The evolution of stage-specific virulence: differential selection of parasites in juveniles

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Abstract

The impact of infectious disease is often very different in juveniles and adults, but theory has focused on the drivers of stage-dependent defense in hosts rather than the potential for stage-dependent virulence evolution. Stage-structure has the potential to be important to the evolution of pathogens because it exposes parasites to heterogeneous environments in terms of both host characteristics and transmission routes. We develop a stage-structured (juvenile-adult) epidemiological model and examine the evolutionary outcomes of stage-specific virulence under the classic assumption of a transmission-virulence trade-off. We show that selection on virulence against adults remains consistent with the classic theory. However, the evolution of juvenile virulence is sensitive to both demography and contact structure with higher virulence against juveniles being favored either when the contact structure is assortative (juveniles preferentially interact together) and the juvenile stage is short, or in contrast when the contact structure is disassortative and the juvenile stage is long. These results highlight the potentially profound effects of host stage-structure on determining parasite virulence in nature. This new perspective may have broad implications for both understanding and managing disease severity.

Introduction

Understanding how parasites are selected to exploit their hosts remains a central research question in the evolutionary ecology of host-parasite interactions (Smith 1904; Ball 1943; Anderson & May 1982; Read 1994; Ebert & Herre 1996; Frank 1996; Alizon *et al.* 2009; Schmid-Hempel 2011; Bull & Lauring 2014; Cressler *et al.* 2016), with important implications for host persistence (Boots & Sasaki 2003; De Castro & Bolker 2005), disease management (Dieckmann 2005), and host-parasite coevolution (Boots *et al.* 2009). Although most of the theory of evolution of virulence (defined in this literature as the increased death rate due to infection) focuses on homogenous host populations, heterogeneity within host populations is ubiquitous in nature (Anderson & May 1992, Chapter 8-11). One typical form of host heterogeneity is stage-related structure (e.g., juveniles and adults), and a number of recent ecological studies have examined the impacts of host populations' stage-related heterogeneity on disease epidemiology (e.g., Dwyer 1991; Fleming-Davies *et al.* 2015; Hite *et al.* 2016; for theory, Ashby & Bruns 2018). In these studies, the differences in virulence across life stages have been explained as age-related variation in tolerance, resistance, exposure, immunocompetence, and susceptibility and affected by maternal and acquired immunity (Hudson & Dobson 1995; Wilson *et al.* 2002).

In addition to age-related variation in the hosts, different host age-classes expose parasites to specific environmental heterogeneity (see Ashby & Bruns 2018, for theory). Given this, parasites may adaptively tune conditional exploitation against certain stage classes, e.g., through plasticity or by infecting tissues and/or cells that are differentially expressed at different stage classes. In principle, stage-specific virulence may occur as a result of parasite adaptation in two ways. First, stage-structure can generate different infectious periods, for instance due to the substantial difference in natural mortality between juveniles and adults (Jones *et al.* 2013). Infectious period is therefore stage-dependent, which, according to the theory (Day 2001; Gandon *et al.* 2001; Day & Proulx 2004; Gandon 2004; Alizon *et al.* 2009; Cressler *et al.* 2016), may induce selection on

virulence such that a shorter infectious period in a certain stage of hosts favors higher virulence. Secondly, the hosts' stage-structure can generate biased transmission-pathways, thereby exposing the parasites to temporal heterogeneity, which may induce additional selective pressures (reviewed in Lion & Metz 2018). For instance, spatio-temporal segregation between juveniles and adults, which is typical of humans (Rohani *et al.* 2010), amphibians (Kilpatrick *et al.* 2010), and insects (Briggs & Godfray 1995), can produce assortative contact structure (i.e., juvenile-juvenile and adult-adult contacts might be more likely than juvenile-adult contacts), such that parasites infecting a certain stage of hosts are likely to be transmitted to the same stage of hosts ("assortative" transmission). Despite these potentially important selective forces on stage-specific virulence, the implications of host stage-structure for parasite fitness and evolution of stage-specific virulence have not been examined.

Here, we extend classic models of virulence evolution to include two host stage-classes (pre and post reproductive) where the juveniles mature into adults, the adults reproduce, and transmission between the stage-classes is characterized by a contact matrix. We explore the evolutionary outcomes of stage-specific virulence in light of classic theory of life-history evolution in heterogeneous populations. We use the adaptive dynamics toolbox (Hofbauer & Sigmund 1990; Dieckmann & Law 1996), first showing that the evolutionary outcomes of virulence against adults ("adult-virulence") are explained by the classic, optimization-principle (Lion & Metz 2018) (i.e., the evolutionarily stable virulence maximizes the number of secondary infection from infected adult host in a fully susceptible population). Second, we show that the evolutionary outcomes of virulence against juveniles ("juvenile-virulence") are critically impacted by the interplay between assortativity and the duration of the adult-stage. This is in part because juvenile-virulence can attenuate successful maturation of juvenile hosts and consequently loses future secondary infection from adults. We then use Fisher's reproductive values (Fisher 1958; Taylor 1990; Williams 2011; Williams & Kamel 2018; Lion 2018) (i.e., the long-term relative contributions of parasites infecting juveniles and adults to future populations), in order to gain a deeper biological insight into the selection gradients. We highlight the pivotal importance of

stage-structure to the evolution of infectious disease.

Method

We consider a host population structured into juvenile (J) and adult (A) stages, in which juveniles are obviously incapable of reproduction. The density of susceptible or infected juveniles is denoted S_J or I_J respectively, and that of susceptible or infected adults is denoted S_A or I_A respectively. Combining an epidemiological SI-model with a stage-structured model yields the following ordinary differential equations (ODEs; Appendix A1):

$$\begin{aligned}
\frac{\mathrm{d}S_\mathrm{J}}{\mathrm{d}t} &= \left(r - \kappa(S_\mathrm{A} + I_\mathrm{A})\right) \cdot (S_\mathrm{A} + I_\mathrm{A}) - \left(u + \varphi_\mathrm{JJ} + \varphi_\mathrm{JA} + m_\mathrm{J}\right) S_\mathrm{J} \\
\frac{\mathrm{d}S_\mathrm{A}}{\mathrm{d}t} &= uS_\mathrm{J} - \left(m_\mathrm{A} + \varphi_\mathrm{AJ} + \varphi_\mathrm{AA}\right) S_\mathrm{A} \\
\frac{\mathrm{d}I_\mathrm{J}}{\mathrm{d}t} &= \left(\varphi_\mathrm{JJ} + \varphi_\mathrm{JA}\right) S_\mathrm{J} - \underbrace{\left(u + m_\mathrm{J} + \upsilon_\mathrm{J}\right)}_{=:\mu_\mathrm{J}} I_\mathrm{J} \\
\frac{\mathrm{d}I_\mathrm{A}}{\mathrm{d}t} &= \left(\varphi_\mathrm{AJ} + \varphi_\mathrm{AA}\right) S_\mathrm{A} + uI_\mathrm{J} - \underbrace{\left(m_\mathrm{A} + \upsilon_\mathrm{A}\right)}_{=:\mu_\mathrm{A}} I_\mathrm{A},
\end{aligned} \tag{1}$$

where: r represents a fecundity of the adult hosts per capita (assumed to be the same for susceptible and infected adults), which is reduced by a density-dependent factor κ; juveniles mature into adults at a rate u; m_X represents the background mortality for a stage-X host; φ_XY represents the rate at which a susceptible stage-X host gets transmitted from an infected stage-Y host (i.e., force of infection from infectious Y to susceptible X per capita, Fig 2; also see below for formula); υ_X represents the virulence against a stage-X host (an evolving trait). The reciprocal of the infectious period for juveniles (or adults) is given by $\mu_\mathrm{J} = u + m_\mathrm{J} + \upsilon_\mathrm{J}$ (or by $\mu_\mathrm{A} = m_\mathrm{A} + \upsilon_\mathrm{A}$ respectively). For alternative approaches including physiologically structured population modeling and infection-age modeling with continuous stage structure, see Day *et al.* (2011), Mideo *et al.* (2011), and de Roos & Persson (2013). The present methodology allows us to evaluate the relative virulence against juveniles

compared to adults.

Maturation and natural mortality can both affect the relative length of a adult-stage of the hosts. To quantify this, let θ_{A} be the expected fraction of time a host individual spends as an adult in the entire lifespan in the absence of disease, which reads (Appendix A2):

$$\theta_{\mathrm{A}} = \frac{u}{u + m_{\mathrm{J}} - m_{\mathrm{A}}} \left(1 + \frac{m_{\mathrm{A}}}{u + m_{\mathrm{J}} - m_{\mathrm{A}}} \cdot \log \left(\frac{m_{\mathrm{A}}}{u + m_{\mathrm{J}}} \right) \right), \tag{2}$$

from which we can check that extremely slow (or fast) maturation, $u \to 0$ (or $u \to +\infty$ respectively), leads to $\theta_{\mathrm{A}} \to 0$ (or 1 respectively. We will omit the degenerated case in which $u + m_{\mathrm{J}} = m_{\mathrm{A}}$, as this situation turns out to give no reasonable measure for stage-period; Appendix A2). We use θ_{A} as a characteristic parameter of the stage-structured host populations.

The force of infection for a stage-X host from a stage-Y host (with X and Y running across J and A) in Eqn (1) involves with three processes: susceptibility α_{X} (the likeliness for which a stage-X host becomes infected, given a reception of disease-propagule), contact structure σ_{XY} (which represents the fraction of time a Y-stage host spends with a X-stage host), and infectiousness β_{Y} (the propagule-production from a stage-Y host; see Fig 2):

$$\begin{aligned} \varphi_{\mathrm{JJ}} &= \frac{\alpha_{\mathrm{J}} \sigma_{\mathrm{JJ}} \beta_{\mathrm{J}} I_{\mathrm{J}}}{H}, \\ \varphi_{\mathrm{JA}} &= \frac{\alpha_{\mathrm{J}} \sigma_{\mathrm{JA}} \beta_{\mathrm{A}} I_{\mathrm{A}}}{H}, \\ \varphi_{\mathrm{AJ}} &= \frac{\alpha_{\mathrm{A}} \sigma_{\mathrm{AJ}} \beta_{\mathrm{J}} I_{\mathrm{J}}}{H}, \\ \varphi_{\mathrm{AA}} &= \frac{\alpha_{\mathrm{A}} \sigma_{\mathrm{AA}} \beta_{\mathrm{A}} I_{\mathrm{A}}}{H}, \end{aligned} \tag{3}$$

with $H = S_{\mathrm{J}} + I_{\mathrm{J}} + S_{\mathrm{A}} + I_{\mathrm{A}}$ the total density of hosts, such that the transmission is frequency-dependent, as is assumed in previous studies of stage-structured epidemiological dynamics (e.g., Bernhauerová 2016). Also, to link virulence and transmission, we use the trade-off relationship given by $\beta_{\mathrm{J}} = \frac{b_{\mathrm{J}} k_{\mathrm{J}} v_{\mathrm{J}}}{1 + k_{\mathrm{J}} v_{\mathrm{J}}}$, $\beta_{\mathrm{A}} = \frac{b_{\mathrm{A}} k_{\mathrm{A}} v_{\mathrm{A}}}{1 + k_{\mathrm{A}} v_{\mathrm{A}}}$, where k_{X}

tunes the efficiency of virulence for infectiousness from stage-X hosts, and b_X represents the upper bound of infectiousness from stage-X hosts. Note that we assumed that transmission is a concave function of virulence to restrict our primary attention to stable evolutionary outcomes (Otto & Day 2007).

For quantifying the contact structure, we use a single parameter given by $\sigma = 1-\sigma_{AJ} = \sigma_{JJ} = 1-\sigma_{JA} = \sigma_{AA}$, (Diekmann *et al.* 2012, Chapter 12). With this symmetry, the measure of assortativity is given by:

$$\rho = \sigma_{JJ} + \sigma_{AA} - 1 = 2\sigma - 1, \tag{4}$$

where ρ varies from -1 to 1. If $-1 \leq \rho < 0$, then within-stage contact is less frequent compared to between-stage contact (such a contact is said to be "disassortative"). Instead, if $0 < \rho \leq 1$, then within-stage contact is more likely than between-stage contact ("assortative" contact). $\rho = 0$ indicates that contact is unbiased ("random" contact). In the extreme case, $\rho = 1$ (or -1) indicates that contact occurs exclusively within the stages (or between the stages, respectively).

We use the adaptive dynamics toolbox (Hofbauer & Sigmund 1990; Dieckmann & Law 1996) to study the long-term evolutionary dynamics of stage-specific virulence. Throughout the paper we assume that parasites show specific virulence: υ_J and υ_A, with no association or correlation between them (i.e., we study the joint evolutionary dynamics of (υ_J, υ_A)). First, suppose that the system of ODEs in Eqn (1) has reached a steady state: $(S_J, S_A, I_J, I_A) = (S_J^{\#}, S_A^{\#}, I_J^{\#}, I_A^{\#})$ for a given (or wild-type) virulence strategy $\mathbf{v} := (\upsilon_J, \upsilon_A)$. We then introduce a rare mutant $\mathbf{v}' := (\upsilon_J', \upsilon_A')$ attempting to invade a monomorphic wild-type virulence $\mathbf{v}$. We assume weak selection ($|\mathbf{v}' - \mathbf{v}|$ is very small). For more details, see Appendix A3.

To assess the possibility of mutant invasion, we define the invasion fitness, denoted w, by using the Next-Generation Theorem (van den Driessche & Watmough 2002; Hurford *et al.* 2010). The "next-generation

matrix" (that determines the long term growth of the mutant) can be written as the product of five matrices:

$$\mathbf{G}' = \underbrace{\begin{pmatrix} S_{\mathrm{J}}^{\#} & 0 \\ 0 & S_{\mathrm{A}}^{\#} \end{pmatrix}}_{\text{no. of susceptibles}} \underbrace{\begin{pmatrix} \alpha_{\mathrm{J}} & 0 \\ 0 & \alpha_{\mathrm{A}} \end{pmatrix}}_{\text{susceptibility}} \underbrace{\begin{pmatrix} \sigma_{\mathrm{JJ}} & \sigma_{\mathrm{JA}} \\ \sigma_{\mathrm{AJ}} & \sigma_{\mathrm{AA}} \end{pmatrix}}_{\text{contact}} \underbrace{\begin{pmatrix} \frac{\beta'_{\mathrm{J}}}{H^{\#}} & 0 \\ 0 & \frac{\beta'_{\mathrm{A}}}{H^{\#}} \end{pmatrix}}_{\text{infectiousness}} \underbrace{\begin{pmatrix} \frac{1}{\mu'_{\mathrm{J}}} & 0 \\ \frac{u}{\mu'_{\mathrm{J}}\mu'_{\mathrm{A}}} & \frac{1}{\mu'_{\mathrm{A}}} \end{pmatrix}}_{\text{infectious period}} \tag{5}$$

(see Appendix), where $H^{\#} = S_{\mathrm{J}}^{\#} + S_{\mathrm{A}}^{\#} + I_{\mathrm{J}}^{\#} + I_{\mathrm{A}}^{\#}$ (the total density of the hosts at the endemic equilibrium), $\mu'_{\mathrm{J}} = u + m_{\mathrm{J}} + \upsilon'_{\mathrm{J}}$ (the reciprocal of the infectious period of juveniles infected by the mutant), and $\mu'_{\mathrm{A}} = m_{\mathrm{A}} + \upsilon'_{\mathrm{A}}$ (the mortality rate of adults infected by the mutant). Eqn (5) offers a natural interpretation of the reproductive success of the mutant by partitioning the epidemiological process, in agreement with models of transmission dynamics in heterogeneous host populations (Craft 2015; VanderWaal & Ezenwa 2016; White *et al.* 2017). The first matrix represents the availability of susceptible hosts, each with a specific susceptibility (the second matrix); the third matrix represents the contact pattern across stages; the fourth matrix represents the infectiousness of infected hosts per capita, and the fifth matrix represents the stage-specific infectious period with the effect of maturation being included.

The invasion fitness is determined by the dominant eigenvalue of $\mathbf{G}'$ (denoted $\Lambda[\mathbf{G}']$), which turns out to exhibit a complicated expression. We therefore use a simpler (but equivalent) measure for the invasion fitness:

$$\begin{aligned} \omega(\mathbf{v}', \mathbf{v}) &= \frac{\alpha_{\mathrm{J}} S_{\mathrm{J}}^{\#} \sigma_{\mathrm{JJ}}}{H^{\#}} \cdot \frac{\beta'_{\mathrm{J}}}{\mu'_{\mathrm{J}}} + \frac{u}{\mu'_{\mathrm{J}}} \cdot \frac{\alpha_{\mathrm{J}} S_{\mathrm{J}}^{\#} \sigma_{\mathrm{JA}}}{H^{\#}} \cdot \frac{\beta'_{\mathrm{A}}}{\mu'_{\mathrm{A}}} + \frac{\alpha_{\mathrm{A}} S_{\mathrm{A}}^{\#} \sigma_{\mathrm{AA}}}{H^{\#}} \cdot \frac{\beta'_{\mathrm{A}}}{\mu'_{\mathrm{A}}} - \rho \frac{\alpha_{\mathrm{J}} S_{\mathrm{J}}^{\#} \alpha_{\mathrm{A}} S_{\mathrm{A}}^{\#}}{\left(H^{\#}\right)^2} \cdot \frac{\beta'_{\mathrm{J}} \beta'_{\mathrm{A}}}{\mu'_{\mathrm{J}} \mu'_{\mathrm{A}}} \\ &= q_{\mathrm{JJ}}^{\#} \frac{\beta'_{\mathrm{J}}}{\mu'_{\mathrm{J}}} + \pi'_{\mathrm{I}} q_{\mathrm{JA}}^{\#} \frac{\beta'_{\mathrm{A}}}{\mu'_{\mathrm{A}}} + q_{\mathrm{AA}}^{\#} \frac{\beta'_{\mathrm{A}}}{\mu'_{\mathrm{A}}} - \left(q_{\mathrm{JJ}}^{\#} q_{\mathrm{AA}}^{\#} - q_{\mathrm{JA}}^{\#} q_{\mathrm{AJ}}^{\#} \right) \frac{\beta'_{\mathrm{J}}}{\mu'_{\mathrm{J}}} \frac{\beta'_{\mathrm{A}}}{\mu'_{\mathrm{A}}}, \end{aligned} \tag{6}$$

with short-hand notation $\pi'_{\mathrm{I}} := u/\mu'_{\mathrm{J}}$ (the probability of maturation of juveniles infected by the mutant) and $q_{\mathrm{XY}}^{\#} := \frac{\alpha_{\mathrm{X}} S_{\mathrm{X}}^{\#} \sigma_{\mathrm{XY}}}{H^{\#}}$ (the availability of X-stage hosts to the parasites infecting a Y-stage host per propagule-production). The factor $\beta'_{\mathrm{X}}/\mu'_{\mathrm{X}}$ represents the total number of propagule produced by a X-stage host infected by the mutant. We find that the condition for which the mutant outcompetes the wild type

$\omega(\mathbf{v}', \mathbf{v}) > 1$ holds if and only if $\Lambda[\mathbf{G}'] > 1$, under weak selection (see Appendix A4).

Direction of selection is determined by selection gradient:

$$g_{\mathrm{J}}(\mathbf{v}) \coloneqq \left.\frac{\partial w(\mathbf{v}', \mathbf{v})}{\partial v'_{\mathrm{J}}}\right|_{\mathbf{v}'=\mathbf{v}}, \qquad g_{\mathrm{A}}(\mathbf{v}) \coloneqq \left.\frac{\partial w(\mathbf{v}', \mathbf{v})}{\partial v'_{\mathrm{A}}}\right|_{\mathbf{v}'=\mathbf{v}}, \tag{7}$$

with the partial derivatives evaluated at $\mathbf{v}' = \mathbf{v}$ ("neutrality"). Virulence evolves in the direction of selection gradient until singular strategy (SS) is reached, $g_{\mathrm{J}}(\mathbf{v}) = g_{\mathrm{A}}(\mathbf{v}) = 0$ at $\mathbf{v} = \mathbf{v}^*$. We assess two stability criteria of SS: the first criterion, attainability (Takada & Kigami 1991; Christiansen 1991), concerns whether SS can be reached by recurrent small mutations. The second is referred to as evolutionary stability (Maynard Smith & Price 1973), which assures that SS can resist against any invasion of alternative, mutant strategies. If SS meets both of these criteria, it is then called as Continuously Stable Strategy (CSS; Eshel 1983). Analytical investigation revealed that the SS is always a CSS, and thus we do not detail the stability analyses in the main text (see results).

We use the following default parameter-values: $r = 6$, $\kappa = 0.06$, $m_{\mathrm{J}} = 1$, $\alpha_{\mathrm{J}} = \alpha_{\mathrm{A}} = 1$, $k_{\mathrm{J}} = k_{\mathrm{A}} = 1$, $b_{\mathrm{J}} = b_{\mathrm{A}} = 10$, while varying m_{A}, u (thus θ_{A}) and ρ. That is, the parameter values are symmetric for juveniles and adults. We subsequently check the effects of the differences in α (susceptibility), k (efficiency of exploitation for transmission), and b (upper bound in infectiousness). In addition, we check whether recovery or tolerance in the host can affect the results. Finally, we examined the outcomes when we assume density-dependent rather than frequency dependent transmission in the dynamics.

Results

The selection gradient for adult-virulence reads:

$$g_{\mathrm{A}}(\mathbf{v}) \propto \left(\frac{1}{\beta_{\mathrm{A}}}\cdot\frac{\mathrm{d}\beta_{\mathrm{A}}}{\mathrm{d}\upsilon_{\mathrm{A}}}-\frac{1}{\mu_{\mathrm{A}}}\cdot\frac{\mathrm{d}\mu_{\mathrm{A}}}{\mathrm{d}\upsilon_{\mathrm{A}}}\right)^{\circ}=\left(\frac{1}{\beta_{\mathrm{A}}}\cdot\frac{\mathrm{d}\beta_{\mathrm{A}}}{\mathrm{d}\upsilon_{\mathrm{A}}}-\frac{1}{\mu_{\mathrm{A}}}\right)^{\circ} \tag{8}$$

(where $^{\circ}$ represents neutrality, $\mathbf{v}'=\mathbf{v}$; Appendix A5), which is consistent with a number of previous studies: under the transmission-virulence trade-off, higher exploitation is expected to increase the infectiousness (i.e., a marginal benefit) at the immediate (marginal) cost owing to a reduced infectious period (Day 2001; Gandon *et al.* 2001; Day & Proulx 2004; Gandon 2004; Alizon *et al.* 2009; Cressler *et al.* 2016). This is because the reproductive success of parasites infecting adults is, in effect, determined by a single transmission-pathway, from adults to any susceptible hosts in the population, regardless of the contact-structure and the stationary stage-distribution. Therefore, the direction of selection on adult virulence is completely determined by the balance between such marginal benefits and costs, regardless of the characteristics of hosts' stage-structure.

In contrast, juvenile-virulence in the model is influenced by additional costs associated with hosts' stage-structure. To make the biological meaning clearer, we present the reproductive-value based form of the selection gradient (Fisher 1958; Taylor 1990; Caswell 2001; Frank 1998; Grafen 2006; Lion 2018). Reproductive values give a proper weightings of fitness effects for age-classes, by taking the contributions of classes to future gene-pool into account (Fisher 1958; Taylor 1990; Caswell 2001; Frank 1998; Grafen 2006; Lion 2018). Using reproductive values, $g_{\mathrm{J}}(\mathbf{v})$ reads:

$$g_{\mathrm{J}}(\mathbf{v})=\overbrace{\left(\underbrace{\ell_{\mathrm{J}}^{\circ}q_{\mathrm{JJ}}^{\#}}_{\text{juveniles}}+\underbrace{\ell_{\mathrm{A}}^{\circ}q_{\mathrm{AJ}}^{\#}}_{\text{adults}}\right)\cdot\frac{\beta_{\mathrm{J}}}{\mu_{\mathrm{J}}}}^{\text{transmission from a juvenile to:}}\cdot\underbrace{\left(\frac{1}{\beta_{\mathrm{J}}}\frac{\mathrm{d}\beta_{\mathrm{J}}}{\mathrm{d}\upsilon_{\mathrm{J}}}-\frac{1}{\mu_{\mathrm{J}}}\frac{\mathrm{d}\mu_{\mathrm{J}}}{\mathrm{d}\upsilon_{\mathrm{J}}}\right)}_{\text{marginal benefit/cost}}-\frac{\pi_{\mathrm{I}}^{\circ}}{\mu_{\mathrm{J}}}\cdot\frac{\mathrm{d}\mu_{\mathrm{J}}}{\mathrm{d}\upsilon_{\mathrm{J}}}\cdot\overbrace{\left(\underbrace{\ell_{\mathrm{J}}^{\circ}q_{\mathrm{JA}}^{\#}}_{\text{juveniles}}+\underbrace{\ell_{\mathrm{A}}^{\circ}q_{\mathrm{AA}}^{\#}}_{\text{adults}}\right)\cdot\frac{\beta_{\mathrm{A}}}{\mu_{\mathrm{A}}}}^{\text{transmission from an adult to:}} \tag{9}$$

(Appendix A6-8), where $(\ell_{\mathrm{J}}^{\circ}, \ell_{\mathrm{A}}^{\circ})$ represents the pair of individual reproductive values of the parasites infecting juvenile and adult hosts (or the left eigenvector of $\mathbf{G}$ at neutrality; Appendix A6) and the factor $\ell_{\mathrm{J}}^{\circ} \times q_{\mathrm{JA}}^{\#}$ for instance represents the reproductive success due to transmission from an adult host to a juvenile per propagule-production. The first term is multiplied by $\left(\ell_{\mathrm{J}}^{\circ} q_{\mathrm{JJ}}^{\#} + \ell_{\mathrm{A}}^{\circ} q_{\mathrm{AJ}}^{\#}\right) \left(\beta_{\mathrm{J}}/\mu_{\mathrm{J}}\right)^{\circ}$, which represents the reproductive success of a parasite infecting juveniles, who can receive the marginal benefit due to increased infectiousness $\left(\mathrm{d}\beta_{\mathrm{J}}/\mathrm{d}\upsilon_{\mathrm{J}}\right)^{\circ}/\beta_{\mathrm{J}}^{\circ}$ but pay the marginal cost due to the reduction in infectious periods $1/\mu_{\mathrm{J}}^{\circ}$ as in the selection gradient for adult-virulence (Eqn (8)). In addition, juvenile-virulence incurs the additional cost of increased mortality of infected juveniles associated with the loss of expected reproductive success via adult hosts that the parasites could otherwise gain through the maturation of the juvenile hosts, and thus multiplied by $\left(\ell_{\mathrm{J}}^{\circ} q_{\mathrm{JA}}^{\#} + \ell_{\mathrm{A}}^{\circ} q_{\mathrm{AA}}^{\#}\right) \left(\beta_{\mathrm{A}}/\mu_{\mathrm{A}}\right)^{\circ}$ (the reproductive success of a parasite infecting adults) and the marginal decrease in the probability of maturation $(\pi_{\mathrm{I}}/\mu_{\mathrm{J}})^{\circ}$. Hence, Eqn (9) clearly captures the selection forces on juvenile-virulence, including the marginal benefits, marginal costs, and maturation-mediated costs.

We investigated the effects of two stage-structure characteristics: (i) post-maturation span θ_{A} and (ii) stage-assortativity ρ on the evolutionary outcomes (i.e., CSS; Appendix A9). Strikingly, the CSS for adult-virulence is necessarily $\upsilon_{\mathrm{A}}^{*} = \sqrt{m_{\mathrm{A}}/k_{\mathrm{A}}}$ which is independent of any demographic and disease characteristics of juveniles (as expected from Eqn (8)). Therefore, we used $\upsilon_{\mathrm{A}}^{*}$ as a reference value in comparison with $\upsilon_{\mathrm{J}}^{*}$.

In contrast, CSS for juvenile-virulence is dramatically affected by hosts' stage-structure and maturation. This is because the parasites infecting the juveniles can utilize two transmission-pathways: either from the juvenile (to any susceptible hosts), or from the adult who has successfully matured from the juvenile stage. The expression for $\upsilon_{\mathrm{J}}^{*}$ is analytically intractable, and as such we numerically evaluated $\upsilon_{\mathrm{J}}^{*}$ by jointly solving the wild-type ODE Eqn (1) and the selection gradients Eqns (8) and (9).

We can immediately see that the evolutionary outcome of adult-virulence increases with adult natural mortality, in agreement with the previous studies (reviewed in Alizon *et al.* 2009; Cressler *et al.* 2016). To assess when selection favors higher juvenile-virulence than adult-virulence, we quantified $\upsilon_{\mathrm{J}}^{*}/\upsilon_{\mathrm{A}}^{*}$ as a function of the

assortatvity (ρ, abscissa) and post-maturation span (θ_A, ordinate; Fig 3). We found that either disassortative hosts with a long post-maturation span or assortative hosts with a short post-maturation span select for higher virulence against juveniles. This result slightly changes given stage-specific mortality rates ($m_J \neq m_A$) such that a higher mortality for juveniles can bias the outcomes towards higher virulence for juveniles, but the general trend is robust (Fig 3A-C). Also, the combination of disassortativity and long post-maturation span (one of the conditions favoring higher virulence against juveniles) leads to parasite extinction as a result of overexploitation against juveniles (Fig 3B, C; Appendix A10). Note that under these conditions, I_J is very small (tending to zero; Fig 3B), while S_J is not (Fig 3C), meaning that hosts do persist but parasites do not.

By relaxing the assumptions of the symmetry in disease-related parameters k_J, k_A (efficiency of exploitation for transmission), b_J, b_A (maximum infectiousness), and α_J, α_A (susceptibility) for juveniles and adults, or by incorporating recovery or tolerance, we showed that the results are robust and qualitatively unchanged (Appendix B). Finally, we checked that density-dependent transmission yields quantitatively similar results (Appendix B). Therefore, we conclude that the combined effects of maturation and assortativity are critical to the evolution of virulence.

Discussion

We have shown how parasites may be subject to different selective pressures when they infect adults as opposed to adults. Our key insight is that the combination between maturation rates and contact-structure determines the evolutionary outcomes of juvenile-virulence. Higher virulence against juveniles is favored either if: (i) the adult-stage is relatively long and the contact-structure is disassortative (between age class interactions are high; Fig 3, left-top zone), or (ii) the juvenile-stage is relatively long and the contact structure is assortative (interactions occur preferentially within classes; Fig 3, right-bottom zone). These results can be understood as follows: when the post-maturation span is long and the contact structure is

disassortative, adult hosts are abundant in the population and the transmission from juveniles to adults is more likely than between juveniles; in this case, the availability of adult hosts is higher, which selects for higher exploitation against juveniles to exploit more abundant resource of adults. Equivalent reasoning explains higher juvenile-virulence in short maturating and assortative hosts. These considerations mean that host-demography alongside the maturation of juveniles strongly affects the evolutionary outcomes of parasite virulence. Spatial and/or temporal segregation in the niches of juveniles and adults therefore has the potential to drive the evolution of differential virulence. Our novel result is therefore, that virulence is highly sensitive to stage-structured life-history characteristics of hosts such as ontogeny and any associated, spatio-temporal niche-shifts.

The incorporation of the maturation shows that higher parasite exploitation against juveniles incurs an additional cost associated with increased maturation failure. In particular, while the marginal value theorem (Charnov 1976) does correctly predict the evolutionary outcomes of adult virulence it does not predict that of juvenile virulence. Therefore, sources of heterogeneity in hosts can clearly lead to different predictions than classic virulence evolution theory based on the marginal value theorem, as claimed in a recent conceptual review (Lion & Metz 2018). Gandon (2004) and Osnas & Dobson (2011) introduced multiple hosts' types or species and studied virulence against them. In previous theory, heterogeneity is incorporated on the basis of hosts species (Regoes *et al.* 2000; Gandon 2004; Osnas & Dobson 2011), vaccination (Gandon *et al.* 2001; Gandon *et al.* 2003; Yates *et al.* 2006; Zurita-Gutiérrez & Lion 2015), or sex (Úbeda & Jansen 2016) (reviewed in Lion & Metz 2018). However, none of these studies incorporated stage-structure with associated stage-specific virulence. Our novel results arise because we explicitly assumed stage-structure with maturation from juveniles to adults and reproduction by adults rather than more generic heterogeneity between different types of hosts.

Finding examples of stage-specific virulence in empirical systems can be difficult due to the intricacies of specific host-pathogen systems. Stage-related trends in virulence can be complicated by age-related

trends in maternal immunity, adaptive immunity, and exposure rate, and specific host-parasite system characteristics including maladaptation and immuno-pathogenicity (Hudson & Dobson 1995; Wilson *et al.* 2002). Additionally, studies looking at age-related virulence or case mortality do not exclusively look at differences between adult and juvenile stages and may focus on old age-mediated declines in immuno-competence. However, despite these issues, we found data on several empirical systems that lend support to our predictions and may offer opportunities for testing our hypotheses (Fig 1). For most of these systems, we were unable to find data on the assortativity of transmission which therefore limited our ability to make conclusions about trends in the data. However, both of the two wildlife systems for which we found data describing all three of our variables ($\upsilon_J^*/\upsilon_A^*$, post-maturation lifespan, and transmission assortativity) matched our model's predictions. Wanelik *et al.* (2017) showed that Great Island Virus (GIV) transmission in guillemots (*Uria aalge*) is assortative across age classes because of the spatial structure of breeding grounds. GIV is transmitted by poorly motile ticks and pre-breeding stages of guillemots do not enter breeding areas of the colony. As a consequence, the virus does not readily transmit between guillemot age-stages (Wanelik *et al.* 2017). Previous work on guillemot life-history shows that the birds spend more than three quarters of their life-span as mature breeders (Harris & Wanless 1995), and therefore the combination of assortative transmission and fast maturation predicts that GIV should be more virulent in breeders. In line with the predictions of our model, infection associated mortality risk is 1.45 times higher for adults than for juveniles (Nunn *et al.* 2006).

In the second example, Jones *et al.* (2008) showed that salmon louse caused morality in juvenile pink salmon (*Oncorhynchus gorbuscha*), but had no effect on mortality risk for adults. Salmon louse is also assortatively transmitted between age classes, because pink salmon have strict two-year lifespans where they are only ever associated with individuals of their same age class (Heard 1991; Krkošek *et al.* 2007). The salmon only reproduce once at the very end of their lives (semelparity), and therefore have a short adult period. This short post-maturation stage and assortative transmission correctly predicts the higher salmon louse virulence

in juveniles.

Better data on mixing matrices for more disease systems could provide interesting insights into the maintenance of either high juvenile or high adult virulence. One system where these insights could prove especially important is in Bd (*Batrachochytrium dendrobatidis*, or chytrid fungus) infection in frogs, which has been causing catastrophic worldwide declines in frog populations (Kilpatrick *et al.* 2010). Bd infection has been shown to have different virulence effects in the different frog life-stages (Medina *et al.* 2015; Hite *et al.* 2016) and these effects also vary by frog species (Berger *et al.* 1998; Blaustein *et al.* 2005). Recent work has shown that adult virulence in several frog populations has not decreased even after 20 years of Bd presence (Voyles *et al.* 2018). Already, frog demography has been implicated as an important factor for population persistence in the face of Bd with frog species where adults move away from breeding waters being more resistant to population declines (Lips *et al.* 2006; McCaffery *et al.* 2015), and frogs in habitats with multi-year larvae having more severe epidemics because the older stages maintain high levels of infection that then spill over to infect other stages and species (Medina *et al.* 2015; Hite *et al.* 2016). Changes in the assortivity of mixing clearly has important implications for disease transmission across stages, and our model suggests that it could also have implications for the maintenance of high virulence in different age stages.

While data on age-related contact patterns are difficult to find in wildlife populations, a wealth of mixing data exists for humans (Mossong *et al.* 2008; Rohani *et al.* 2010). These suggest that contacts relevant for the transmission of directly transmitted pathogens are highly assortative by age. While the evolutionary drivers of human pathogens are often complicated, we posit that chickenpox (varicella virus) virulence in humans proves an intriguing case study. Given that humans have a long juvenile period in the context of our model, even when we only consider pre-reproductive and reproductive periods (Bogin & Smith 1996), the higher virulence in adults of chickenpox (23-29 times higher mortality risk in adults (Heininger & Seward 2006) for primary infections in naïve individuals fits the predictions of our model. This higher mortality risk corresponds to increased viral titers with age (Malavige *et al.* 2008) and, perhaps most interestingly,

while varicella virus infects many cell-types, T cell infection is thought to be important for transport and pathogenesis (Zerboni & Arvin 2016). Therefore, age-related trends in T-cell abundance could be implicated in chickenpox pathogenesis, although this relationship is complicated by the fact that VSV-specific T-cell responses are also correlated with decreased viral titer and diminish with age (Erkeller-Yuksel *et al.* 1992; Nader *et al.* 1995; Malavige *et al.* 2008). Still, this example points towards one mechanism that may underlie the mediation of age-specific virulence in pathogens.

Our models have implications for disease management especially in farmed and other managed animal populations. For instance, if the post-maturation span is short (i.e. if u is small), then artificial restriction of the contacts between stages is predicted to select for higher virulence. However, if the post-maturation span is long, restricting the contacts into juvenile-juvenile and adult-adult (by e.g., separating the cohorts) can lead to the parasite extinction as a result of overexploitation against the juveniles. These contrasting outcomes can occur for any given host species, depending on how management modulates host stage-structure. Our models thus predict that, to prevent evolutionary changes towards higher virulence, one needs to carefully take into account the cohort structure.

For simplicity and tractability we chose to use simple two-stage models rather than continuous "infection-age" models (which would entail the formalism based on partial differential equations and dynamic programming approach). Future studies that capture more continuous age structure are an important next step. Also, although we assumed that parasites can express conditional virulence depending on the stage of the hosts they infect with, more data are needed to test this idea. In addition, coevolutionary models and multiple infections are both likely to give further important insights to the determinants of age-dependent disease interactions in nature. Our approach offers the basis for modeling these coevolutionary dynamics between hosts and parasites when there is stage structure.

References

Alizon, S. *et al.* (2009). Virulence evolution and the trade-off hypothesis: history, current state of affairs and the future. *J. Evol. Biol.* **22**.2, pp. 245–259.

Anderson, R. M. & May, R. (1982). Coevolution of hosts and parasites. *Parasitology* **85**.2, pp. 411–426.

Anderson, R. M. & May, R. M. (1992). *Infectious diseases of humans: dynamics and control*. Oxford University Press.

Ashby, B. & Bruns, E. (2018). The evolution of juvenile susceptibility to infectious disease. *Proc. Roy. Soc. B.* **285**.1881, p. 20180844.

Ball, G. H. (1943). Parasitism and evolution. *Am. Nat.* **77**.771, pp. 345–364.

Berger, L. *et al.* (1998). Chytridiomycosis causes amphibian mortality associated with population declines in the rain forests of Australia and Central America. *PNAS* **95**.15, pp. 9031–9036.

Bernhauerová, V. (2016). Vaccine-driven evolution of parasite virulence and immune evasion in age-structured population: the case of pertussis. *Theor. Ecol.* **9**.4, pp. 431–442.

Blaustein, A. R. *et al.* (2005). Interspecific variation in susceptibility of frog tadpoles to the pathogenic fungus *Batrachochytrium dendrobatidis*. *Cons. Biol.* **19**.5, pp. 1460–1468.

Bogin, B. & Smith, B. H. (1996). Evolution of the human life cycle. *Am. J. Hum. Biol.* **8**.6, pp. 703–716.

Boots, M. & Sasaki, A. (2003). Parasite evolution and extinctions. *Ecol. Lett.* **6**.3, pp. 176–182.

Boots, M. *et al.* (2009). The role of ecological feedbacks in the evolution of host defence: what does theory tell us? *Phil. Trans. Roy. Soc. B* **364**.1513, p. 27.

Briggs, C. & Godfray, H. (1995). The dynamics of insect-pathogen interactions in stage-structured populations. *Am. Nat.* **145**.6, pp. 855–887.

Bull, J. J. & Lauring, A. S. (2014). Theory and empiricism in virulence evolution. *PLoS Pathogens* **10**.10, e1004387.

Caswell, H. (2001). *Matrix population models*. Wiley Online Library.

Charnov, E. L. (1976). Optimal foraging, the marginal value theorem. *Theor. Popul. Biol.* **9**.2, pp. 129–136.

Christiansen, F. B. (1991). On conditions for evolutionary stability for a continuously varying character. *Am. Nat.* Pp. 37–50.

Cornell, S. J. *et al.* (2008). Seasonality, cohort-dependence and the development of immunity in a natural host–nematode system. *Proc. Roy. Soc. B* **275**.1634, pp. 511–518.

Craft, M. E. (2015). Infectious disease transmission and contact networks in wildlife and livestock. *Phil. Trans. Roy. Soc. B.* **370**.1669, p. 20140107.

Cressler, C. E. *et al.* (2016). The adaptive evolution of virulence: a review of theoretical predictions and empirical tests. *Parasitology* **143**.7, pp. 915–30.

Day, T. (2001). Parasite transmission modes and the evolution of virulence. *Evolution* **55**.12, pp. 2389–2400.

Day, T. & Proulx, S. R. (2004). A general theory for the evolutionary dynamics of virulence. *Am. Nat.* **163**.4, E40–E63.

Day, T. *et al.* (2011). Bridging scales in the evolution of infectious disease life histories: theory. *Evolution* **65**.12, pp. 3448–3461.

De Castro, F. & Bolker, B. (2005). Mechanisms of disease-induced extinction. *Ecol. Lett.* **8**.1, pp. 117–126.

Dieckmann, U. (2005). *Adaptive dynamics of infectious diseases: in pursuit of virulence management*. **2**. Cambridge University Press.

Dieckmann, U. & Law, R. (1996). The dynamical theory of coevolution: a derivation from stochastic ecological processes. *J. Math. Biol.* **34**.5-6, pp. 579–612.

Diekmann, O. *et al.* (2012). *Mathematical tools for understanding infectious disease dynamics*. Princeton University Press.

Dwyer, G. (1991). The roles of density, stage, and patchiness in the transmission of an insect virus. *Ecology* **72**.2, pp. 559–574.

Ebert, D. & Herre, E. A. (1996). The evolution of parasitic diseases. *Parasitol. Tod.* **12**.3, pp. 96–101.

Erkeller-Yuksel, F. M. *et al.* (1992). Age-related changes in human blood lymphocyte subpopulations. *J. Pediatr.* **120**.2, pp. 216–222.

Eshel, I. (1983). Evolutionary and continuous stability. *J. Theor. Biol.* **103**.1, pp. 99–111.

Fisher, R. A. (1958). *The genetical theory of natural selection.* Tech. rep. Dover Publications,

Fleming-Davies, A. E. *et al.* (2015). Effects of host heterogeneity on pathogen diversity and evolution. *Ecol. Lett.* **18**.11, pp. 1252–1261.

Frank, S. A. (1996). Models of parasite virulence. *Q. Rev. Biol.* Pp. 37–78.

— (1998). *Foundations of social evolution*. Princeton University Press.

Gandon, S. *et al.* (2003). Imperfect vaccination: some epidemiological and evolutionary consequences. *Proc. Roy. Soc. B.* **270**.1520, pp. 1129–1136.

Gandon, S. (2004). Evolution of multihost parasites. *Evolution* **58**.3, pp. 455–469.

Gandon, S. *et al.* (2001). Host life history and the evolution of parasite virulence. *Evolution* **55**.5, pp. 1056–1062.

Grafen, A. (2006). A theory of Fisher's reproductive value. *J. Math. Biol.* **53**.1, pp. 15–60.

Harris, M. & Wanless, S (1995). Survival and non-breeding of adult Common Guillemots *Uria aalge*. *Ibis* **137**.2, pp. 192–197.

Hawlena, H. *et al.* (2006). Ectoparasites and age-dependent survival in a desert rodent. *Oecologia* **148**.1, pp. 30–39.

Heard, W. R. (1991). Life history of pink salmon (*Oncorhynchus gorbuscha*). *Pacific salmon life histories*, pp. 119–230.

Heininger, U. & Seward, J. F. (2006). Varicella. *The Lancet* **368**.9544, pp. 1365–1376.

Hite, J. L. *et al.* (2016). Parasites destabilize host populations by shifting stage-structured interactions. *Ecology* **97**.2, pp. 439–449.

Hofbauer, J. & Sigmund, K. (1990). Adaptive dynamics and evolutionary stability. *Appl. Math. Lett.* **3**.4, pp. 75–79.

Holst, D. von *et al.* (2002). Social rank, fecundity and lifetime reproductive success in wild European rabbits (*Oryctolagus cuniculus*). *Behav. Ecol. Sociobiol.* **51**.3, pp. 245–254.

Hudson, P. J. & Dobson, A. P. (1995). "Macroparasites: observed patterns". *Ecology of Infectious Diseases in Natural Populations*. Ed. by B. T. Grenfell & A. P. Dobson. Cambridge University Press, pp. 144–176.

Hurford, A. *et al.* (2010). Next-generation tools for evolutionary invasion analyses. *J. Roy. Soc. Int.* **7**.45, pp. 561–571.

Jones, O. R. *et al.* (2013). Diversity of ageing across the tree of life. *Nature* **505**.7482, pp. 169–173.

Jones, S *et al.* (2008). Early development of resistance to the salmon louse, *Lepeophtheirus salmonis* (Krøyer), in juvenile pink salmon, *Oncorhynchus gorbuscha* (Walbaum). *J. Fish Diseas.* **31**.8, pp. 591–600.

Kilpatrick, A. M. *et al.* (2010). The ecology and impact of chytridiomycosis: an emerging disease of amphibians. *TREE* **25**.2, pp. 109–118.

Krkošek, M. *et al.* (2007). Effects of host migration, diversity and aquaculture on sea lice threats to Pacific salmon populations. *Proc. Roy. Soc. B* **274**.1629, pp. 3141–3149.

Lack, D. L. (1968). Ecological adaptations for breeding in birds.

Lion, S. (2018). Class structure, demography, and selection: reproductive-value weighting in nonequilibrium, polymorphic populations. *Am. Nat.* **191**.5, pp. 620–637.

Lion, S. & Metz, J. A. J. (2018). Beyond R_0 maximisation: on pathogen evolution and environmental dimensions. *TREE* **33**, pp. 75–90.

Lips, K. R. *et al.* (2006). Emerging infectious disease and the loss of biodiversity in a Neotropical amphibian community. *PNAS* **103**.9, pp. 3165–3170.

Lynsdale, C. L. *et al.* (2017). Parasite-associated mortality in a long-lived mammal: Variation with host age, sex, and reproduction. *Ecol. Evol.* **7**.24, pp. 10904–10915.

Malavige, G. N. *et al.* (2008). Viral load, clinical disease severity and cellular immune responses in primary varicella zoster virus infection in Sri Lanka. *PloS one* **3**.11, e3789.

Maynard Smith, J. & Price, G. R. (1973). The Logic of Animal Conflict. *Nature* **246**, p. 15.

McCaffery, R. *et al.* (2015). The demography of *Atelopus decline*: Harlequin frog survival and abundance in central Panama prior to and during a disease outbreak. *Glob. Ecol. Cons.* **4**, pp. 232–242.

Medina, D. *et al.* (2015). Delayed metamorphosis of amphibian larvae facilitates *Batrachochytrium dendrobatidis* transmission and persistence. *Diseases of Aquatic Organisms* **117**.2, pp. 85–92.

Mideo, N. *et al.* (2011). Bridging scales in the evolution of infectious disease life histories: application. *Evolution* **65**.11, pp. 3298–3310.

Morisse, J. *et al.* (1991). Hepatitis of viral origin in Leporidae: introduction and aetiological hypotheses. *Revue scientifique et technique (International Office of Epizootics)* **10**.2, pp. 269–310.

Mossong, J. *et al.* (2008). Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS Medicine* **5**.3, e74.

Nader, S. *et al.* (1995). Age-related differences in cell-mediated immunity to varicella-zoster virus among children and adults immunized with live attenuated varicella vaccine. *J. Infect. Diseas.* **171**.1, pp. 13–17.

Nunn, M. *et al.* (2006). Tick-borne Great Island Virus:(II) Impact of age-related acquired immunity on transmission in a natural seabird host. *Parasitology* **132**.2, pp. 241–253.

Osnas, E. E. & Dobson, A. P. (2011). Evolution of virulence in heterogeneous host communities under multiple trade-offs. *Evolution* **66**.2, pp. 391–401.

Otto, S. P. & Day, T. (2007). *A biologist's guide to mathematical modeling in ecology and evolution*. **13**. Princeton University Press.

Read, A. F. (1994). The evolution of virulence. *Tr. Microbiol.* **2**.3, pp. 73–76.

Regoes, R. R. *et al.* (2000). Evolution of virulence in a heterogeneous host population. *Evolution* **54**.1, pp. 64–71.

Reluga, T. C. *et al.* (2007). Optimal timing of disease transmission in an age-structured population. *Bull. Math. Biol.* **69**.8, pp. 2711–2722.

Rohani, P. *et al.* (2010). Contact network structure explains the changing epidemiology of pertussis. *Science* **330**.6006, pp. 982–985.

de Roos, A. M. & Persson, L. (2013). *Population and community ecology of ontogenetic development*. Princeton University Press.

Schmid-Hempel, P. (2011). *Evolutionary parasitology: the integrated study of infections, immunology, ecology, and genetics*. Oxford University Press, New York.

Smith, T. (1904). Some problems in the life history of pathogenic microorganisms. *Science* **20**.520, pp. 817–832.

Sol, D. *et al.* (2003). Parasite mediated mortality and host immune response explain age-related differences in blood parasitism in birds. *Oecologia* **135**.4, pp. 542–547.

Sukumar, R *et al.* (1997). Demography of captive Asian elephants (*Elephas maximus*) in southern India. *Zoo Biology: Published in affiliation with the American Zoo and Aquarium Association* **16**.3, pp. 263–272.

Takada, T. & Kigami, J. (1991). The dynamical attainability of ESS in evolutionary games. *J. Math. Biol.* **29**.6, pp. 513–529.

Taylor, P. D. (1990). Allele-frequency change in a class-structured population. *Am. Nat.* **135**, pp. 95–106.

Úbeda, F. & Jansen, V. A. A. (2016). The evolution of sex-specific virulence in infectious diseases. *Nat. Comm.* **7**, p. 13849.

van den Driessche, P. & Watmough, J. (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Math. Biosci.* **180**.1, pp. 29–48.

VanderWaal, K. L. & Ezenwa, V. O. (2016). Heterogeneity in pathogen transmission: mechanisms and methodology. *Funct. Ecol.* **30**.10. Ed. by D. Hawley, pp. 1606–1622.

Voyles, J. *et al.* (2018). Shifts in disease dynamics in a tropical amphibian assemblage are not due to pathogen attenuation. *Science* **359**.6383, pp. 1517–1519.

Wanelik, K. M. *et al.* (2017). Investigating the effects of age-related spatial structuring on the transmission of a tick-borne virus in a colonially breeding host. *Ecol. Evol.* **7**.24, pp. 10930–10940.

Wassif, K. & Soliman, S. (1980). "Population studies on gerbils of the western desert of Egypt, with special reference to *Gerbillus andersoni de Winton*". *Proceedings of the 9th Vertebrate Pest Conference (1980)*, p. 41.

White, L. A. *et al.* (2017). Using contact networks to explore mechanisms of parasite transmission in wildlife. *Biol. Rev.* **92**.1, pp. 389–409.

Williams, P. D. (2011). New insights into virulence evolution in multigroup hosts. *Am. Nat.* **179**.2, pp. 228–239.

Williams, P. D. & Kamel, S. J. (2018). The evolution of pathogen virulence: Effects of transitions between host types. *J. Theor. Biol.* **438**, pp. 1–8.

Wilson, K. *et al.* (2002). Heterogeneities in macroparasite infections: patterns and processes. *The Ecology of Wildlife Diseases* **44**, pp. 6–44.

Yates, A. *et al.* (2006). How do pathogen evolution and host heterogeneity interact in disease emergence? *Proc. Roy. Soc. B.* **273**.1605, pp. 3075–3083.

Zerboni, L. & Arvin, A. M. (2016). "The pathogenesis of varicella-zoster virus neurotropism and infection". *Neurotropic viral infections*. Springer, pp. 135–173.

Zurita-Gutiérrez, Y. H. & Lion, S. (2015). Spatial structure, host heterogeneity and parasite virulence: implications for vaccine-driven evolution. *Ecol. Lett.* **18**.8, pp. 779–789.

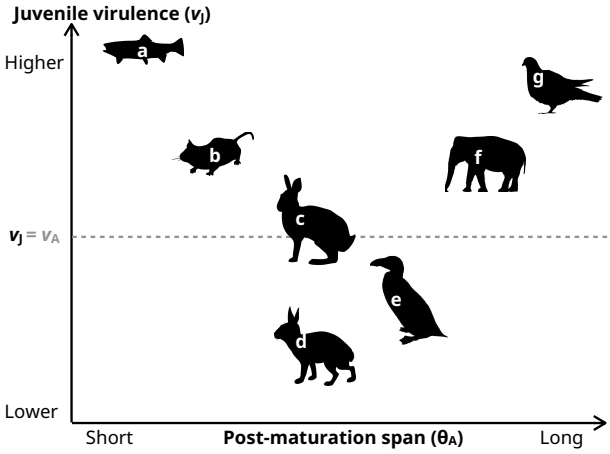

Figure 1: A graphical representation of the empirical data on stage-specific virulence. In the following, H indicates "host" while P indicates "parasites" : (a) H: Pink Salmon (*Oncorhynchus gorbuscha*); P: Salmon Louse (Heard 1991; Jones *et al.* 2008). (b) H: Gerbil (*Gerbillus andersoni*); P: Ectoparasites (Wassif & Soliman 1980; Hawlena *et al.* 2006). (c) H: European Rabbit (*Oryctolagus cuniculus*); P: Nematode (Holst *et al.* 2002; Cornell *et al.* 2008). (d) H: Rabbits (*Leporidae*); P: RHD Virus (Morisse *et al.* 1991; Reluga *et al.* 2007). (e) H: Common Guillemot (*Uria aalge*); P: Great Island Virus (Harris & Wanless 1995; Nunn *et al.* 2006; Wanelik *et al.* 2017). (f) H: Asian Elephant (*Elephas maximus*); P: Parasites (Sukumar *et al.* 1997; Lynsdale *et al.* 2017). (g) H: Pigeon (*Columba livia*) P: Blood parasites (Lack 1968; Sol *et al.* 2003)

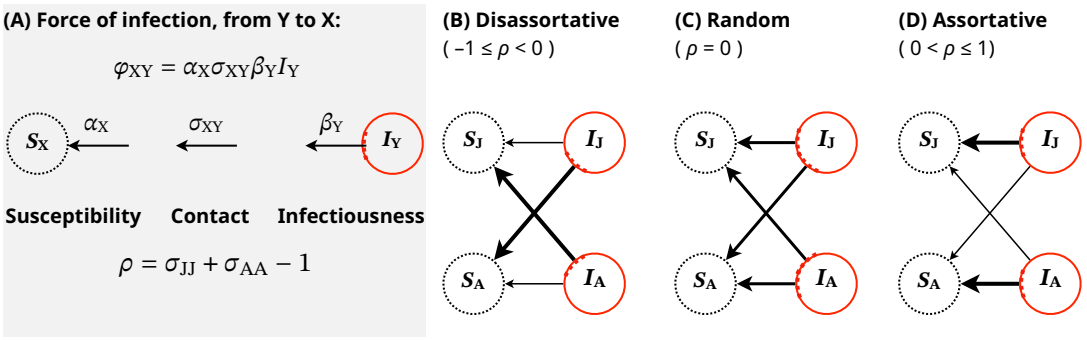

Figure 2: A schematic illustration of the model on the force of infection and assortativity. (A) Force of infection from Y to X, φ_{XY}, is a compound factor of susceptibility (likeliness of X-hosts becoming infected), contact intensity (likeliness of contacts between X and Y), and infectiousness (propagule production of the parasite carried by Y). (B-D) Degrees of assortativity. Negative assortativity indicates that contacts occur more frequently between stages than within stages (panel B). The contact structure is unbiased (random) when $\rho = 0$ (panel C). Positive assortativity indicates that contacts occur more frequently within stages than between stages (panel D).

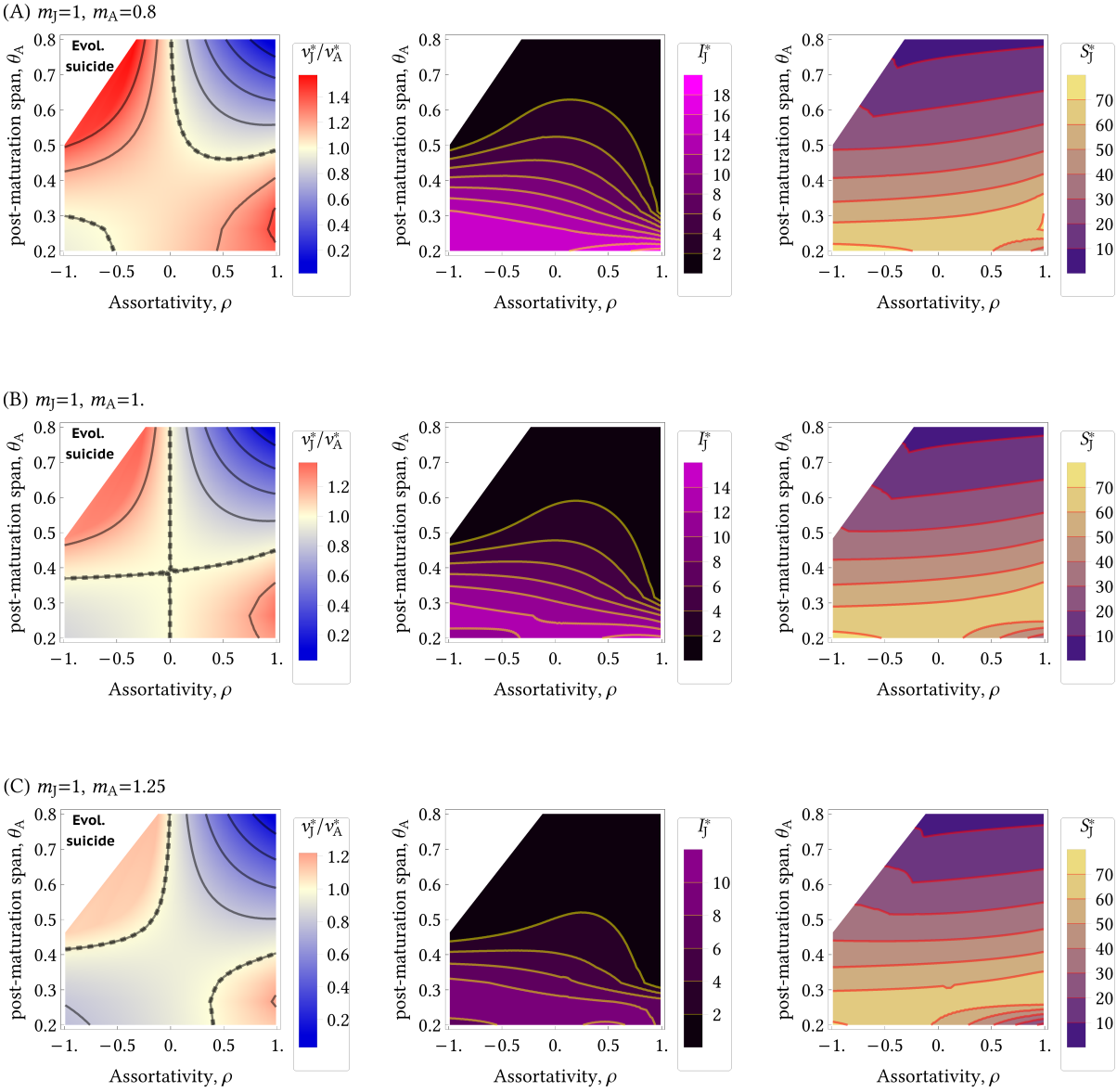

Figure 3: Left panels: Evolutionary outcomes of relative virulence (v_J^*/v_A^*), in which red color indicates $v_J^* > v_A^*$ and blue color indicates $v_J^* < v_A^*$. Color scales used are the same in the three panels. Middle panels: Densities of infected juveniles at equilibrium, I_J^*. Right panels: Densities of susceptible juveniles at equilibrium, S_J^*. In each panel, abscissa: assortativity; ordinate: post-maturation span θ_A; from (A) to (C): $m_A = 0.8, 1.0, 1.25$ as indicated; White zone: evolutionary suicide; dotted curve: $v_J^* = v_A^*$ (equal virulence); parameters: default values. We numerically evaluated CSS-virulence and densities of infected juveniles and adults.