When parasites are selected to kill the young

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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 stage-dependent virulence evolution. 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; Mideo *et al.* 2008; 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). Theory on parasite evolution is typically based on trade-offs imposed between transmission rate and virulence (defined in this literature as the increased death rate due to infection; Anderson & May 1982; Ewald 1983). Specifically, the transmission-virulence trade-off hypothesis posits that high host exploitation by the parasite leads to high transmission but also results in higher virulence (reviewed in Ewald 1983; Alizon *et al.* 2009). Theoretically, evolutionarily stable exploitation occurs when the marginal increase in transmission due to exploitation equals the marginal increase in host mortality due to exploitation. This consequently optimizes parasite fitness (e.g., Charnov 1976; Anderson & May 1982; Bulmer 1994; Otto & Day 2007; but see Lion & Metz 2018). Another, less studied trade-off is between virulence and rate of recovery, with more rapidly growing parasites being harder to clear but causing more damage (Anderson & May 1982). Such trade-offs are fundamental to understanding the evolutionary drivers of the virulence of infectious diseases and offer a number of important insights for disease management (Van Baalen & Sabelis 1995). However, despite the considerable variation in virulence that

is found at different life-stages in nature (Hudson & Dobson 1995), the implications of host stage structure to parasite virulence has not been examined and the differences in virulence between adults and juveniles are typically explained in terms of differences in host defense (Hudson & Dobson 1995; Wilson *et al.* 2002).

A number of recent ecological studies have examined the impact of a host populations' stage-related heterogeneities in disease response on disease epidemiology (e.g., Dwyer 1991; Fleming-Davies *et al.* 2015; Hite *et al.* 2016). In these studies, the differences in the impact of infection between life stages have been assumed to be properties of the host and driven by processes like maternal and acquired immunity and age-related variation in tolerance, resistance, exposure, immunocompetence, and susceptibility (Hudson & Dobson 1995; Wilson *et al.* 2002). In principle, however, this variation in disease outcomes across different host life-stages (e.g., egg, larvae, juvenile, adult, etc) has the potential to significantly impact the evolutionary dynamics of virulence. Additionally, stage structure in host populations can also lead to variation in transmission routes between and across stages (reviewed in Craft 2015; VanderWaal & Ezenwa 2016; White *et al.* 2017). For instance, juvenile-juvenile and adult-adult contacts might be more likely than juvenile-adult contacts if juvenile and adult hosts are segregated in spatio-temporal niches, typical of humans (Rohani *et al.* 2010), amphibians (Kilpatrick *et al.* 2010), and insects (Briggs & Godfray 1995). Such variation in assortativity or disassortivity of transmission between life stages can create differential selection pressures where a parasite may be selected to bias its virulence towards different stages ("stage-specific virulence"). We propose that the differences in virulence at different ages may not necessarily

be properties of the host, but instead could be selected for as adaptive properties of the parasites (Fig 1).

Here, we show that hosts' stage-related contact structure and the period of reproductive (and thus adult) stage can in concert drive the evolution of stage-specific virulence. We develop a mathematical model and explore the evolutionary outcomes of stage-specific virulence under different patterns of contacts across stages. We explicitly model the stage-structured host population dynamics for juveniles and adults including epidemiology, and analyze the evolutionary dynamics using the adaptive dynamics toolbox (Hofbauer & Sigmund 1990; Dieckmann & Law 1996). We first show that the evolutionary outcomes of virulence against adults ("adult-virulence") follow classic results such that background mortality rate in adults favors higher virulence. Second, we show that the evolutionary outcomes of virulence against juveniles ("juvenile-virulence") are critically impacted by the interplay between assortativity and maturation. We explain the results in terms of Fisher's reproductive value to account for life-history evolution of parasites (Fisher 1958; Taylor 1990; Frank 1998; Caswell 2001; Gandon 2004; Grafen 2006; Otto & Day 2007; Williams 2011; Williams & Kamel 2018; Lion 2018) and in terms of transmission pathways (and thus the pathways to reproductive success of parasites). We find a number of robust examples in the empirical literature that match our predictions and therefore highlight the importance of age-structure to the evolution of infectious disease.

Method

We consider a host population subdivided 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 (Schreiber & Rudolf 2008) yields the following ordinary differential equations (ODEs; Appendix A1):

$$\begin{aligned}
\frac{\mathrm{d}S_J}{\mathrm{d}t} &= \left(r - \kappa(S_A + I_A)\right) \cdot (S_A + I_A) - \left(u + \phi_{JA} + \phi_{JJ} + m_J\right) S_J, \\
\frac{\mathrm{d}S_A}{\mathrm{d}t} &= uS_J - \left(m_A + \phi_{AJ} + \phi_{AA}\right) S_A \\
\frac{\mathrm{d}I_J}{\mathrm{d}t} &= \left(\phi_{JJ} + \phi_{JA}\right) S_J - \left(u + m_J + v_J\right) I_J \\
\frac{\mathrm{d}I_A}{\mathrm{d}t} &= \left(\phi_{AJ} + \phi_{AA}\right) S_A + uI_J - \left(m_A + v_A\right) I_A,
\end{aligned} \tag{1}$$

where: r represents an intrinsic growth rate of the adult hosts per capita, and we assume that susceptible and infected hosts have the same fecundity; there is no reproduction from juveniles. Reproduction is reduced by s density-dependent factor κ; juveniles mature at a rate u; 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); m_X represents the background mortality for a stage-X host; v_X represents the virulence against a stage-X host, as an evolving trait. Note that we choose to consider discrete stages rather than continuous stages. For other approaches including physiologically structured population modeling and

infection-age modeling frameworks, see Roos & Persson 2013; Day *et al.* 2011; Mideo *et al.* 2011. Our methodology here allows to evaluate the relative strength of exploitation against juveniles compared to adults.

Maturation and natural death rates can both affect the relative length of a adult-stage of the hosts. To quantify this, we define the expected fraction of time a host individual spends as an adult in the entire lifespan in the absence of disease by θ_{A}. In Appendix A2, we showed that θ_{A} is given by:

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

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 (where X and Y run across J and A) involves with three processes: susceptibility α_{X} (the rate at which a stage-X host becomes infected given exposure to infectious propagules), contact structure σ_{XY} (which represents the intensity of interaction between a stage-Y host and a stage-X host), and infectiousness β_{Y} (the rate of propagule production from a stage-Y host; reviewed in VanderWaal & Ezenwa 2016):

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

(see Fig 2). Here, Eqn (3) assumes that the transmission follows a frequency-dependent mass-action model (McCallum *et al.* 2001). To quantify the contact structure, we use a single parameter of contct structure $\sigma = 1 - \sigma_{AJ} = \sigma_{JJ} = 1 - \sigma_{JA} = \sigma_{AA}$, accounting for the assumption that within-class contacts decrease linearly with between-class contacts (and vice versa; but see Rohani *et al.* 2010; Glasser *et al.* 2012; Craft 2015). With this symmetry, "assortativity" is given by:

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

where ρ varies from -1 to 1 (Massol & Cheptou 2011; Rodrigues & Gardner 2012; Massol & Débarre 2015; Iritani & Cheptou 2017). 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 (and consequently transmission) occurs exclusively within stages.

A final ingredient is the transmission-virulence trade-off, formulated by:

$$\begin{aligned} \beta_J &= b_J \frac{k_J v_J}{1 + k_J v_J}, \\ \beta_A &= b_A \frac{k_A v_A}{1 + k_A v_A}, \end{aligned} \tag{5}$$

where k_X tunes the degree of steepness or the efficiency of virulence for infectiousness from stage-X hosts; b_X represent the upper bounds of infectiousness from stage-X hosts. Here, we have assumed that infectiousness increases with virulence; hence, the trade-off is explicitly

imposed between infectiousness and virulence.

We use the adaptive dynamics toolbox (Hofbauer & Sigmund 1990; Dieckmann & Law 1996) to study the long-term evolutionary dynamics. First, suppose that the demographic and epidemiological dynamics have quickly reached a steady state: $(S_\mathrm{J}, S_\mathrm{A}, I_\mathrm{J}, I_\mathrm{A}) = (S_\mathrm{J}^*, S_\mathrm{A}^*, I_\mathrm{J}^*, I_\mathrm{A}^*)$, which is a solution of the ODEs for a given value of $(v_\mathrm{J}, v_\mathrm{A})$. We then introduce a rare mutant of small phenotypic changes in host stage-specific virulence, $\mathbf{v}' := (v'_\mathrm{J}, v'_\mathrm{A})$ attempting to invade a monomorphic, resident type ("wild type") virulence $\mathbf{v} := (v_\mathrm{J}, v_\mathrm{A})$. We assume that the differences in virulence between mutant and wild types are very small (phenotypically weak selection). We detailed the outline of the analysis in Appendix A3.

To assess the possibility of mutant invasion, we define the invasion fitness, denoted w, by using the Next-Generation Theorem (Driessche & Watmough 2002; Hurford *et al.* 2010). The "next-generation matrix" (that governs the population dynamics of the rare mutant and thus its long term growth) can be written as the product of five matrices, given by:

$$\mathbf{G}' = \underbrace{\begin{pmatrix} S_\mathrm{J}^* & 0 \\ 0 & S_\mathrm{A}^* \end{pmatrix}}_{\text{availability}} \underbrace{\begin{pmatrix} \alpha_\mathrm{J} & 0 \\ 0 & \alpha_\mathrm{A} \end{pmatrix}}_{\text{susceptibility}} \underbrace{\begin{pmatrix} \sigma_{\mathrm{JJ}} & \sigma_{\mathrm{JA}} \\ \sigma_{\mathrm{AJ}} & \sigma_{\mathrm{AA}} \end{pmatrix}}_{\text{contact}} \underbrace{\begin{pmatrix} \frac{\beta'_\mathrm{J}}{H^*} & 0 \\ 0 & \frac{\beta'_\mathrm{A}}{H^*} \end{pmatrix}}_{\text{infectiousness}} \underbrace{\begin{pmatrix} \frac{1}{\mu'_\mathrm{J}} & 0 \\ \frac{u}{\mu'_\mathrm{J}\mu'_\mathrm{A}} & \frac{1}{\mu'_\mathrm{A}} \end{pmatrix}}_{\text{infectious period}} \tag{6}$$

(see Appendix), where $H^* = S_\mathrm{J}^* + S_\mathrm{A}^* + I_\mathrm{J}^* + I_\mathrm{A}^*$ (the total density of the hosts), $\mu'_\mathrm{J} = u + m_\mathrm{J} + v'_\mathrm{J}$ (the loss rate of infected juveniles with maturation being included), and $\mu'_\mathrm{A} = m_\mathrm{A} + v'_\mathrm{A}$ (the mortality rate of infected adults). The decomposition of $\mathbf{G}'$ into the product of matrices allows

for a natural interpretation by partitioning the epidemiological process and is consistent with the proposed approach to transmission dynamics in heterogeneous host populations (reviewed in Craft 2015; VanderWaal & Ezenwa 2016; White *et al.* 2017). The first matrix restores the availability of susceptible hosts, each with a specific susceptibility (the second matrix); the third matrix represents the contact pattern with infected hosts; the fourth matrix represents the infectiousness of infected hosts per capita, and parasites impact the infectious period among hosts with the effect of maturation from juveniles to adults being included (the fifth matrix).

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

$$w(\mathbf{v}', \mathbf{v}) = \alpha_{\mathrm{J}} \frac{S^*_{\mathrm{J}}}{H^*} \sigma_{\mathrm{JJ}} \frac{\beta'_{\mathrm{J}}}{\mu'_{\mathrm{J}}} + \frac{u}{\mu'_{\mathrm{J}}} \cdot \alpha_{\mathrm{J}} \frac{S^*_{\mathrm{J}}}{H^*} \sigma_{\mathrm{JA}} \frac{\beta'_{\mathrm{A}}}{\mu'_{\mathrm{A}}} + \alpha_{\mathrm{A}} \frac{S^*_{\mathrm{A}}}{H^*} \sigma_{\mathrm{AA}} \frac{\beta'_{\mathrm{A}}}{\mu'_{\mathrm{A}}} - \alpha_{\mathrm{J}} \alpha_{\mathrm{A}} \frac{\rho S^*_{\mathrm{J}} S^*_{\mathrm{A}}}{(H^*)^2} \cdot \frac{\beta'_{\mathrm{J}} \beta'_{\mathrm{A}}}{\mu'_{\mathrm{J}} \mu'_{\mathrm{A}}} \tag{7}$$

(also see Gandon 2004; Camino Beck & Lewis 2007; Camino Beck & Lewis 2008; Camino Beck *et al.* 2008; Hurford *et al.* 2010; Best *et al.* 2014; Iritani & Cheptou 2017). The condition for the mutant type to outcompete the wild type (i.e., invadability condition), $w(\mathbf{v}', \mathbf{v}) > 1$, holds if and only if $\Lambda[\mathbf{G}'] > 1$ (for more details, see Appendix A4).

Virulence evolves in the direction of selection gradient, given by:

$$\begin{aligned} g_{\mathrm{J}}(\mathbf{v}) &= \frac{\partial w(\mathbf{v}', \mathbf{v})}{\partial v'_{\mathrm{J}}}, \\ g_{\mathrm{A}}(\mathbf{v}) &= \frac{\partial w(\mathbf{v}', \mathbf{v})}{\partial v'_{\mathrm{A}}}, \end{aligned} \tag{8}$$

where the partial derivatives are evaluated at $\mathbf{v}' = \mathbf{v}$ ("neutrality"). Evolution ceases at which both gradients are nullified ("Singular Strategy", SS).

We assess two stability criteria of the singular strategy. The first criterion, attainability (Takada & Kigami 1991; Christiansen 1991), concerns whether recurrent substitutions of genes from wild to mutant can lead to the convergence of the strategy to SS. 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 below. We will hereafter superscriptize an asterisk (*) on CSS.

We use the following default parameter-values: $r = 6$, $\kappa = 0.06, h = 0, m_{\mathrm{J}} = 1, \alpha_{\mathrm{J}} = \alpha_{\mathrm{A}} = 1, k_{\mathrm{J}} = k_{\mathrm{A}} = 1, b_{\mathrm{J}} = b_{\mathrm{A}} = 10$, while varying u and ρ. That is, the parameter values are symmetric for juveniles and adults. We subsequently check the effects of the difference in α (susceptibility), k (efficiency of exploitation for transmission), and b (upper bound in infectiousness). Finally, we check whether recovery or tolerance in the host can affect the results.

Results

We first derive the selection gradient along v_{A}:

$$g_{\mathrm{A}}(\mathbf{v}) = \left\{ \frac{\alpha_{\mathrm{A}} S^*_{\mathrm{A}} \sigma_{\mathrm{AA}}}{H^*} \cdot \left(1 - \frac{\alpha_{\mathrm{J}} S^*_{\mathrm{J}} \sigma_{\mathrm{JJ}}}{H^*} \cdot \frac{\beta_{\mathrm{J}}}{\mu_{\mathrm{J}}} \right) + \frac{\alpha_{\mathrm{J}} S^*_{\mathrm{J}} \sigma_{\mathrm{JA}}}{H^*} \cdot \left(\frac{u}{\mu_{\mathrm{J}}} + \frac{\alpha_{\mathrm{A}} S^*_{\mathrm{A}} \sigma_{\mathrm{AJ}}}{H^*} \cdot \frac{\beta_{\mathrm{J}}}{\mu_{\mathrm{J}}} \right) \right\} \times \frac{\beta_{\mathrm{A}}}{\mu_{\mathrm{A}}} \cdot \left(\frac{1}{\beta_{\mathrm{A}}} \cdot \frac{\mathrm{d}\beta_{\mathrm{A}}}{\mathrm{d}v_{\mathrm{A}}} - \frac{1}{\mu_{\mathrm{A}}} \right) \tag{9}$$

(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) costs owing to reduced infectious period (Day 2001; Gandon *et al.* 2001; Day & Proulx 2004; Gandon 2004; Alizon *et al.* 2009; Cressler *et al.* 2016; Williams & Kamel 2018). Therefore, the direction of selection on adult virulence is completely determined by the balance between such benefits and costs.

In terms of juvenile-virulence, however, an additional term emerges in the present model because of the host maturation rate u. To make the biological meaning of this term clearer, we use the reproductive-value based form of the selection gradient (Fisher 1958; Taylor 1990; Caswell 2001; Gandon 2004; Grafen 2006; Otto & Day 2007; Williams 2011; Williams & Kamel 2018; Lion 2018), which reads:

$$g_{\mathrm{J}}(\mathbf{v}) \propto \left(\ell^*_{\mathrm{J}} \cdot \underbrace{\frac{\alpha_{\mathrm{J}} S^*_{\mathrm{J}} \sigma_{\mathrm{JJ}}}{H^*}}_{\text{from J to J}} + \ell^*_{\mathrm{A}} \cdot \underbrace{\frac{\alpha_{\mathrm{A}} S^*_{\mathrm{A}} \sigma_{\mathrm{AJ}}}{H^*}}_{\text{from J to A}} \right) \cdot \frac{\beta_{\mathrm{J}}}{\mu_{\mathrm{J}}} \times \left(\frac{1}{\beta_{\mathrm{J}}} \cdot \frac{\mathrm{d}\beta_{\mathrm{J}}}{\mathrm{d}v_{\mathrm{J}}} - \frac{1}{\mu_{\mathrm{J}}} \right) - \ell^*_{\mathrm{A}} \cdot \frac{1}{\mu_{\mathrm{J}}} \cdot \frac{u}{\mu_{\mathrm{J}}} \tag{10}$$

(Appendix A6-8), where $(\ell_{\mathrm{J}}^*, \ell_{\mathrm{A}}^*)$ represents the pair of individual reproductive values of the parasites carried by juvenile and adult hosts (or the left eigenvector of $\mathbf{G}$ at neutrality; Appendix). The first term represents the sum of reproductive success owing to transmission from an infected juvenile hosts to a susceptible juvenile and to a susceptible adult; once transmitted to a juvenile (or adult) host, the parasites can gain the relative reproductive success ℓ_{J}^* (or ℓ_{A}^*, respectively). In total, the first term obeys classic marginal value theorem (Charnov 1976; Bulmer 1994; Day 2001; Gandon *et al.* 2001; Day & Proulx 2004; Gandon 2004; Alizon *et al.* 2009; Cressler *et al.* 2016; Williams & Kamel 2018) such that the marginal increase in transmission due to exploitation confers a benefit (associated with increased transmission) but the marginal decrease in infectious period imposes a cost on exploitation. The second term represents the reduction in successful maturation due to killing the juveniles and this term involves $1/\mu_{\mathrm{J}}$ (the marginal increase in juvenile mortality due to increasing virulence) times ℓ_{A}^* (the individual reproductive value of the parasites infecting adults) times the probability of maturation of infected juveniles u/μ_{J}. This is because killing juveniles can lead to the loss of expected reproductive success via adult hosts that the parasites could otherwise gain through the maturation of the juvenile host (Williams & Kamel 2018). In other words, killing the juvenile hosts can result in the reduction of prospective fitness.

We investigated the effects of (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 $v_{\mathrm{A}}^* = \sqrt{m_{\mathrm{A}}/k_{\mathrm{A}}}$, which is independent of any demographic and disease characteristics of juveniles. This is because the parasites infecting adults can utilize a single transmission

pathway from adults (to any susceptible hosts in the population). Hence, we used v^*_{A} as a benchmark result and compared it with v^*_{J}.

In contrast, CSS for juvenile-virulence is dramatically affected by the densities of susceptible hosts (ecological feedback), the adult virulence (epidemiological feedback), and stage-assortativity (demographic feedback). This is because the parasites infecting the juveniles can utilize two pathways of transmission: either from the juvenile (to any susceptible hosts), or from the adult who has successfully matured from the juvenile stage. The analytical expression for v^*_{J} is intractable, and thus we numerically evaluated v^*_{J}.

We can immediately see that v^*_{A} increases with m_{A}, in agreement with the previous studies (reviewed in Alizon *et al.* 2009; Cressler *et al.* 2016). To assess when selection favours higher juvenile-virulence than adult-virulence, we quantified $v^*_{\mathrm{J}}/v^*_{\mathrm{A}}$ 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 ($m_{\mathrm{J}} \neq m_{\mathrm{A}}$), but the general trend is robust (Fig 3A-C). Also, the combination of disassortativity and long post-maturation span leads to parasite extinction as a result of overexploitation against juveniles (Fig 3A; Appendix A10).

By relaxing the assumptions of the symmetry in disease-related parameters $k_{\mathrm{J}}, k_{\mathrm{A}}$ (efficiency of exploitation for transmission), $b_{\mathrm{J}}, b_{\mathrm{A}}$ (maximum transmissibility), and $\alpha_{\mathrm{J}}, \alpha_{\mathrm{A}}$ (susceptibility) for juveniles and adults, or by incorporating recovery or tolerance, we showed that the results are robust and qualitatively unchanged (Appendix B). Therefore, we conclude that the combined

effects of maturation and assortativity are critical to the evolution of virulence.

Discussion

We have shown theoretically how parasites are subject to different selective pressures when they infect adults or juveniles. In particular, the key prediction is that the combination between maturation and contact-structure – fast maturation with disassortativity, or slow maturation with assortativity – has a dramatic impact on optimal juvenile-virulence. Higher virulence against juveniles is favored either if: (i) adult-stage is relatively long and the contact-structure is disassortative (between age class interactions are high; Fig 3, left-top zone), (ii) juvenile-stage is relatively long and the contact structure is assortative (interactions occur preferentially within classes; Fig 3, right-bottom zone). This result can be understood as follows: given that 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 access to more abundant resource. The same reasoning works for the results of higher juvenile-virulence in short maturating and assortative hosts. Spatial and/or temporal segregation in the niches of juveniles and adults therefore has the potential to be an important evolutionary driver of virulence. Previous theory has overlooked the phenomena that virulence is highly sensitive to stage-structured life-history characteristics of hosts such as ontogeny and associated, spatio-temporal niche-shifts.

The incorporation of the maturation of the hosts in our model shows that higher parasite exploitation against juveniles incurs an additional cost associated with increased maturation

failure (Williams & Kamel 2018). In addition, non-random assortativity generates additional selective pressures (Gandon 2004; Osnas & Dobson 2011). In particular, while marginal value theorem 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 and the trade-off hypothesis. Gandon (2004) and Osnas & Dobson (2011) introduced multiple hosts' types or species and studied conditional virulence against them, and Williams and colleagues (Williams *et al.* 2006; Williams 2011; Williams *et al.* 2014; Williams & Kamel 2018) have proposed to use reproductive value theory to study parasite evolution in heterogeneous host populations. However, none of these studies are devoted to 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. In particular, 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-breeder 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), so 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 contrast, (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). The salmon only reproduce once at the very end of their lives (semelparity), and therefore have a short adult period by our model. This short post-maturation stage and assortative transmission 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), but habitats with multi-year larvae have 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 assortiveness 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 access for 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 is sometimes 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)) 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 a more 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 are 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.

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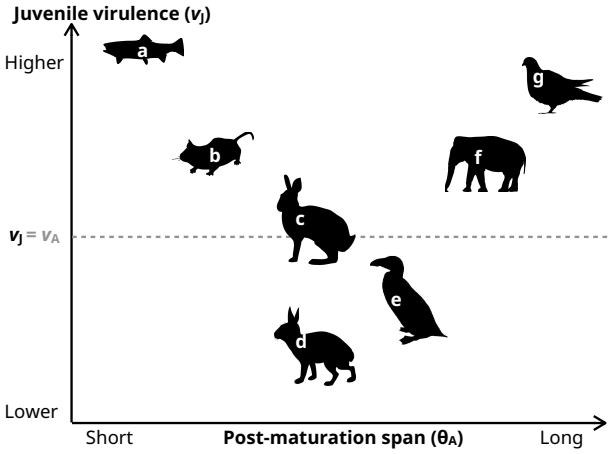

Figure 1: A graphical representation of the empirical data on stage-specific virulence. In the following, H indicates "host" while P indicates "parasites" : (a) H: Pink Salmon (*Oncorhynchus gorbuscha*); P: Salmon Louse (Heard 1991; Jones *et al.* 2008). (b) H: Gerbil (*Gerbillus andersoni*); P: Ectoparasites (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)

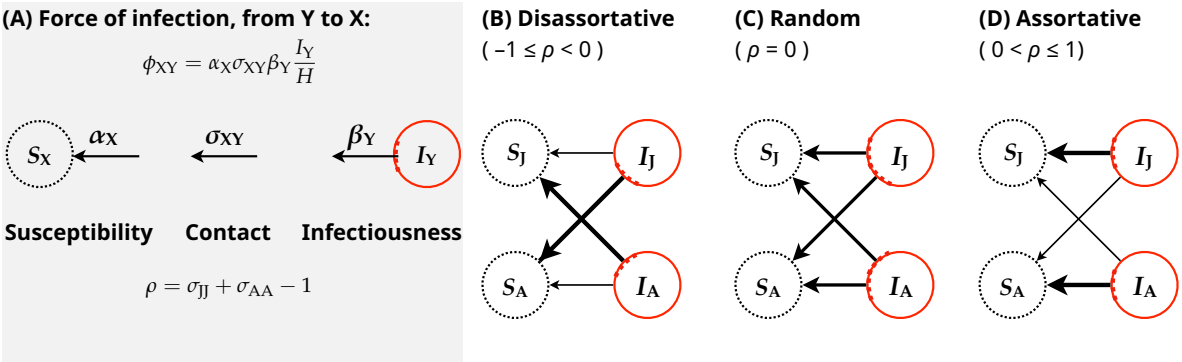

Figure 2: A schematic illustration of the model on the force of infection and assortativity. (A) Force of infection from Y to X, ϕ_{XY}, is a compound factor of susceptibility (likeliness of X-hosts becoming infected), contact intensity (likeliness of contacts between X and Y), and infectiousness (propagule 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).

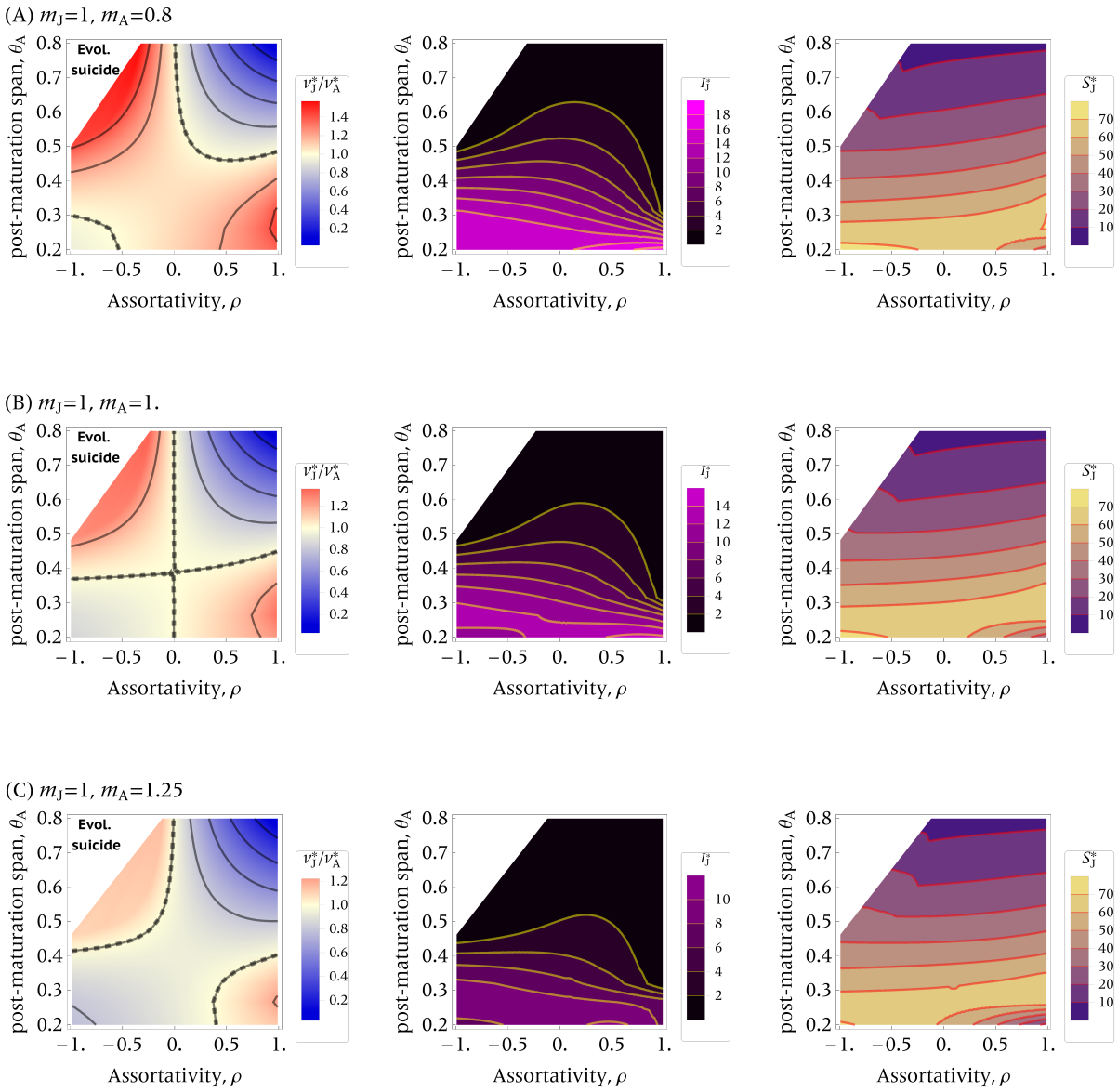

Figure 3: Left panels: Evolutionary outcomes of relative virulence (v_J^*/v_A^*), in which red color indicates $v_J^* > v_A^*$ and blue color indicates $v_J^* < v_A^*$. Color scales used are the same in the three panels. Middle panels: Densities of infected juveniles at equilibrium, I_J^*. Right panels: 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.