

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

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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 in parasites. 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 pathways. 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 transmission pathway with higher virulence against juveniles being favored either when the transmission pathway is assortative (juveniles preferentially interact together) and the juvenile stage is long, or in contrast when the transmission pathway is disassortative and the juvenile stage is short. 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.

KEY WORDS: Adaptive dynamics, age-structured population, life-history evolution, parasite virulence, senescence.

Impact summary

Understanding the evolution of parasite virulence remains one of the most important questions in evolutionary ecology. Virulence is often very different in young and old hosts, but previous theory has presumed that these differences are attributed to adaptation in host defense rather than parasite adaptation. However, stage structure within host populations can expose parasites to heterogeneous environments, which may lead to differential selection on parasite virulence (stage-specific virulence). Surprisingly, no study has investigated the effects of hosts' stage structure on the evolution of stage-specific virulence. We present a theoretical analysis to examine when selection can favor higher virulence

against juveniles (juvenile–virulence) versus adults (adult–virulence). Our key result is that higher juvenile–virulence is selected for either when the transmission is assortative within age classes and maturation is slow, or when the transmission is disassortative (occurring predominantly between classes) and maturation is relatively fast. These at first sight contrasting outcomes can be understood as adaptation to the exploitation of the more available host stage. Although the data on assortativity in infectious disease systems are limited, empirical studies for the virulence of Great Island Virus in guillemots (*Uria aalge*) and for salmon louse in pink salmon (*Oncorhynchus gorbuscha*) are consistent with our predictions. Our work provides testable predictions for stage-specific virulence and presents a novel

mechanism that may explain variation in virulence in nature. There are also management implications for conservation, public health, vaccination programs, agriculture, and animal husbandry to understanding the drivers of stage-dependent virulence.

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 and May 1982; Read 1994; Ebert and Herre 1996; Frank 1996; Alizon et al. 2009; Schmid-Hempel 2011; Bull and Lauring 2014; Cressler et al. 2016), with important implications for host persistence (Boots and Sasaki 2003; De Castro and 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 homogeneous host populations, heterogeneity within host populations is ubiquitous in nature (Anderson and May 1992, Chap. 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 and 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 and Dobson 1995; Wilson et al. 2002).

In addition to stage-related variation in the hosts, different host stage classes expose parasites to specific environmental heterogeneity (see Ashby and Bruns 2018, for theory). Given this, parasites may adaptively tune conditional exploitation against certain stage classes, for example, 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 and 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. Second, the hosts' stage structure can generate biased transmission pathways, thereby exposing the parasites to temporal heterogeneity, which may induce additional se-

lective pressures (reviewed in Lion and Metz 2018). For instance, spatiotemporal segregation between juveniles and adults, which is typical of humans (Rohani et al. 2010), amphibians (Kilpatrick et al. 2010), and insects (Briggs and Godfray 1995), can produce assortative transmission pathway (i.e., juvenile–juvenile and adult–adult transmission might be more likely than juvenile–adult transmission), such that parasites infecting a certain stage of hosts are likely to be transmitted to the same stage of hosts. Assortativity in transmission can thus facilitate or limit the access of parasites to differential quality of resources in terms of hosts. 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 matrix of transmission pathways. 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 and Sigmund 1990; Dieckmann and Law 1996), and assess the joint evolution of virulence against adults (adult–juvenile) and that against juveniles (juvenile–virulence). We show when selection for virulence differs in juveniles compared to adults.

Method

We consider a host population structured into juvenile (J) and adult (A) stages, in which juveniles are by definition 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):

$$\begin{aligned} \frac{dS_J}{dt} &= (r - \kappa \cdot (S_A + I_A)) \cdot (S_A + I_A) \\ &\quad - (u + m_J + \phi_{JJ} + \phi_{JA}) \cdot S_J, \\ \frac{dS_A}{dt} &= u \cdot S_J - (m_A + \phi_{AJ} + \phi_{AA}) \cdot S_A, \\ \frac{dI_J}{dt} &= (\phi_{JJ} + \phi_{JA}) \cdot S_J - (u + m_J + v_J) \cdot I_J, \\ \frac{dI_A}{dt} &= u \cdot I_J + (\phi_{AJ} + \phi_{AA}) \cdot S_A \\ &\quad - (u + m_A + v_A) \cdot I_A, \end{aligned} \quad (1)$$

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

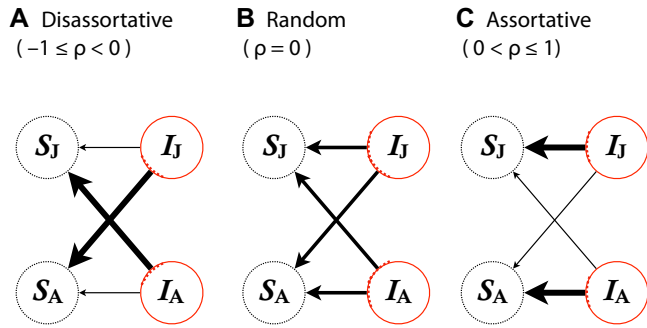


Figure 1. A schematic illustration of the assortativity parameter ρ . Negative assortativity indicates that contacts occur more frequently between stages than within stages (panel A). The transmission pathway is unbiased (random) when $\rho = 0$ (panel B). Positive assortativity indicates that transmission occurs more frequently within stages than between stages (panel C).

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. 1; also see below for formula); v_J (or v_A) represents the virulence against a juvenile (or adult) host. The reciprocal of the infectious period for juveniles (or adults) is given by $\mu_J = u + m_J + v_J$ (or by $\mu_A = m_A + v_A$, 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 and Persson (2013).

The force of infection for a stage- X host from a stage- Y host (with X and Y running across J and A) in equation (1) involves three processes: susceptibility α_X (the likeliness for which a stage- X host becomes infected, given a reception of pathogen propagule), transmission pathway σ_{XY} (which represents the probability that a pathogen propagule, given that it was produced within Y -stage host, is transferred to a X -stage host), and infectiousness β_Y (the propagule production from a stage- Y host; see Fig. 1A):

$$\phi_{XY} = \frac{\alpha_X \sigma_{XY} \beta_Y I_Y}{H} \tag{2}$$

with $H = S_J + I_J + S_A + I_A$ 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 $\beta_J = b_J k_J v_J / (1 + k_J v_J)$, $\beta_A = b_A k_A v_A / (1 + k_A v_A)$, 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 and Day 2007).

Maturation and natural mortality can both affect the relative length of the adult stage. To quantify this, we write θ_A for the expected fraction of time a host individual spends as an adult in the entire life span in the absence of disease, which reads (Appendix A2):

$$\theta_A = \frac{u}{u + m_J - m_A} \cdot \left(1 + \frac{m_A}{u + m_J - m_A} \cdot \log \left(\frac{m_A}{u + m_J} \right) \right) \tag{3}$$

from which we can check that extremely slow (or fast) maturation, $u \rightarrow 0$ (or $u \rightarrow +\infty$, respectively), leads to $\theta_A \rightarrow +0$ (or 1, respectively; note, a special case for $u + m_J = m_A$ yields $\theta_A = u / (2(u + m_J))$; Appendix A2). We use θ_A as a characteristic parameter of the stage-structured host populations.

For quantifying the structure of transmission pathways with a single parameter, we first assume symmetry, $\sigma_{AJ} = \sigma_{JA}$ (“consistency condition” for mixing structure; Diekmann et al. 2012, Chap. 12). Also, we normalize the system, and assume that $\sigma = \sigma_{JJ} = 1 - \sigma_{AJ} = 1 - \sigma_{JA} = \sigma_{AA}$. With these assumptions, the assortativity measure is given by:

$$\rho = 2\sigma - 1, \tag{4}$$

where ρ varies from -1 to 1 (and note that these assumptions on the symmetric, normalized transmission pathways will be relaxed in subsequent analyses). If $-1 \leq \rho < 0$, then within-stage transmission is less likely compared to between-stage transmission (such a structure of transmission pathways is said to be “disassortative”). Instead, if $0 < \rho \leq 1$, then within-stage transmission is more likely than between-stage transmission (assortative transmission). $\rho = 0$ indicates that transmission is unbiased (“random” transmission). In the extreme case, $\rho = 1$ (or -1) indicates that transmission occurs exclusively within the stages (or between the stages, respectively; Fig. 1B–D). For a more general treatment of contact structure, see Brauer and Castillo-Chavez (2012, Chaps. 3–5) and Diekmann et al. (2012, Chap. 12).

We use the adaptive dynamics toolbox (Hofbauer and Sigmund 1990; Diekmann and Law 1996) to study the long-term evolutionary dynamics of stage-specific virulence. Throughout the article, we assume that parasites show stage-specific virulence, v_J and v_A , with no association or correlation between them (i.e., we study the joint evolutionary dynamics of (v_J, v_A)). First, suppose that the system of ODEs in equation (1) has reached an endemic equilibrium: $(S_J, S_A, I_J, I_A) = (S_J^\#, S_A^\#, I_J^\#, I_A^\#)$ for a given (or wild-type) virulence $\mathbf{v} := (v_J, v_A)$ (where the symbol “:=” will be henceforth used for defining a quantity). We then introduce a rare mutant $\mathbf{v}' := (v'_J, v'_A)$ attempting to invade a monomorphic wild-type virulence \mathbf{v} , assuming 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 ω by using the Next-Generation Theorem (van den Driessche and Watmough 2002; Hurford et al. 2010). The

“next-generation matrix” (that determines the long-term growth of the mutant, denoted \mathbf{G}') can be written as the product of five matrices:

$$\mathbf{G}' := \underbrace{\begin{pmatrix} S_J^\# & 0 \\ H^\# & S_A^\# \\ 0 & H^\# \end{pmatrix}}_{\text{susceptibles}} \underbrace{\begin{pmatrix} \alpha_J & 0 \\ 0 & \alpha_A \end{pmatrix}}_{\text{susceptibility}} \underbrace{\begin{pmatrix} \sigma_{JJ} & \sigma_{JA} \\ \sigma_{JJ} & \sigma_{AA} \end{pmatrix}}_{\text{transmission pathway}} \underbrace{\begin{pmatrix} \beta'_J & 0 \\ 0 & \beta'_A \end{pmatrix}}_{\text{infectivity}} \underbrace{\begin{pmatrix} 1 & 0 \\ \mu'_J & 1 \\ u & 1 \\ \mu'_J & \mu'_A \end{pmatrix}}_{\text{infectious period}}, \quad (5)$$

where $H^\# := S_J^\# + S_A^\# + I_J^\# + I_A^\#$ (the total density of the hosts at the endemic equilibrium), $\mu'_J := u + m_J + v'_J$ (the reciprocal of the infectious period of juveniles infected by the mutant), and $\mu'_A := m_A + v'_A$ (the reciprocal of the infectious period of adults infected by the mutant). Equation (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 and 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 transmission pathways across stages, the fourth matrix represents the infectiousness of infected hosts per capita, and the fifth matrix represents the stage-specific infectious period; the left bottom element represents a conditional, expected infectious period of adult hosts, given by the maturation probability of a juvenile infected by the mutant (u/μ'_J) times the expected infectious period of adult hosts ($1/\mu'_A$).

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:

$$\omega(\mathbf{v}', \mathbf{v}) := q_{JJ}^\# \frac{\beta'_J}{\mu'_J} + \pi'_1 q_{JA}^\# \frac{\beta'_J}{\mu'_J} + q_{AA}^\# \frac{\beta'_A}{\mu'_A} - (q_{JJ}^\# q_{AA}^\# - q_{JA}^\# q_{AJ}^\#) \frac{\beta'_J}{\mu'_J} \cdot \frac{\beta'_A}{\mu'_A} \quad (6)$$

with short-hand notation: $\pi'_1 := u\mu'_J$ (probability of maturation of juveniles infected by the mutant) and $q_{XY}^\# := \alpha_X S_X^\# \sigma_{XY} / H^\#$ (the availability of X-stage hosts to the parasites infecting a Y-stage host per propagule-production). We find that under weak selection regime (i.e., $|\mathbf{v}' - \mathbf{v}|$ is very small, as detailed in Appendix A4) “invadability condition,” for which the mutant outcompetes the wild type ($\omega(\mathbf{v}', \mathbf{v}) > 1$), holds if and only if $\Lambda[\mathbf{G}'] > 1$.

The initial phases of evolutionary dynamics are determined by the selection gradient $g_X(\mathbf{v}) := \frac{\partial \omega(\mathbf{v}', \mathbf{v})}{\partial v'_X} |_{\mathbf{v}'=\mathbf{v}}$ for the corresponding virulence, until a pair of singular strategies $\mathbf{v} = \mathbf{v}^*$ is attained, with $g_J(\mathbf{v}^*) = g_A(\mathbf{v}^*) = 0$. For more detail, see Appendix A5.

We investigate the effects of two stage-structured characteristics: (1) post-maturation span θ_A and (ii) stage assortativity, ρ , on the evolutionary outcomes (i.e., the singular strategies that is attainable and can resist any rare mutants with small phenotypic differences, or continuously stable strategy, CSS; Appendices A6–A9). We use the following default parameter values: $r = 6$, $\kappa = 0.06$, $m_J = 1$, $\alpha_J = \alpha_A = 1$, $k_J = k_A = 1$, $b_J = b_A = 10$, while varying m_A and 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_J and α_A (susceptibility), k_J and k_A (efficiency of exploitation for transmission), and b_J and b_A (upper bound in infectiousness). We also check whether recovery, tolerance, or fecundity shift in the hosts can affect the results. In addition, we examined the outcomes when we assume density-dependent rather than frequency-dependent transmission in the dynamics. Finally, we investigated more general transmission pathways with (1) σ_{JJ} , σ_{AA} , and $\sigma_{JA} = \sigma_{AJ}$ all varying freely, and (2) $\sigma_{JJ} = 1 - \sigma_{AJ}$ and $\sigma_{AA} = 1 - \sigma_{JA}$ both varying freely.

Results

The selection gradient for adult-virulence reads:

$$g_A(\mathbf{v}) \propto \left(\frac{1}{\beta_A} \cdot \frac{d\beta_A}{dv_A} - \frac{1}{\mu_A} \cdot \frac{d\mu_A}{dv_A} \right)^\circ = \left(\frac{1}{\beta_A} \cdot \frac{d\beta_A}{dv_A} - \frac{1}{\mu_A} \right)^\circ \quad (7)$$

(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 and 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 stage structure. 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. The resulting CSS for adult-virulence is always $v_A^* = \sqrt{m_A/k_A}$, which is independent of any demographic and disease characteristics of juveniles. We can immediately see that the evolutionary outcome of adult-virulence increases with adult natural mortality (reviewed in Alizon et al. 2009; Cressler et al. 2016).

In contrast, juvenile-virulence in the model is influenced by additional costs associated with hosts’ stage structure. This is because the parasites infecting the juveniles can spread either from the juvenile (to any susceptible hosts), or from the adult who has successfully matured from the juvenile stage. To ease biological interpretation, we present the reproductive value-based form of the selection gradient (Fisher 1958; Taylor 1990; Frank 1998;

Caswell 2001; Grafen 2006; Lion 2018). Reproductive values give a proper weighting of fitness effects for age-classes by taking the contributions of the classes to future gene pool into account (Fisher 1958; Taylor 1990; Frank 1998; Caswell 2001; Grafen 2006; Lion 2018). Using reproductive values, $g_J(\mathbf{v})$ reads:

$$g_J(\mathbf{v}) = \underbrace{\left(\ell_J^\circ q_{JJ}^\# + \ell_A^\circ q_{AJ}^\# \right)}_{\text{transmission from a juvenile to:}} \cdot \underbrace{\frac{\beta_J^\circ}{\mu_J^\circ} \cdot \left(\frac{1}{\beta_J} \cdot \frac{d\beta_J}{dv_J} - \frac{1}{\mu_J} \right)}_{\text{marginal benefit}} - \underbrace{\frac{\pi_J^\circ}{\mu_J^\circ}}_{\text{maturation failure}} \cdot \underbrace{\left(\ell_J^\circ q_{JA}^\# + \ell_A^\circ q_{AA}^\# \right)}_{\text{transmission from an adult to:}} \cdot \frac{\beta_A^\circ}{\mu_A^\circ} \quad (8)$$

(Appendices A6–A8), where $(\ell_J^\circ, \ell_A^\circ)$ represents the pair of individual reproductive values of the parasites infecting juvenile and adult hosts (defined by the left eigenvector of \mathbf{G} at neutrality; Appendix A6) and the factor $\ell_J^\circ \times q_{JA}^\#$ 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 $(\ell_J^\circ q_{JJ}^\# + \ell_A^\circ q_{AJ}^\#) \times (\beta_J/\mu_J)^\circ$, which represents the reproductive success of a parasite infecting juveniles, who can receive the marginal benefit due to increased infectiousness $(d\beta_J/dv_J)^\circ/\beta_J^\circ$ but pay the marginal cost due to the reduction in infectious periods $1/\mu_J^\circ$ as in the selection gradient for adult-virulence (equation 7). In addition, juvenile-virulence incurs the additional cost associated with the reduced maturation probability $(\pi_J/\mu_J)^\circ$ and the subsequent loss of expected reproductive success via adult hosts that the parasites could otherwise gain through the maturation of the juvenile hosts, $(\ell_J^\circ q_{JA}^\# + \ell_A^\circ q_{AA}^\#)(\beta_A/\mu_A)^\circ$ (the reproductive success of a parasite infecting adults). Hence, equation (8) clearly captures the selection forces on juvenile-virulence, including the marginal benefits, marginal costs, and maturation-mediated costs. The expression for the CSS of juvenile-virulence, v_J^* , is analytically intractable, and as such we numerically evaluated v_J^* by jointly solving the wild-type ODEs in equation (1) and the selection gradients in equations (7) and (8).

To assess when selection favors higher juvenile-virulence than adult-virulence, we quantified v_J^*/v_A^* as a function of the assortativity (ρ , abscissa) and post-maturation span (θ_A , ordinate; Fig. 2). 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 toward higher virulence for juveniles, but the general trend is robust (Fig. 2A–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. 2B and C; see Appendix A10).

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). In addition, we showed that density-dependent transmission yields quantitatively similar results (Appendix B). We further found that fecundity shift (i.e., infected adults have different fecundity output than do susceptible hosts, as in *Daphnia*; Hite et al. 2017) have minor impacts upon the results. Finally, we found that varying σ_{JJ}, σ_{AJ} , and σ_{AA} yields the quantitatively similar results (Appendix C). 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 juveniles as opposed to adults. Our key insight is that the combination between maturation rates and transmission pathway determines the evolutionary outcomes of juvenile-virulence. Higher virulence against juveniles is favored either if: (1) the adult stage is relatively long and the transmission pathway is disassortative (between age-class transmission likely; Fig. 2, left top zone), or (ii) the juvenile stage is relatively long and the transmission pathway is assortative (transmission occurs preferentially within classes; Fig. 2, right bottom zone). These results can be understood as follows: when the post-maturation span is long and the transmission pathway is disassortative, adult hosts are abundant in the population and the transmission from juveniles to adults is more likely than between juveniles. The higher availability of adult hosts selects for higher transmission and therefore virulence in juveniles to exploit more abundant resource of adults. Equivalent reasoning explains higher juvenile-virulence when maturation is fast and hosts are assortative. As such the hosts' demography alongside the maturation of juveniles strongly affects the evolutionary outcomes of parasite virulence. The results suggest that spatial and/or temporal segregation in the niches of juveniles and adults 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, including ontogeny and any associated, spatiotemporal niche shifts.

Higher parasite exploitation against juveniles incurs an additional cost associated with increased maturation failure. In contrast, the evolutionary outcome of adult virulence can be fully

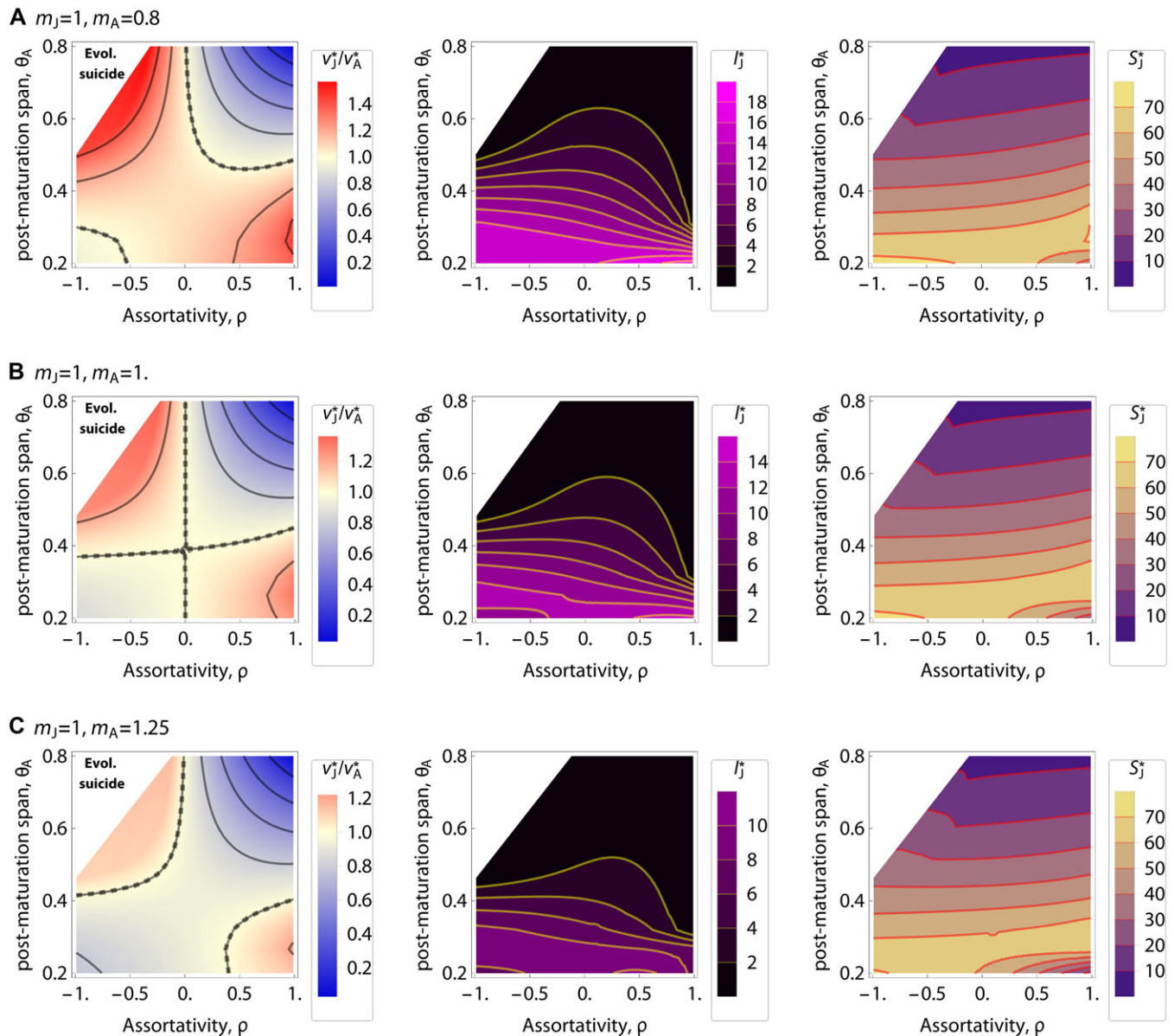


Figure 2. Left panels: Evolutionary outcomes of relative virulence v_j^*/v_A^* , in which red color indicates $v_j^* > v_A^*$ and blue color indicates the opposite situation, $v_j^* < v_A^*$. Color scales used are the same in the three panels. Middle panels: densities of infected juveniles at equilibrium, 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. Middle and right panel can clearly demonstrate that evolutionary suicide does occur in the white zone, as I_j^* is very small but S_j^* is not.

understood from the classic perspective of optimizing the secondary infections from infected adults. This is an example where sources of heterogeneity in hosts can lead to different predictions than classic virulence evolution theory based on the optimization principle (Lion and Metz 2018). Our novel results arise because we explicitly assumed stage structure with maturation from juveniles to adults and reproduction by adults, rather than more generic host heterogeneity, for example, multiple host species (Regoes et al. 2000; Gandon 2004; Osnas and Dobson 2011), vaccination

(Gandon et al. 2001, 2003; Yates et al. 2006; Zurita-Gutiérrez and Lion 2015), or sex (Úbeda and Jansen 2016).

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, alongside the impact of maladaptation and immunopathogenicity (Hudson and Dobson 1995; Wilson et al. 2002). Additionally, studies looking at

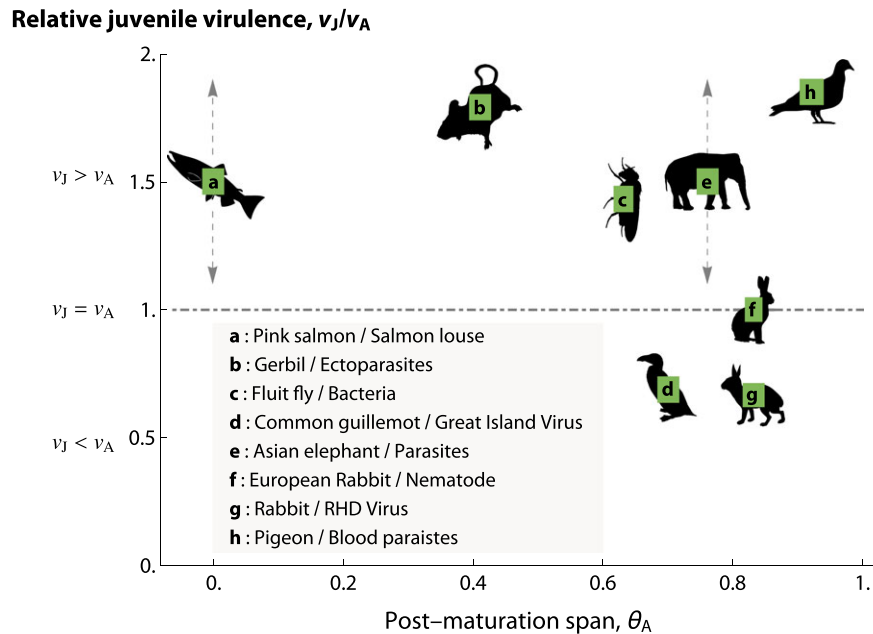


Figure 3. A graphical representation of the empirical data on stage-specific virulence. Each position of labels (from a to h, each within a green square) corresponds to a reported value of v_J/v_A . In the following, H indicates “host” while P indicates “parasite(s)/pathogen(s)”. (a) H: pink salmon (*Oncorhynchus gorbuscha*); P: salmon louse (Heard 1991; Jones et al. 2008). (b) H: gerbil (*Gerbillus andersoni*); P: ectoparasites, including fleas (*Synosternus cleopatrae*), mites (*Androlaelaps centrocarpus*, *A. insculptus*, *A. hirsti*, *A. marshalli*, and *A. androgynus*), and ticks (*Hyalomma impeltatum*) (Wassif & Soliman 1980; Delany 1986; Hawlena et al. 2006). (c) H: fluit fly (*Drosophila melanogaster*); P: bacteria (*Pseudomonas entomophila*; Luckinbill et al. 1984; Vodovar et al. 2005); (d) H: common guillemot (*Uria aalge*); P: Great Island Virus (Harris & Wanless 1995; Nunn et al. 2006; Wanelik et al. 2017). (e) H: Asian elephant (*Elephas maximus*); P: parasites (Sukumar et al. 1997; Lynsdale et al. 2017). (f) H: European rabbit (*Oryctolagus cuniculus*); P: nematode (von Holst et al. 2002; Cornell et al. 2008). (g) H: rabbits (*Leporidae*); P: RHD virus (Morisse et al. 1991; Reluga et al. 2007). (h) H: pigeon (*Columba livia*); P: blood parasites (Lack 1968; Holmes & Ottinger 2003; Sol et al. 2003). For (a) and (e), we were able to find qualitative data ($v_J > v_A$), but not quantitative ones. As such, we placed them at the height of 1.5 (> 1), and indicated variations by dashed, gray arrows thereon. Data behind this figure are shown in SI Table in Appendix D. Animal drawings are from phylopic.org, with full credit in Appendix D.

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 immunocompetence. However, despite these issues, we found data on several empirical systems in an intensive literature review (Appendix D) where age-biased virulence effects can be distinguished from the other factors and which lend support to our predictions and offer opportunities for testing our hypotheses (Fig. 3; also see Appendix D). 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 (v_J/v_A , post-maturation life span, and transmission assortativity) matched our model’s predictions (Fig. 3). 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 prebreeding 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 and Wanless 1995), and therefore the combination of assortative transmission and long adult period predicts that GIV should be more virulent in breeders. In line with the predictions of our model, infection-associated mortality risk is 0.63 times lower for juveniles than for adults (Nunn et al. 2006).

In the second example, Jones et al. (2008) showed that salmon louse caused mortality 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 life spans 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 would 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 (Briggs et al. 2010; 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 multiyear 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). The assortativity 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.

Although data on age-related transmission pathways are difficult to find in wildlife populations, a wealth of mixing data exist 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. Given that humans have a long juvenile period in the context of our model (Bogin and Smith 1996), our model predicts that directly transmitted human-adapted pathogens would be selected to have higher virulence in naive adults, but cannot be applied to pathogens that are adapted to multiple host species or are vector or sexually transmitted. Measles and chickenpox, both of which are directly transmitted human-specific pathogens, have case mortality rates that are 1.7 times and 23–29 times, respectively, higher in unvaccinated, unexposed adults than in juveniles (Orenstein et al. 2004; Heining and Seward 2006). Furthermore, poliovirus also has a 8.75 times higher case mortality rate for adults than juveniles (Weinstein et al. 1952), though the assortativity of its transmission seems to depend on the relative contribution of direct (oral–oral) and environmental (fecal–oral) transmission (Blake et al. 2014). Although the evolutionary drivers of human pathogens are often complicated, we posit that chickenpox (varicella-zoster virus, or VSV) virulence in humans proves an intriguing case study. The higher mortality risk in adults corresponds to increased viral titers with age, suggesting that there may be a trade-off between virulence and transmission (Malavige et al. 2008). Perhaps most interestingly, while varicella virus infects many cell types, T-cell infection is thought to

be important for transport and pathogenesis (Zerboni and 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). Altogether, the implications for human pathogens entail deeper understanding of mechanisms for immunocompetence and modes of transmission (sexual and/or environmental), but the examples point toward one mechanism that may contribute to the mediation of age-specific virulence in human 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 physical 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. Therefore to prevent evolutionary changes toward higher virulence, we should 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. 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.

AUTHOR CONTRIBUTION

All authors conceived and designed the study, RI carried out model analyses, RI and EV drafted the initial version of the manuscript, EV surveyed empirical literature, and all authors contributed to later versions of the manuscript.

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DATA ARCHIVING

No data is used for this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Mathematica code for evaluating the stage-period.

Figure S2. Graph-theoretical reduction of reproductive success pathways.

Figure S3. Effects of varying susceptibility.

Figure S4. Effects of varying tolerance.

Figure S5. Effects of varying recovery rates.

Figure S6. Effects of varying infectiousness.

Figure S7. Effects of density-dependence.

Figure S8. Effects of constant fecundity virulence.

Figure S9. Effects of the normalized pathway structure, with $\sigma_{JA} = 1 - \sigma_{AA}$ and $\sigma_{AJ} = 1 - \sigma_{JJ}$.

Figure S10. Effect of the symmetric pathway structure, with $\sigma_{JA} = \sigma_{AJ}$ varied and $\sigma_{AA} = 0.5$ fixed.

Table S1. Data on empirical host-parasite systems.