental conditions. Colour 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 in the legend. Each axis is labelled with the interacting trait, with the spectrum of ageing from juvenescence (-1) to senescence (1) representing proportional change in each performance measure with age. Column 1 = low extrinsic mortality ($\delta < m$; $\delta = 0.1$), column 2 = medium extrinsic mortality ($\delta = m$; $\delta = 0.5$) and column 3 = high extrinsic mortality ($\delta > m$; $\delta = 1$). In each plot, the two measures of senescence not considered are set to zero. The animals in figures D-F highlight a specific ageing example given in the text. Other parameters; $r = k = 5$; $c = 0.1$; $m = 0.5$; $\alpha = 0.9$; $\beta = 0.9$.

Figure 5. The case where any ageing intervention increases physiological performance within a population, and the effects on R_0 (y-axis). Note the different x-axis to previous modelling figures. Here the x-axis is the efficacy of any intervention that slows senescence, maintaining optimal performance for longer. 0 on the x-axis represents no treatment and moving right represents the corresponding increase in performance capability of a particular trait. Yellow; reproductive senescence; Blue; mortality senescence; Green; age specific pathogen defence; Pink; transgenerational effect of age on defence. Other parameters; $\delta = 0.1$; $r = k = 5$; $c = 0.1$; $m = 0.5$; $\alpha = 1.5$; $\beta = 0.9$ with each remaining ageing trait held constant at 0.5.