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Why disease ecology needs life-history theory: a host perspective

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Abstract

When facing an emerging infectious disease of conservation concern, we often have little information on the nature of the host-parasite interaction to inform management decisions. However, it is becoming increasingly clear that the life-history strategies of host species can be predictive of individual- and population-level responses to infectious disease, even without detailed knowledge on the specifics of the host-parasite interaction. Here, we argue that a deeper integration of life-history theory into disease ecology is timely and necessary to improve our capacity to understand, predict, and mitigate the impact of endemic and emerging infectious diseases in wild populations. Using wild vertebrates as an example, we show that host life-history characteristics influence host responses to parasitism at different levels of organization, from individuals to communities. We also highlight knowledge gaps and future directions for the study of life-history and host responses to parasitism. We conclude by illustrating how this theoretical insight can inform the monitoring and control of infectious diseases in wildlife.

Keywords

demography, demographic compensation, outbreak, pace of life, pathogen, slow-fast continuum, vertebrates

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We present a novel synthesis on the intersection of life-history and host responses to parasitism, to demonstrate that a deeper integration of life-history theory into disease ecology is a fruitful avenue of research to advance the understanding and mitigation of wildlife infectious diseases. This synthesis highlights that life-history strategies can lead to a variety of host responses to parasitism, modulating host immune responses, the mechanisms of host demographic compensation, the potential for rapid evolution of resistance or tolerance mechanisms, and the efficiency of parasite transmission and disease risk in multi-host parasite systems.

INTRODUCTION

Infectious diseases are an important threat to biodiversity (Daszak *et al.,* 2000). This is particularly true for emerging infectious diseases, for which the lack of host-parasite coevolutionary history can lead to extreme levels of parasite virulence and/or host susceptibility, ultimately inducing strong population-level impacts (e.g., Daszak *et al.,* 2000, 2001; Fisher *et al.,* 2012; Scheele *et al.,* 2019a). Nonetheless, empirical evidence further reveals that host population collapse is not the only outcome from a novel host-parasite interaction (Tompkins *et al.,* 2011). Some populations of susceptible hosts can persist despite initial marked population declines (e.g., fish, Rogowski *et al.,* 2020; amphibians, Briggs *et al.,* 2010; marsupials, Wells *et al.,* 2019). Understanding the factors that determine these alternative, sometimes contrasting, population-level impacts of infectious disease has interested disease ecologists for decades and numerous factors about the parasite, the host, and the environment have been identified as important in the dynamics of host-parasite systems (Fig. 1; Anderson and May, 1979; Tompkins *et al.,* 2011).

We argue that a deeper integration of life-history theory (hereafter LHT) into disease ecology is both timely and necessary to improve our capacity to understand, predict, and mitigate the impact of endemic and emerging infectious diseases in wild populations. A related approach that has provided a fruitful avenue of research is the study of how epidemiological parameters, such as parasite transmission rates (De Leo and Dobson, 1996), epidemiological thresholds (Bolzoni *et al.,* 2018), and host competence (Downs *et al.,* 2019), scale allometrically with host body size. As body size is the main factor shaping interspecific variation in life-history traits (Gaillard *et al.,* 2016; Healy *et al.,*

2019), the allometric scaling of epidemiological parameters with host body size is expected to be, at least partially, associated with host life-history characteristics. Yet, body size is not always an accurate proxy of host life-history traits, especially when high-level taxonomic ranks (e.g., class level or higher) are considered. For example, within mammals, humans and bats show a particularly long lifespan and low fecundity for their relatively small body sizes (Gaillard *et al.,* 2016; Healy *et al.,* 2019). Indeed, after controlling for allometric constraints, considerable interspecific variation in life-history traits remains and other factors, such as life-history trade-offs, phylogeny, and mode of life, are known to play important roles in shaping the diversity of host life histories (Gaillard *et al.,* 2016; Healy *et al.,* 2019). Here, we argue that the position of a host species along the classical slow-fast life-history continuum (see below) can determine their response to parasitic infection (Fig. 1). It is worth noting that other host traits, such as population density and the level of sociality (Han *et al.,* 2015, 2020), as well as parasite life-history traits (Barrett *et al.,* 2008; Silk and Hodgson, 2020), also play critical roles in host-parasite dynamics, but those aspects are beyond the scope of this review.

We focus this review on LHT predictions relative to host responses to infectious disease at different levels of organization, from individual-level susceptibility to host community assembly (Fig. 1). Although these theoretical predictions are broad in scope, with empirical validations in plant and animal species (e.g., plants, Pagán *et al.,* 2008; invertebrates, Agnew *et al.,* 2008; vertebrates, Johnson *et al.,* 2012), we emphasize examples in wild vertebrate hosts, a group largely underrepresented in previous syntheses on the intersection of life-history and host responses to parasitism (e.g., Michalakis and Hochberg, 1994; Agnew *et al.,* 2000). The review is structured in eight sections. In the first

section, we introduce the theory and empirical evidence supporting the existence of a slow-fast continuum of life-history variation in vertebrates. In the second section, which is related to the field of ecoimmunology (see Brock *et al.,* 2014), we briefly discuss how the position of hosts along the slow-fast continuum can help predict the type and strength of host immune defences (for more detailed coverage refer to previous reviews, e.g., Lee (2006), Martin *et al*. (2006), Tieleman (2018), and Albery and Becker (2020)). In the third section, we discuss how life-history constrains the speed of recovery of host populations after short-term disturbances such as disease outbreaks. In the fourth section, we focus on active demographic compensation, a process particularly relevant for the persistence of host populations impacted by emerging infectious diseases. We define the types of active demographic compensation in the context of infectious diseases and discuss how these responses could be modulated by host life histories, introducing a simple theoretical model to illustrate how life-history strategies can be predictive of the magnitude of the negative effects of disease-induced mortality on populations exhibiting density-dependent compensation. In the fifth section, we discuss how host life-history strategies could modulate the rapid evolution of mechanisms of resistance (i.e., the ability of a host to limit or reduce parasite burden) or tolerance (i.e., the ability of a host to limit the negative effects of a given parasite burden). In the sixth section, we briefly review the integration of host life-history, community assembly, and infectious disease. In the seventh section, we discuss how the insights of the previous sections can inform the monitoring and control of infectious diseases in wildlife. In the eighth and concluding section we provide pointers for future directions for the incorporation of LHT in disease ecology.

SECTION 1: LIFE-HISTORY TRADE-OFFS AND THE SLOW-FAST CONTINUUM OF LIFE-HISTORY VARIATION

The pervasiveness of life-history trade-offs (i.e., beneficial change in one life-history trait has a negative impact on another trait) has been central to the development of classical LHT (Stearns, 1989a). The idea of these trade-offs is grounded in the "principle of allocation" of time and energy (Cody, 1966), such that organisms have a limited amount of time and energy to expend, and natural selection acts as a force operating on the allocation of resources to different functions (e.g., growth, reproduction, locomotion, immune function) to maximize fitness (Ricklefs and Wikelski, 2002; Lee, 2006). The most prominent and well-supported life-history trade-offs involve survival and reproduction (Stearns, 1989a; Lebreton, 2006; Healy *et al.,* 2019). The covariation among traits related to survival and reproduction are structured along a major axis of life-history variation termed the slow-fast life-history continuum (Fig. 1): species at the fast end of the continuum are characterized by high fecundity per time unit (e.g., annual fecundity), early age at first reproduction, and short lifespan, while the opposite is expected for species at the slow end (Gaillard *et al.,* 2016).

It has been proposed that the concept of the slow-fast life-history continuum should be restricted to the pattern of covariation in raw (i.e., size-uncorrected) life-history traits sharing the dimension of time (Jeschke and Kokko, 2009; Gaillard *et al.,* 2016). Empirical evidence supports the existence of this "raw" slow-fast continuum in mammals and birds (Herrando-Pérez *et al.,* 2012; Gaillard *et al.,* 2016), while in amphibians and reptiles a comprehensive analysis on the subject is still lacking (Gaillard *et al.,* 2016; but see Fig. 2 in Herrando-Pérez *et al.* (2012) which suggests the existence of the continuum in these taxa).

In contrast, for fish species, annual fecundity appears to covary positively with pace of life metrics, although for a given position on the slow-fast continuum the interspecific variation in annual fecundity is notoriously high (see Fig. 2 in Herrando-Pérez *et al.* (2012)). Theory to better understand this counterintuitive "slow-type survival with fast-type reproduction" strategy observed in several fish species is beginning to emerge (see Wright *et al.,* 2020). It is also worth noting that resources can be allocated to facets of reproduction other than fecundity, such as offspring quality and parental investment, a situation that might lead to a lack of covariation between fecundity and pace of life metrics in some ectotherms (Healy *et al.,* 2019). How this deviation from the classical slow-fast continuum modulates the effect of life histories on host responses to infectious disease is still an untapped question.

SECTION 2: HOST LIFE-HISTORY AND IMMUNE DEFENCES

The principle of allocation and the ubiquity of parasites suggest that immune defences should covary with the position of a species on the slow-fast life-history continuum, with fast-living species trading investment in immune defence for growth and reproduction (Lee, 2006; Martin *et al.,* 2006). In contrast, the longer lifespan of slow-living species means that they: 1) may encounter more individual infections during their lifetime, increasing the benefits of allocating resources to immune defences; and 2) may encounter a wider range/diversity of infections (e.g., Gutiérrez *et al.,* 2019), creating selective pressures for adaptive (specific, less self-damaging) immunity (Lee, 2006; Woodhams *et al.,* 2016).

The differential allocation of energy and resources to immunity between fast-living and slow-living species suggests that when exposed to the same parasite and under similar

environmental conditions, individuals from species at different positions along the slow-fast life-history continuum should exhibit different susceptibilities to acquiring infection and developing disease (Joseph *et al.,* 2013). There is evidence of this relationship in two recent experimental studies in amphibians. In the first study, Johnson *et al.* (2012) experimentally exposed individuals of 13 amphibian species to the trematode *Ribeiroia ondatrae*. They showed that fast-living species were more prone to infection and the development of lesions than slow-living species. In the second study, using a standardized challenge of 20 North American amphibian species, Gervasi *et al.* (2017) found that individuals from fast-living species were more susceptible to lethal *B. dendrobatidis* infection.

Empirical evidence also reveals that the relative importance of coarse immunity components, which differ in terms of energetic investment (e.g., innate vs adaptive immunity), tend to vary along the slow-fast continuum in vertebrates, with fast-living species favouring components that can be less costly such as innate immunity and behavioural mechanisms of resistance/tolerance (Fig. 1; Lee 2006; Tieleman *et al.,* 2005; Martin *et al.,* 2006; Previtali *et al.,* 2012; Sears *et al.,* 2015; Woodhams *et al.,* 2016; but see Tieleman (2018) for mixed empirical support for a link between host life-history and host immunity in birds).

Although we have highlighted empirical evidence supporting the covariation of immunity with host life-history strategies (i.e., fast-living species tend to invest less in immunity and to favour less costly mechanisms of resistance/tolerance), there is little robust evidence to support the generality of these patterns in vertebrates or other taxa (Albery and Becker, 2020). Given the complexity of the vertebrate immune system (Brock

et al., 2014) and its high responsiveness to environmental conditions (e.g., food availability, temperature, microbial environment; Sandland and Minchella, 2003; Palacios *et al.,* 2011), providing robust validation to these LHT predictions is not a trivial task. Such validations could represent a major advance in the study of wildlife diseases, allowing improvements in forecasting host susceptibility to novel parasitic infections and assisting the design of disease mitigation strategies (e.g., mass vaccination or habitat management targeting behavioural resistance/tolerance mechanisms, Hettyey *et al.,* 2019).

SECTION 3: HOST LIFE-HISTORY CONSTRAINS POPULATION RECOVERY AFTER A DISEASE OUTBREAK

The ability of populations to recover from short-term disturbances such as disease outbreaks depends on their demographic resilience (i.e., the inherent ability of a population to prevent a decrease in size after a disturbance; reviewed in Capdevila *et al.* (2020)). An important prediction in the context of infectious diseases is that, all else being equal, a population of a slow-living species would require a longer time to recover in size after a disease outbreak than a population of a fast-living species (Lebreton, 2006; Capdevila *et al.,* 2020; see Benhaiem *et al.* (2018) for an example in mammalian hosts). This arises because the maximum population growth rate, which sets the upper limit of the speed of recovery, is expected to decrease towards the slow end of the life-history continuum (Niel and Lebreton, 2005; Lebreton, 2006). Capdevila *et al.* (2020) introduced an analytical framework to study demographic resilience and its components that can be used to provide further empirical support to the above-mentioned prediction. This approach, however, is based on the analysis of density-independent, time-invariant matrix population models and

does not consider changes in vital rates over time (Capdevila *et al.,* 2020). In the following sections, we show that compensatory changes in vital rates over time are important in determining the resilience of host populations to emerging and endemic infectious diseases, especially considering that parasites often operate as long-term sustained perturbations (e.g., endemic infection dynamics).

SECTION 4: HOST LIFE-HISTORY INFLUENCES THE MECHANISM OF ACTIVE DEMOGRAPHIC COMPENSATION

Active demographic compensation (defined as the change in one or more demographic rates [e.g., survival, recruitment] to compensate for a reduction in that, or another, demographic rate) determines the capacity of a population to counteract the detrimental effects of infectious diseases. We use "active" to differentiate this concept from Capdevila *et al.* (2020)'s definition of demographic compensation which focuses on changes in demographic structure rather than changes in the vital rates. We identify two general mechanisms of active demographic compensation in response to infectious disease: 1) a non-specific response that arises from the effect of parasitic infection on host population density (i.e., density-dependent compensation); and 2) an adaptive plastic response of individual hosts to infection (i.e., parasite-induced plasticity of life-history traits).

The role of density-dependent processes in active demographic compensation

Early theoretical studies showed that density-dependent compensation could be a key demographic mechanism to offset disease impacts on population growth rate, an idea that

was supported by empirical evidence in invertebrate hosts (Anderson and May 1981). Essentially, for a parasite to regulate a host population, disease-induced mortality needs to be additive (i.e., any individual that dies from the disease would have survived if the disease was not present) rather than compensatory (i.e., any individual that dies from the disease would have died from other causes if the disease was not present) to other natural sources of density-dependent mortality (Jolles *et al.,* 2006). For example, in overcrowded populations, parasite infection may primarily remove individuals that otherwise would die due to causes linked to overcrowding (e.g., food or space limitations), resulting in negligible differences in net survival rates between infected and uninfected populations (Kistner and Belovsky, 2014). Additionally, a reduction in population size can boost recruitment in a density-dependent fashion, compensating for the reduced survival of infected hosts (e.g., Anderson and May, 1981; Ohlberger *et al.,* 2011; McDonald *et al.,* 2016; Rogowski *et al.,* 2020). In a population of susceptible hosts, density-dependent compensatory responses can lead to effective compensation (i.e., no change in population size) or even overcompensation (i.e., increase in population size; reviewed in Schröder et al. (2014)). To our knowledge, however, there is only a single demonstration of density-dependent overcompensation in this context, involving a protozoan parasite and a larval mosquito host (Washburn *et al.,* 1991).

The demographic buffering hypothesis states that to alleviate negative effects of environmental stochasticity on the long-run population growth rate, vital rates with the largest contribution to the population growth rate (i.e., vital rates exhibiting a high elasticity) should be buffered against environmental variation (reviewed in Hilde *et al.* (2020)). This means that vital rates with a high elasticity should be canalised (i.e., are

insensitive to environmental variation). From this hypothesis, McDonald *et al.* (2016) proposed that vital rates with high elasticity could also be buffered against internal pressures, exhibiting weak dependence on local population density. This knowledge can help predict the type of density-dependent compensatory mechanisms likely to occur in a host population. In the context of host-parasite systems, this hypothesis suggests that, in slow-living species, recruitment should be more sensitive than adult survival to local population density and density-dependent recruitment should be more commonly observed as a mechanism of compensation for infectious diseases (McDonald *et al.,* 2016). This contrasts with fast-living species, where recruitment is expected to be less sensitive to population density than adult survival and, therefore, density-dependent compensatory recruitment would be expected to be less effective and thus less commonly observed. Instead, in fast-living species, as adult survival is expected to be more sensitive to population density, the increased mortality rates due to disease are more likely to be compensatory rather than additive. In a rare test of these LHT predictions, McDonald *et al.* (2016) found that density-dependent compensatory recruitment contributed to the persistence of a badger (*Meles meles*) population naturally infected with the bacterium *Mycobacterium bovis* (Fig. 2a). This response is in accordance with the above-mentioned LHT predictions, as badgers exhibit a slow life-history strategy (McDonald *et al.,* 2016).

Life-history strategies and host population depression due to parasite-induced mortality

We use a susceptible-infected disease model to theoretically explore how life-history modulates the negative effects of disease on host populations exhibiting density-dependent compensation. The purpose of this analysis is to illustrate that distinguishing between slow

and fast-living life-history strategies can help predict the magnitude of the negative effects of disease-induced mortality on host populations. The models we analyse here are similar to those used in previous studies of disease-induced depression of host populations and the effects of life-history on disease dynamics (e.g., Anderson and May, 1981; De Leo and Dobson, 1996; Lloyd-Smith *et al.,* 2005; Bolzoni *et al.,* 2008, Han *et al.,* 2015). The key contribution of our analysis is that, in addition to examining how variation in demographic and infection rates between slow- and fast-living species affect disease dynamics (e.g., De Leo and Dobson, 1996; Bolzoni *et al.,* 2008; Han *et al.,* 2015), we also directly compare how structural assumptions regarding the location of density-dependence affect the negative impacts of disease on slow- and fast-living species.

Consider a host population with some density of susceptible hosts A_S and infected hosts A_I. Assume that hosts become infected through density-dependent transmission, where increasing host density increases host contact rate (Anderson and May, 1981; McCallum, 2001; see Fig. S2 for frequency-dependent transmission). Also assume that infected hosts suffer disease-induced mortality at some rate α (yr^{-1}) and infected hosts can recover at some rate γ (yr^{-1}). We model these processes as

$$\begin{aligned} \frac{dA_S}{dt} &= f(A_S + A_I)[A_S + A_I] - g(A_S + A_I)A_S - \beta A_I A_S + \gamma A_I \\ \frac{dA_I}{dt} &= \beta A_I A_S - [g(A_S + A_I) + \gamma + \alpha]A_I \end{aligned} \quad (1)$$

where βA_I is the force of infection (yr^{-1}). The function $f(A_S + A_I)$ defines the per capita host reproductive rate as a function of total host population density $A_S + A_I$. Consistent

with the demographic buffering hypothesis, we assume that the per capita reproductive rate of fast-living species is canalized and density-independent such that $f(A_S + A_I) = a$. In contrast, the per capita reproductive rate of slow-living species is predicted to be less canalized and to exhibit density-dependence (e.g., McDonald *et al.,* 2016) and we assume that it takes the form $f(A_S + A_I) = a - s[A_S + A_I]$ (Gurney and Nisbet, 1998), where s is the strength of density-dependence. The function $g(A_S + A_I)$ defines the per capita mortality rate of a host as a function of host density. For fast-living species, the per capita mortality rate can vary with host density and we consider the form $g(A_S + A_I) = \mu + s[A_S + A_I]$ (Anderson and May, 1981). The per capita mortality rates of slow-living species, on the other hand, are predicted to be canalized (e.g., McDonald *et al.,* 2016) such that per capita mortality rate is density-independent, $g(A_S + A_I) = \mu$. In what follows, we refer to the 'fast model' as the model with density-dependence in per capita mortality and the 'slow model' as the model with density-dependence in per capita reproductive rate.

In addition to where density-dependence operates, another distinguishing feature of fast and slow-living species are the magnitudes of their per capita mortality and reproductive rates in the absence of density-dependence. Slow-living species tend to be long-lived (low μ) with low reproductive rates (low a), while fast-living species tend to be short-lived (high μ) with high reproductive rates (high a) (Gaillard *et al.,* 2016). This well-known life-history trade-off is reflected in the model in the host's fundamental recruitment number, which under the assumptions of equation 1 is $R_{0,\text{host}} = \frac{a}{\mu}$. $R_{0,\text{host}}$ defines the expected number of new hosts produced by a host over its lifetime when density-dependent processes are absent. A host can obtain the same reproductive number by trading-off between a and μ. In this way, fast-living and slow-living species may have the same

fundamental recruitment number, but using contrasting strategies (e.g., low a, low μ vs. high a, high μ). Here we consider a slow-living species that lives on average ten years ($\mu = 0.1$ yr^{-1}) and a fast-living species that lives on average half a year ($\mu = 2$ yr^{-1}).

When a parasite successfully invades it will depress the host population below its parasite free equilibrium density, which is $A^*_{\text{parasite free}} = \frac{a-\mu}{s}$ for both the slow and fast model. How does the amount of host depression depend on the life-history strategy of the host? To answer this question, we varied both the disease-induced mortality rate α and the host fundamental recruitment number $R_{0,\text{host}}$ for the slow and fast model and compared how much host equilibrium density was depressed in the presence of the parasite relative to the parasite free equilibrium. Following Anderson and May (1981), we defined population depression as $1 - A^*_{\text{parasite present}}/A^*_{\text{parasite free}}$, where $A^*_{\text{parasite present}}$ is the total equilibrium population density in the presence of the parasite. Zero indicates no population depression from disease, and a value closer to one indicates a higher population depression.

To adequately compare population depression between the two life-history strategies, we also need to consider R_0 of the parasite. This describes the expected number of infected individuals produced over the lifetime of an average infected host in a fully susceptible host population. The proportion of a host population infected by a parasite increases with increasing R_0 (Keeling and Rohani, 2008) and will affect the percentage of the host population that experiences disease-induced mortality. Parasite R_0 for the slow model is $R_{0,\text{parasite,slow}} = \frac{A^*_{\text{parasite free}}\beta}{\alpha+\gamma+\mu}$ and for the fast model is $R_{0,\text{parasite,fast}} = \frac{A^*_{\text{parasite free}}\beta}{\alpha+\gamma+\mu+sA^*_{\text{parasite free}}}$. When $R_{0,\text{parasite,}.} > 1$, the parasite can invade and transmission can be sustained in a host population whose density is at $A^*_{\text{parasite free}}$. As the value of $A^*_{\text{parasite free}}$

will vary between the slow and fast model, so will parasite R_0. To account for this, we ensured that parasite R_0 was the same for the slow and fast model for any parameter set by adjusting the transmission parameter β for the slow model once disease-induced mortality α and $R_{0,\text{host}}$ had been chosen. Biologically, this means that we assumed that parasites of slow-living species generally had a higher transmission rate than those of fast-living species. This assumption is reasonable given that 1) slow-living species generally have a lower population density and a larger body size than fast-living species (Han *et al.,* 2015), and 2) transmission rate β scales positively with body size under the assumption of density-dependent transmission (De Leo and Dobson, 1996; but see Joseph *et al.,* 2013).

Our analysis shows that, given the same parasite R_0 and host fundamental recruitment number $R_{0,\text{host}}$, the parasite depressed the population of slow-living species more than fast-living species (Fig 3a,b). For both life-history strategies, population depression was maximized for intermediate levels of disease-induced mortality α and tended to increase with increasing host fundamental recruitment number (Fig. 3a,b). The unimodal relationship between disease-induced mortality α and population depression is an inevitable consequence of the fact that population depression has to be zero when $\alpha = 0$ and when α gets high enough that the parasite can no longer persist. Increasing the host fundamental recruitment number in our model, on the other hand, increases equilibrium host density, which increases transmission efficiency and increases population depression. However, when the host fundamental recruitment number gets high enough, host births can eventually compensate for disease-induced mortality and population depression will decrease (Anderson and May, 1981).

There are two non-exclusive explanations for the comparatively stronger population depression in slow-living species. First, despite ensuring identical parasite R_0 values for the slow and fast model, differences in intrinsic mortality rate or reproductive rate between fast and slow-living species, for example, can directly affect equilibrium parasite prevalence. If the slow model had higher disease prevalence than the fast model, this could explain the increased population depression. In Fig. 3c,d we show that the opposite occurred in most cases, i.e., the equilibrium prevalence was generally higher for the fast model compared to the slow model, given comparable parameters. Second, the stronger depression for slow-living species could be due to either the location of density-dependence (i.e., host survival vs host reproduction) or the differences in mortality rate between the two life-history strategies. If we ignore the biological implausibility and set the mortality rate μ to be the same for the slow and fast model, the stark differences in population depression are largely removed (Fig. S1). This indicates that the differences in population depression between the slow and fast models are driven largely by differences in mortality rate between the two life-history strategies, and not by the location of density-dependence.

We can further understand this result by considering how a proportional change in mortality rate proportionally affects $R_{0,\text{host}}$ (i.e., the elasticity of $R_{0,\text{host}}$ with respect to μ). Specifically, we can write the elasticity as $\frac{\partial R_{0,\text{host}}}{R_{0,\text{host}}} = -T\partial\mu$, where $T = 1/\mu$ is the average lifespan of the host (Lebreton 2005). When hosts have a short lifespan (i.e., T is small), consistent with a fast life-history strategy, a small change in host death rate μ given by $\partial\mu$ will have a small proportional change on $R_{0,\text{host}}$. In contrast, when hosts have a long lifespan (i.e., T is large), consistent with a slow life-history strategy, a small change in host death rate μ will have a large proportional change on $R_{0,\text{host}}$. Because equation 1 assumes

that the parasite affects host population dynamics by modifying mortality from μ to $\mu + \alpha$ for infected hosts, the above elasticity analysis suggests that, for a slow- and a fast-living species with the same values of $R_{0,\text{host}}$, the proportional impact of disease will be larger for the slow-living species (small μ) than for the fast-living one (large μ). This result is unchanged for frequency-dependent transmission (Fig. S2).

As a final note, this simple model only considers a host with a single life stage. When hosts have multiple life stages (e.g., juvenile and adult) that are differentially affected by a parasite, the location of density-dependence can interact in more complex ways with underlying host and parasite parameters determining the extent of population depression in fast and slow-living species. For example, in a slow-living species where juveniles are substantially less susceptible to infection than adults, disease-induced mortality in adults could lead to density-dependent increases in per capita reproductive rates and a proportional increase in juvenile population density in the presence of disease. However, in a species with density-dependence in juvenile mortality, this type of compensation would be harder to obtain. These predicted patterns provide an interesting future direction to explore at the intersection of disease ecology and LHT.

The role of life-history plasticity in active demographic compensation

Disease-associated risk can induce plastic changes in life-history traits that can potentially result in active demographic compensation. For example, in the Tasmanian devil (*Sarcophilus harrisii*), females from populations decimated by a transmissible tumour

decreased their age at first reproduction and produced more offspring, a response that partially offset the long-term impact of the disease and allowed persistence of Tasmanian devil populations (Jones *et al.,* 2008; Lachish *et al.,* 2009; Lazenby *et al.,* 2018). Although a reduced population density due to infectious disease could potentially induce plasticity in life-history traits, several empirical studies in vertebrates indicate that cues pertaining to a parasite (e.g., antigens) or infected conspecifics are enough to trigger plasticity in life-history traits (Wedekind, 2002; Bonneaud *et al.,* 2004; Velando *et al.,* 2006; Hanssen, 2006; Pompini *et al.,* 2013; Sköld-Chiriac *et al.,* 2019). We argue that this evidence reinforces the traditional idea of the existence of a density-independent plastic response of hosts to the increased risk of death or reduced fecundity associated with a parasitic infection (Stearns, 1989b).

In animals, empirical demonstrations of parasite-induced plasticity in life-history traits were traditionally restricted to invertebrates (e.g., Michalakis and Hochberg, 1994; Agnew *et al.,* 2000), but evidence is accumulating that this occurs across all vertebrate classes as well (Fig. 2b-f; Table S1). Despite being well described at the individual level, it is unclear how parasite-induced plasticity of life-history traits affects host demography and long-term host-parasite dynamics in vertebrates or other taxa. Like the results in invertebrates (Agnew *et al.,* 2000), examples from wild vertebrates support theoretical expectations that the most common type of parasite-induced plasticity in life-history are associated with reproduction. First, LHT predicts that if parasitism reduces an individual's residual reproductive value (which is a measure of future reproductive opportunities) due to reduced fecundity, reduced survival, or chronic disease, selective benefits should exist for individuals that can divert resources from self-maintenance to increase their current

reproductive effort, in a "terminal investment" strategy to maximize fitness (Minchella, 1985; Forbes, 1993; Sorci *et al.,* 1996; Hanssen, 2006; Schwanz, 2008). Second, for individuals that have not reached sexual maturity, reducing the age of first reproduction (i.e., diverting resources from growth to reproduction) should also enhance host fitness since the chances of successful reproduction before either death or sterility are increased (Stearns, 1989b; Hochberg *et al.,* 1992; Michalakis and Hochberg, 1994). Also, in vertebrates with complex life cycles, parasites can induce changes in the timing of life-history transitions and niche shifts (e.g., hatching time in fish and amphibians) that permit hosts to escape stage-specific parasitic infection (Warkentin *et al.,* 2001; Wedekind, 2002; Pompini *et al.,* 2013).

It is worth noting that infected hosts do not always exhibit increased reproductive effort (Duffield *et al.,* 2017). First, the direct negative effects of infectious disease can inhibit reproduction (Richner, 1998). Second, if the prospects of future reproduction are not diminished (e.g., CDV in spotted hyenas; Benhaiem *et al.,* 2018), it would be more efficient to reallocate resources to immune defences rather than to reproduction (but see Perrin *et al.,* 1996). Third, the activation of the immune system is costly, and to sustain an immune response, hosts may need to reallocate resources away from reproduction (Ilmonen *et al.,* 2000). Lastly, even if an infectious disease reduces a host's residual reproductive value, investing in immunity could pay off. For instance, using a theoretical evolutionary model of a sexually-transmitted disease producing sterility in females, Johns *et al.* (2019) showed that, even though terminal investment evolved under most scenarios, when immunity was highly cost-effective in delaying sterility, infected females increased immune response at the expense of reproductive effort.

It is unclear how plasticity in host life-history traits covaries with the position of a species on the slow-fast continuum (but see Fig. 1), highlighting the urgent need for theoretical and empirical development of this subject. In a general context, empirical evidence shows that, in contrast to mammals with an intermediate to fast life-history strategy (e.g., Tasmanian devils, wild boars), slow-living mammals are not able to bring forward the onset of reproduction as a mechanism to compensate for an extrinsic cause of increased mortality rate (see Servanty *et al.* (2011) and references therein).

SECTION 5: HOST LIFE-HISTORY AND EVOLUTIONARY RESPONSES TO INFECTIOUS DISEASES

Parasites could also drive rapid evolutionary changes in host life-history traits (Stearns *et al.,* 2000; Koella and Restif, 2001; but see Steiner and Tuljapurkar, 2012). Indeed, parasites are ubiquitous in nature and exert selective pressures influencing the evolution of host-life history strategies and maintaining plasticity of host life-history traits (Hochberg *et al.,* 1992; Koella and Restif, 2001). This rapid evolution of host life-history traits could lead to evolutionary rescue, i.e., when adaptive evolutionary change halt population decline and prevents extinction (Carlson *et al.,* 2014). Yet, we are unaware of any empirical demonstration of rapid evolutionary change of life-history traits (e.g., fecundity, age at first reproduction) in response to parasitism in vertebrate hosts (but see below for examples of rapid evolution of tolerance/resistance mechanisms). The distinction between rapid evolution of life-history traits and active demographic compensation in response to

infectious disease is of practical relevance because evolutionary responses are expected to be more hard-wired and slower to reverse than density-dependent and plastic responses, and could alter population dynamics and resilience to other stressors (e.g., extreme climatic events) even after the parasite has disappeared from the host population.

Additionally, rapid adaptive evolutionary changes of resistance or tolerance mechanisms can have important effects on host-parasite dynamics (Duffy and Sivars-Becker, 2007), allowing evolutionary rescue in susceptible hosts (e.g., Gignoux-Wolfsohn *et al.,* 2019). There are several examples of rapid evolution of resistance or tolerance mechanisms in wild vertebrates, including amphibians (Savage and Zamudio, 2016), birds (Bonneaud *et al.,* 2011), and mammals (Epstein *et al.,* 2016; Gignoux-Wolfsohn *et al.,* 2019). This rapid evolution is more likely to arise if the genetic variants involved in the response to infectious disease are from pre-existing genetic variation rather than from the recruitment of *de novo* mutations (Barrett and Schluter, 2008; Bonneaud *et al.,* 2011; Hedrick, 2013). For example, populations of little brown bats (*Myotis lucifugus*) experienced a dramatic and rapid decline due to white-nose syndrome (one monitored colony declined by 98% between 2009-2015) but then started to recover slowly. Gignoux-Wolfsohn *et al.* (2019) reported that this recovery was associated with rapid evolution that occurred as a soft selection at multiple loci in genes linked to hibernation behaviour. These authors concluded that this occurred from standing genetic variation because the short timescale of fungal infection, mortality, and recovery processes makes selection of novel mutations very unlikely (Gignoux-Wolfsohn *et al.,* 2019).

Our current knowledge about the genetic architecture of resistance and tolerance and the central role of standing genetic variation in the evolvability of host responses to

parasitic infection leads to two important predictions that remain to be empirically tested in vertebrate hosts. First, at the intraspecific level, resistance and tolerance are less likely to evolve rapidly in small, isolated populations where small effective population size (N_e) increases the risk of resistance/tolerance allele loss due to genetic drift and decreases selection effectiveness in response to infectious disease (Eimes *et al.,* 2011). This prediction is supported by information from taxa other than vertebrates. For instance, in plants, individuals from highly connected populations can exhibit higher levels of disease resistance making those populations less susceptible to parasite-driven extinction (Jousimo *et al.,* 2014; Carlsson-Granér and Thrall, 2015). Second, at the interspecific level, covariation between life-history and species' genetic characteristics likely determines the speed of the evolution of parasite resistance and tolerance. Small-sized species with fast life histories usually have higher genetic diversity than large, slow-living species (Wooten and Smith, 1985; McCusker and Bentzen, 2010; Eo *et al.,* 2011). In addition, because of their short generation times, species at the fast end of the life-history continuum evolve at a faster rate than those at the slow end (Bromham, 2011) and have higher non-synonymous to synonymous substitution rate ratios (reflecting selection efficiency due to large N_e) (Figuet *et al.,* 2016). These two predictions suggest that fast-living species should benefit from a higher capacity for rapid evolution than slow-living species in response to infectious disease emergence. In contrast, Bruns *et al.* (2015) provided theoretical evidence that long-lived hosts can evolve resistance more rapidly than short-lived hosts when the likelihood of exposure to parasites and, therefore, the strength of selection for resistance, increases with longevity. Testing these theoretical expectations is a major challenge but would allow us to

better predict the susceptibility of species and populations to the emergence of infectious diseases.

In addition to evolution, rapid changes in host life-history traits or resistance/tolerance mechanisms can be attributed to parasite-induced epigenetic variation (Gómez-Díaz *et al.,* 2012). To date, the role of epigenetic mechanisms on host responses to parasitism remains poorly understood. Available evidence shows that parasite-induced changes in DNA methylation (an epigenetic mechanism) can occur within the sequence of protein-coding genes involved in host immunity and can also affect genes regulating a broad range of molecular and intracellular processes (Zhang *et al.,* 2016; Sagonas *et al.,* 2020). Methylation is a strong predictor of lifespan and aging (Lowe *et al.,* 2018; Anastasiadi and Piferrer, 2020) and partially regulates fertility in vertebrates (e.g., Woods *et al.,* 2018). Therefore, parasite-induced methylation changes could produce aberrant DNA expression, which might alter individual phenome, eventually influencing compensatory responses. Depending on the extent of the germline reprogramming, epigenetic marks driven by parasite infection could be retained and could be transmitted from one generation to the next, allowing the transgenerational inheritance of resistance/tolerance mechanisms or life-history traits in some organisms (Greer *et al.,* 2011; Bošković and Rando, 2018).

SECTION 6: FROM POPULATIONS TO COMMUNITIES: INTEGRATING HOST LIFE-HISTORY, COMMUNITY ASSEMBLY, AND INFECTIOUS DISEASE

Life-history traits can be further considered at the scale of ecological communities. The position of a species along the slow-fast life-history continuum can covary with both their

epidemiological potential (i.e., host competence, which is defined as the capacity of a host to maintain and transmit a parasite) and their position within communities (i.e., assembly order). Thus, LHT offers an intriguing opportunity to more mechanistically link epidemiological and ecological frameworks in the study of disease, particularly for multi-host parasites.

One arena in which this topic has begun to receive more attention is in the study of how changes in community diversity influence parasite transmission and disease risk. Debate over whether biodiversity losses should consistently lead to higher disease risk (e.g., the dilution effect) has prompted efforts to understand transmission within complex multi-host communities from a more mechanistic perspective (e.g., Ostfeld and Keesing, 2012). When life-history traits covary with aspects such colonization ability, competitive dominance, or extinction risk, species composition may be predictable along gradients of species richness, disturbance regime, productivity, or community age. In amphibian communities, for instance, Johnson *et al.* (2013) reported up to a 78% decrease in trematode parasite transmission with an increase in amphibian host diversity. This result was due to the non-random assembly of host communities: fast-living species with high colonization abilities tended to be the most competent hosts for the trematode. Because these species predominated in low-richness communities, parasite transmission tended to decline with community diversity. As these species were increasingly accompanied or replaced by lower-competence hosts at higher levels of species richness, the overall infection competence of the community decreased. If communities were instead assembled at random with respect to species composition (in laboratory experiments), there was no such relationship between species richness and parasite transmission (Johnson *et al.,* 2019;

but see Becker *et al.,* 2014). This highlights the importance of host life-history characteristics in affecting both interspecific variation in host infection competence as well as patterns of realistic assembly in ecological communities, which together could be used to more broadly consider landscape-level transmission dynamics.

SECTION 7: FROM THEORY TO PRACTICE: HOST LIFE-HISTORY AND MITIGATION OF INFECTIOUS DISEASES IN WILDLIFE

We argue that a better understanding of the relationship between host life-history and disease dynamics can improve the accuracy of disease risk analysis and inform mitigation efforts at different stages of parasite invasion (*sensu* Langwig *et al.,* 2015).

Disease risk analysis focuses on characterizing the potential disease hazards to an animal, a population, or a species prior to their occurrence (Sainsbury and Vaughan-Higgins, 2012; Jakob-Hoff *et al.,* 2014). Risk largely depends on the adaptive capacity of the host population/species, which we define as its capacity to cope with, or respond to, an infectious disease. Because life-history permeates all components of host adaptive capacity (Jakob-Hoff *et al.,* 2014), life-history traits could be used to identify species at greater risk and prioritize surveillance efforts (Grogan *et al.,* 2014).

During the epizootic phase of parasite invasion, a rapid assessment of life-history traits can help to identify those host species at greater risk and guide resource allocation accordingly. For example, an initial, coarse assessment might prioritize naïve slow-living species, populations of which are more likely to be impacted more severely by infectious

disease (Fig. 3a,b). Also, given the greater capacity for an adaptive immune response, LHT suggests that vaccine development would be more effective for slow-living species. LHT insights can help refine initial assessments. For example, mitigation decisions in fast or slow-living species might change depending on whether juveniles, adults or both life stages are affected. Parasite-driven adult mortality will have a greater impact on the population dynamics of slow-living than fast-living species, and high rates of parasite-driven juvenile mortality can limit the efficacy of compensatory recruitment in slow-living species (Valenzuela-Sánchez *et al.,* 2017).

After the epizootic phase, fast-living host species might be managed by facilitating host-parasite co-existence by reducing non-disease stressors to indirectly reduce additive mortality (Scheele *et al.,* 2019b). Conversely, slow-living species with slower recovery might be managed more directly, by improving recruitment through habitat manipulation (e.g., Haydon *et al.,* 2002) or by population supplementation through the release of captive-bred or translocated individuals (e.g., Gerber *et al.,* 2019; Mendelson *et al.,* 2019).

Importantly, while conservation plans intuitively seek to protect species at greater risk of extinction, in a disease context the protection of one species will often require managing additional species (Dobson, 2004). Life-history theory could help to predict the potential and relative importance of other species to act as a disease reservoir (Han *et al.,* 2020), enabling the causative parasite to persist (Gog *et al.,* 2002; Haydon *et al.,* 2002; Plourde *et al.,* 2017). Empirical evidence shows that fast-living species commonly have a higher host competence (Johnson *et al.,* 2012; Joseph *et al.,* 2013; Plourde *et al.,* 2017; Albery and Becker, 2020). This likely arises due to the lower investment of fast-living species on immune defences, the adaptation of parasites to locally abundant hosts, or both

(Joseph *et al.,* 2013; Albery and Becker, 2020). Therefore, locally abundant fast-living species could be targeted to protect a more vulnerable species at risk, pre-emptively or reactively (Canessa *et al.,* 2019a; Martel *et al.,* 2020). A recent study presented theoretical evidence that challenges the idea that fast-living species will invariably have a higher host competence. Using age-structured, susceptible-infected models, Silk and Hodgson (2020) showed that the demographic host competence (i.e., the ability of host populations to sustain endemic prevalence) of slow-living species can be similar or even higher (especially in the case of density-dependent parasite transmission) than that of fast-living species. Disentangling how immune and nonimmune mechanisms (e.g., demography, behaviour, density-dependence) of host competence interact at the population level seems to be a critical step to better understand the relationship between host competence and life history in multi-host parasite systems.

We foresee two major barriers to the use of LHT to inform wildlife disease mitigation. First, relatively few proven, feasible options exist for disease control in wild vertebrates (e.g., Garner *et al.,* 2016). General trade bans for disease prevention (Shea *et al.,* 2014) or culling for outbreak control (Carter *et al.,* 2009; Mysterud *et al.,* 2018) are more likely to be focused on the potential of species to act as vectors of parasite entry than on long-term disease dynamics (Pavlin *et al.,* 2009). Actions deployed during the invasion phase are likely to be broad-scope measures applied to a wide range of potential hosts and vectors within a landscape or ecological setting (e.g., culling; Gortazar *et al.,* 2014). The second barrier is the scarcity of life-history data for many threatened species (Conde *et al.,* 2019). Understanding long-term demographic processes requires long-term data. Managers can respond to such uncertainty by delaying actions until such knowledge is accumulated

(but risking parasite spread during this period) (Grantham *et al.,* 2009; Wintle *et al.,* 2010), or by making decisions under uncertainty and assessing their effectiveness adaptively (e.g., Shea *et al.,* 2014). Such assessments should be faster and more reliable for fast-living species with shorter generation times and larger cohorts, and hence larger sample sizes.

Despite these limitations, disease risk assessments and mitigation plans generally are conducted with a limited knowledge of the system and depend on expert opinion and extrapolation (Canessa *et al.,* 2019b). Therefore, we encourage scientists and practitioners to incorporate knowledge about broad LHT-disease relationships into expert assessments to narrow the decision space (Wintle *et al.,* 2010), even in species where life-history data might be limited.

SECTION 8: CONCLUSIONS AND FUTURE DIRECTIONS

Host life-history characteristics strongly influence host responses to parasitism at different levels of organization, from individuals to communities. While we highlight several empirical examples supporting LHT predictions about host responses to infectious disease in vertebrates, most theoretical expectations lack robust empirical validation. Addressing this challenge is critical for the advancement of theory and practice in infectious disease ecology. We have highlighted several mechanisms that allow host populations to compensate for an increased mortality or reduced fertility due to infectious disease, and how life-history can constrain these responses. While our capacity to disentangle these mechanisms in wild populations has been limited to date, new opportunities are arising to deal with this problem. These include the integration of experimental and observational

approaches (e.g., Washburn *et al.,* 1991; Rogowski *et al.,* 2020) including through new analytical tools, such as integrated population models, that incorporate multiple data types and processes occurring at different levels of organization (e.g., McDonald *et al.,* 2016; Wilber *et al.,* 2016). Although we focused this review on interspecific differences in host life histories, the life-history traits of a species are not strictly static: within and among population variation in life-history traits can depend on biotic or abiotic environmental conditions. How the intraspecific variation in life-history traits influence host responses to parasitism remains poorly understood, but it probably accounts for some of the interpopulation variation in disease impacts that we observe in nature (e.g., Stephenson and Cable, 2015). Accordingly, efforts to quantify trait distributions within communities which capture both intraspecific and interspecific variation in key life-history traits are essential to better understand the importance of host life-history on complex multi-host parasite systems. LHT is a rich source of information that has not been fully applied to meeting the challenges of wildlife disease mitigation. We suggest that applying information gleaned from broad LHT-disease relationships (considering extrapolation in species where life-history data might be limited or non-existent) can contribute significantly to disease risk assessment and the identification of innovative mitigation strategies to address disease threats to wildlife.

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---------- Figures ----------

Figure 1

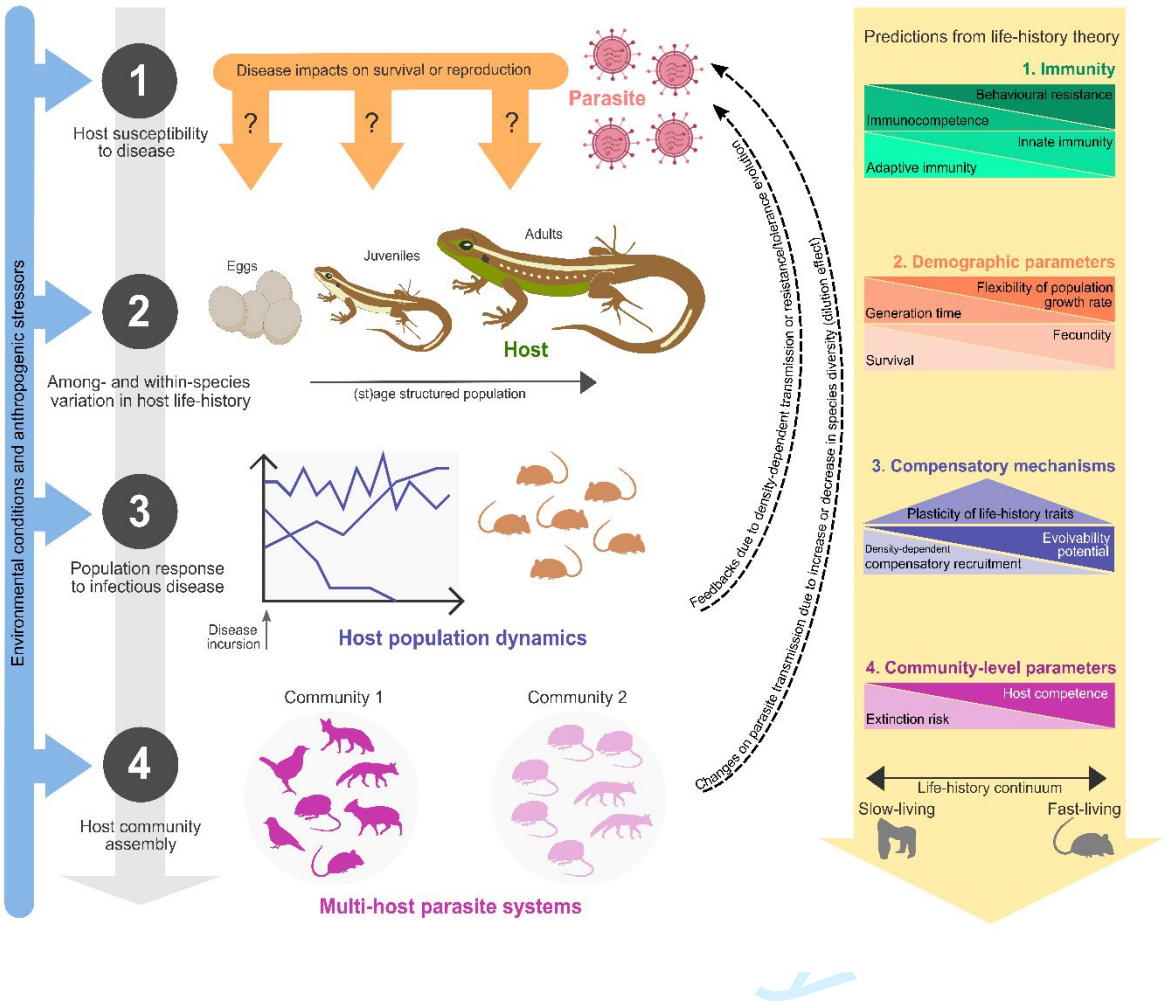


Figure 2

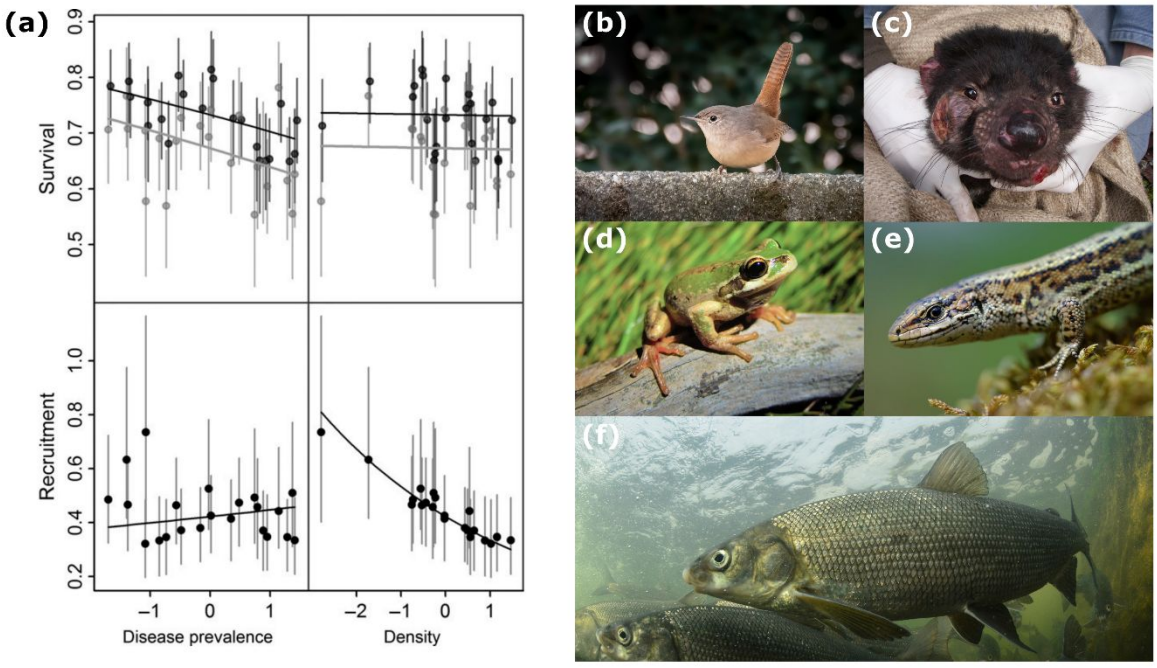
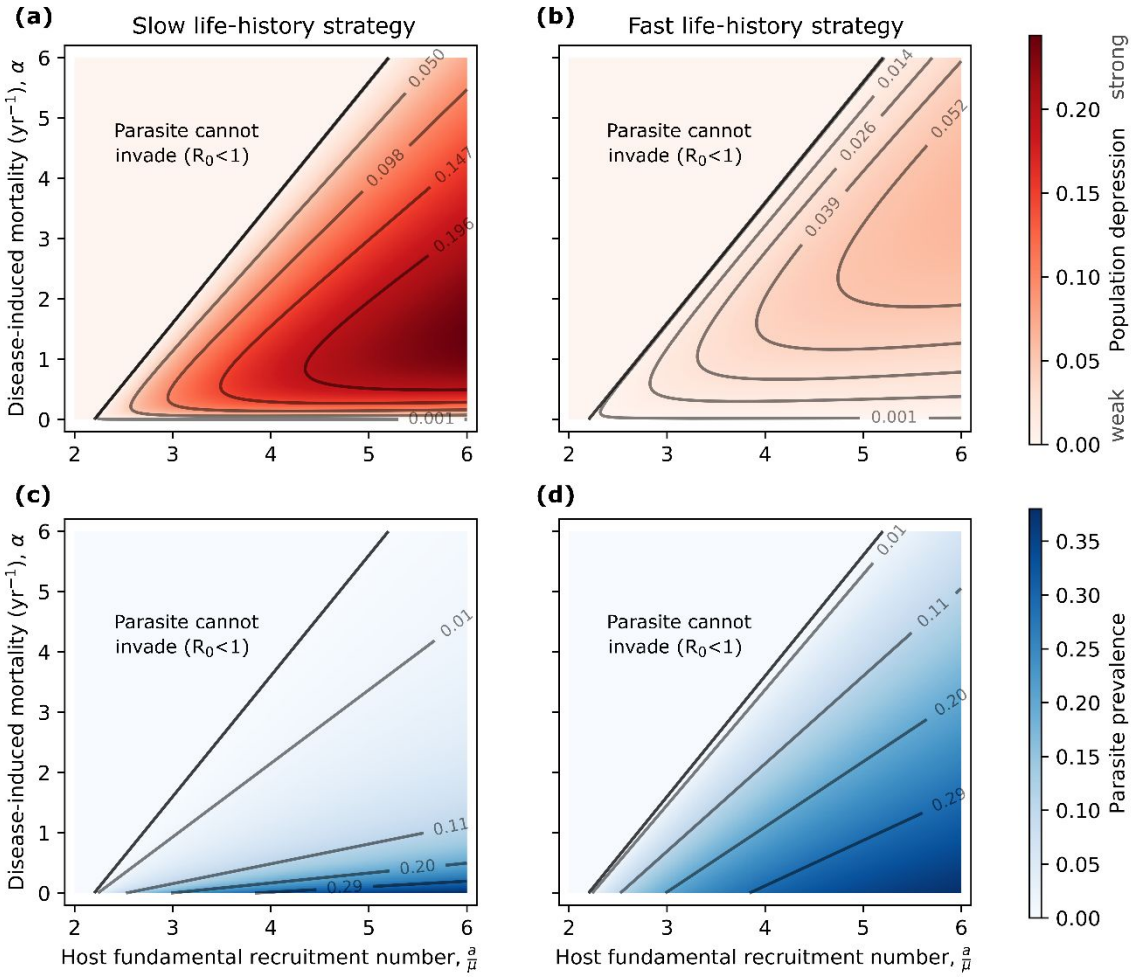


Figure 3


(a)
Slow life-history strategy
(b)
Fast life-history strategy
Parasite cannot invade (R_0<1)
0.050
0.098
0.147
0.196
0.001
0.014
0.026
0.039
0.052
0.001
Disease-induced mortality (yr^{-1}), α
Population depression
strong
weak
0.00
0.05
0.10
0.15
0.20
(c)
(d)
0.01
0.11
0.20
0.29
Host fundamental recruitment number, $\frac{a}{\mu}$
Parasite prevalence
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35

---------- Figure legends ----------

Figure 1 Host life-history characteristics affect the host-parasite interaction at different levels of organization, from individual-level susceptibility, to population-level responses to host community assembly. Life-history theory predicts different outcomes of parasitic infection across these organizational levels, which are related to the position of the host species (or populations) along the slow-fast continuum of life-history variation. Note that several of these predictions lack robust empirical validations, and some have not been tested at all (see main text). For example, we speculate that host species with intermediate life-history strategies should exhibit higher plasticity of life-history traits. This is because species on the fast end of the life-history continuum are expected to have low plasticity in fecundity parameters due to the high canalization of recruitment-related traits. Species on the slow end, in contrast, are expected to have a low canalization of recruitment-related traits. However, physical constraints imposed by their reproductive systems (e.g., large size of the offspring compared to the size of the uterus in slow-living mammals or large eggs compared to the size of the ovaries and oviducts in slow-living amphibians) and a potentially costly immune response against infection could limit the potential for active demographic compensation through increased reproductive effort. Importantly, fully understanding the effects of infectious disease relies on understanding a range of factors (e.g. parasite transmission, environmental effects) that depend on the system evaluated.

Figure 2 Empirical examples of density-dependent compensation (a) and plasticity in life-history traits (b-f) in response to infectious disease in vertebrates. In (a) the correlation of adult survival and recruitment with disease prevalence and host population density in the

badger–*Mycobacterium bovis* system is shown. The dark grey and light grey lines in the top panels of this figure represent the survival of males and females, respectively. Density-dependent compensatory recruitment allowed the long-term persistence of this badger population with endemic *M. bovis* infection (adapted from McDonald *et al.* [2016]). (b) *Troglodytes aedon* females experimentally exposed to *Salmonella enterica* LPS increased the amount of yolk per unit of egg mass and food provisioning to nestlings (photo: Mylthon Jiménez-Castillo). (c) *Sarcophilus harrisii* females from populations with the transmissible Devil facial tumour disease have an earlier onset of reproduction and more pouch young (photo: Rodrigo Hamede). (d) *Litoria verreauxii alpine* individuals experimentally infected with *Batrachochytrium dendrobatidis* have more spermatic cell bundles and a larger proportion of spermatozoa bundles (males), and larger ovaries and oviducts (females) (photo: Matt West). (e) *Zootoca vivipara* females naturally infected with Hematozoa exhibited a larger relative clutch mass and higher maternal investment per young (photo: Matthieu Berroneau). (f) *Coregonus* sp. eggs exposed to water-borne cues from *Pseudomonas fluorescens* or conspecific infected eggs hatched earlier (photo: Paul Vecsei). References and study details (b-f) can be found in the Appendix S2 in Supporting Information.

Figure 3 Life-history strategies and host population depression due to parasite-induced mortality. (a,b) We used equation 1 to compute the equilibrium total host density when the parasite was absent and when the parasite was present and depressed the host population. We calculated population depression as $1 - A^*_{\text{parasite present}}/A^*_{\text{parasite free}}$, where zero indicates no population depression. We varied the host fundamental recruitment number $R_{0,\text{host}} = \frac{a}{\mu}$ between 2 and 6. To do this, we held intrinsic mortality μ fixed at 0.1 yr^{-1} for

the slow-living species and at 2 yr^{-1} for the fast-living species and chose the reproductive rate a yr^{-1} to ensure the host fundamental recruitment numbers were the same between hosts. We varied disease-induced mortality rate α between 0 and 6 yr^{-1}. The transmission parameter β was fixed at 2 yr^{-1} for fast-living species and varied for slow-living species such that $R_{0,\text{parasite,fast}} = R_{0,\text{parasite,slow}}$. The other parameters were $s = 1$ and $\gamma = 0.4$ yr^{-1}. We also varied the strength of density-dependence s between 0.1 and 1 and γ between 0.1 and 4 and the qualitative results were unaffected (not shown). The color indicates the magnitude of population depression, gray lines and numbers give specific contours of population depression, and the black line indicates where $R_{0,\text{parasite},.} = 1$, to the left of which the parasite could not invade the host population. (c,d) Same as (a,b), except parasite prevalence is plotted for the two life-history strategies. See the main text for details on parameter names.

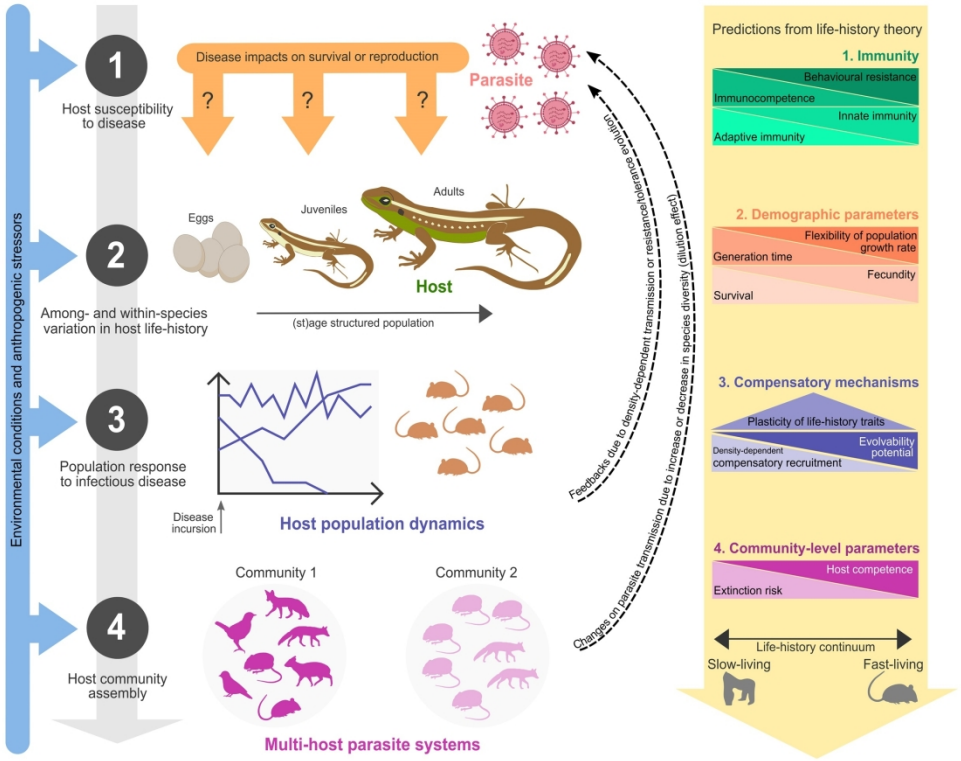


Figure 1

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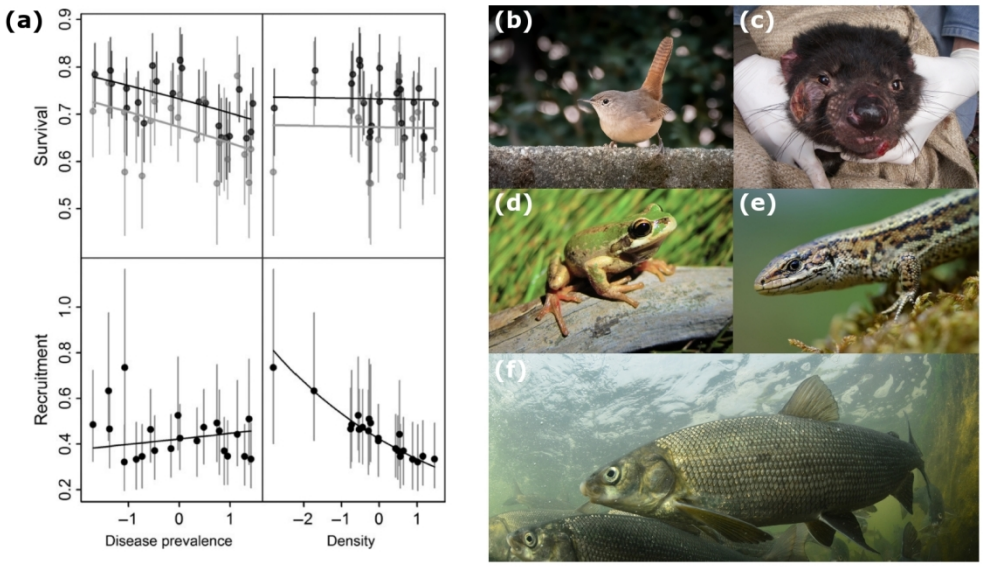

Figure 2

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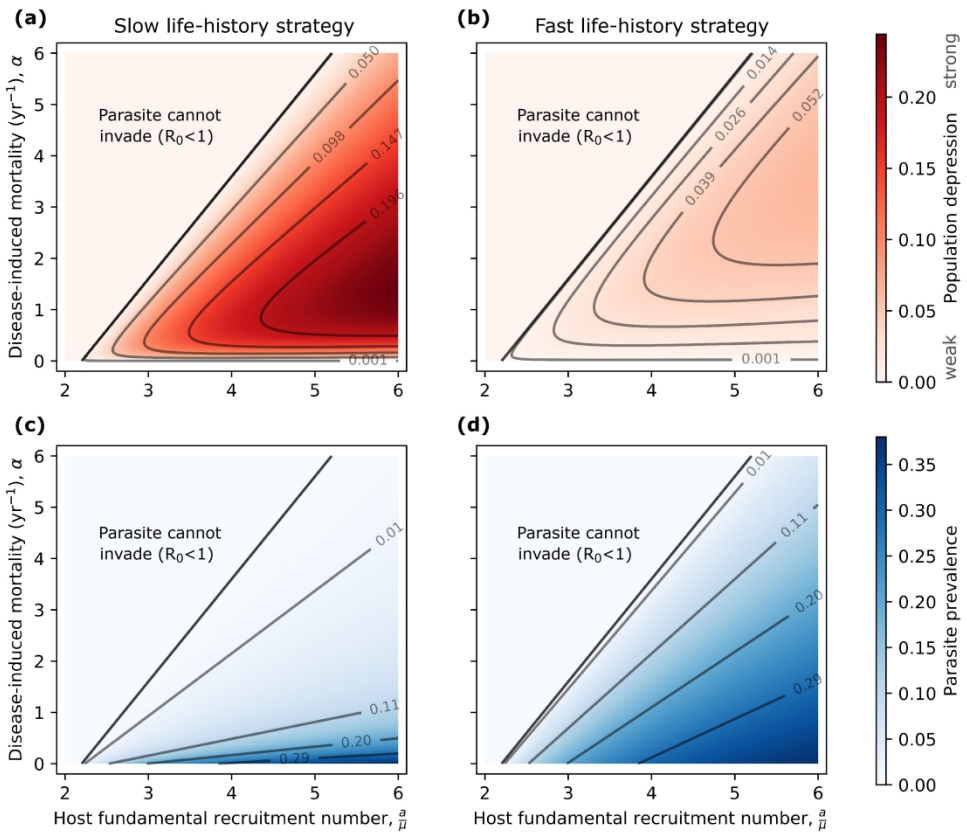

Figure 3

842x718mm (96 x 96 DPI)