Trends in Parasitology

CellPress
REVIEWS

Review

Host Age Effects in Invertebrates: Epidemiological, Ecological, and Evolutionary Implications

Frida Ben-Ami [1,*]

In most species, variation in age among individuals is the strongest and most visible form of phenotypic variation. Individual-level age effects on disease traits, caused by differences in the age at exposure of the host or its parents, have been widely documented in invertebrates. They can influence diverse traits, such as host susceptibility, virulence, parasite reproduction and further transmission, and may cascade to the population level, influencing disease prevalence and within-host competition. Here, I summarize what is known about the relationship between individual-level age/stage effects and infectious disease in invertebrates. I also attempt to link age effects to the theory of aging (senescence), and highlight the importance of population age structure to disease epidemiology and evolution. I conclude by identifying gaps in our understanding of individual- and population-level age effects in invertebrates. As the age structure of populations varies across space and time, age effects have strong epidemiological, ecological, and evolutionary implications for explaining variation in infectious diseases of invertebrates.

Highlights

The age at exposure of a host or its parents can influence disease traits, such as host susceptibility, virulence, parasite reproduction, and further transmission.

Individual-level age effects have been widely documented in a variety of invertebrates, including insects and mollusks.

Stage effects – those arising from the life stage of an individual – differ from age effects, because different stages may differ profoundly in their ecology, physiology, and life history, and thus disease exposure risk.

Individual-level age effects may cascade to the population level, influencing disease prevalence and the outcome of within-host competition.

Differences in age structure across space and time can cause variation within populations over time and among populations.

Age Matters

Parasitic diseases are ubiquitous in that they can affect almost any aspect of life. They influence host populations and entire communities, up to the point of driving local host populations to extinction. A major challenge of **infectious disease epidemiology** (see Glossary) and evolutionary ecology is to explain why and when epidemics will emerge, how big an outbreak will be, and what are its evolutionary consequences. Comparative epidemiological studies have identified a number of key determinants of epidemics, among them a high proportion of susceptible hosts, a high **force of infection** [1,2], the genetic structure of host and parasite populations, virulence, as well as environmental and spatiotemporal variation [3–6]. A further factor pertinent to this list is the variation in disease susceptibility and expression among hosts of different age or life stage (e.g., insect larvae) [7]. Given that many host populations show tremendous variation in **demography**, that is, the **age structure** or **stage structure** across space and time (sometimes seasonal), age effects can strongly influence disease dynamics and spread. Age and stage are essential components of epidemiological analysis, but have been largely overlooked in studies of evolutionary ecology of invertebrates [8,9]. While some aspects of host demography (e.g., host density and its spatial distribution, sex ratios) have received considerable attention by both theoreticians and empiricists, host age structure is usually considered an intrinsic property of the population [10]. A better understanding of the interplay among the epidemiology, ecology, and demography of host and parasite populations could thus help explain the distributions of disease, strengthen epidemiological predictions, and improve timely responses to epidemics.

[1]School of Zoology, George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel

*Correspondence:
frida@tauex.tau.ac.il (F. Ben-Ami).

Individual variation in age ranks among the most prominent aspects of phenotypic variation within a population, and populations may vary strongly in the distribution of age classes across space and time [11]. In humans and other vertebrates, phenomena relating host age to infectious disease biology are well known: childhood diseases (e.g., rubella, mumps, polio, measles), **herd immunity** (via **herd effect**), high disease-associated child mortality (e.g., malaria), and diseases with a high risk for the elderly (e.g., pneumonia) are textbook examples. However, we know little about the interactions between age-related susceptibility and virulence of disease and the age structure of the host population, and the impact of host age structure on the spread of infectious diseases. Particularly in invertebrates, age effects on disease traits have only recently been investigated [12,13], despite their importance in diverse areas, such as apiculture, vector biology, maintenance of biodiversity, and ecosystem functioning. Invertebrates are also important as the first host of diseases with complex life cycles (Figure 1). In this review, I begin by describing the peculiarities of studying age effects in invertebrates, followed by a summary of what is known about the relationship between individual-level age and stage effects and infectious disease. Thereafter, I attempt to link age effects to the theory of aging (senescence), and population age structure to disease epidemiology and evolution. My aim is to understand how individual-level effects of host age cascade to population-level effects. At times, when discussing ways to examine and assess these effects, I refer to studies of age effects in humans, for the simple reason that such effects have rarely been examined in invertebrates, be it empirically or theoretically.

Why Study Age Effects in Invertebrates?

There are several important differences between vertebrates and invertebrates when it comes to understanding disease dynamics and age effects. In invertebrates, many infections cannot be cleared after the parasite has penetrated the host and begun to develop, meaning that they are **chronic**, while vertebrates are often able to clear infections. For example, infections of the freshwater snail *Biomphalaria glabrata* by the trematodes *Echinostoma caproni* and *Schistosoma mansoni* can be cleared upon penetration using humoral factors and hemocytes [14–16]. Bacterial infections of the bumblebee *Bombus terrestris* by *Pseudomonas* spp. can be cleared at low, but not high, doses within 24 h [17]. Large losses of malaria parasites, sometimes up to complete elimination, occur during the invasion of its *Anopheles* mosquito vector [18]. In *Drosophila melanogaster*, hemocytes can clear early infections via phagocytosis, encapsulation, and melanization and clotting [19,20]. However, many viral, bacterial, and protozoan parasites of invertebrates must kill their host to transmit, hence, the host cannot usually recover from infection (obligate killers [21]). This is also true with parasitic castrators [22]. It should be emphasized that there are cases of clearance late in the infection process (e.g., oral infections of RNA viruses acquired at larval stage are cleared in adult *Drosophila* [23]), but such cases seem to be rare.

Invertebrates rely mainly on innate immune defense (germline-encoded), while vertebrates have, in addition, an adaptive immune defense (based on somatic recombination and other somatic adaptations [24]). While there is considerable evidence that invertebrates possess immune memory or priming, the underlying molecular and physiological mechanisms differ largely across taxa, with many mechanisms, as well as their relation to host age, still not fully understood [25–27]. Additionally, invertebrates and vertebrates differ in the duration of their immunological memory, from a few days in some invertebrates to several decades or even the entire life in mammals [24]. Since the life span of invertebrates is usually shorter than that of vertebrates, and the optimal investment in the duration of immune memory increases with life span, short-lived invertebrates may not evolve any immunity [28,29].

Populations of invertebrates are also set apart from most vertebrates in the diversity of their age and stage structures. For example, populations of many insects are made up of age/stage

Glossary

Age polyethism: a common phenomenon in social insects whereby members of the colony exhibit different forms of behavior or perform different tasks at different ages.
Age–prevalence curve: the relationship between host age and infection prevalence.
Age structure: the age distribution of individuals in a population.
Chronic infection: a long-term, persistent infection that is not cleared by the host immune system.
Cohort: a group of individuals sharing a characteristic, such as age or developmental stage [101].
Demography: the study of characteristics of populations, such as size, density, age structure, fecundity, growth, mortality, sex ratio, and distribution [101]. In its narrow sense, demography refers to human populations, as the prefix 'demo' stems from Ancient Greek and means 'the people'.
Density-dependent prophylaxis (DDP) hypothesis: organisms use population density as a cue to the risk of becoming infected and should increase investment in resistance mechanisms as density rises [75].
Force of infection: the rate at which new infected individuals are produced. It is the product of λ (per capita rate at which susceptible individuals contract the infection) and the number of susceptible individuals.
Herd effect: the reduction of infection or disease in the unimmunized segment as a result of immunizing a proportion of the population [102].
Herd immunity: the proportion of subjects with immunity in a given population [102].
Infectious disease epidemiology: the study of the emergence, incidence, spread, and determinants of infections in populations over time.
Monoculture: cultivation or growth consisting of a single crop, plant, or organism. Often a single genotype (clone) is used.
Stage structure: the stage distribution of individuals in a population.

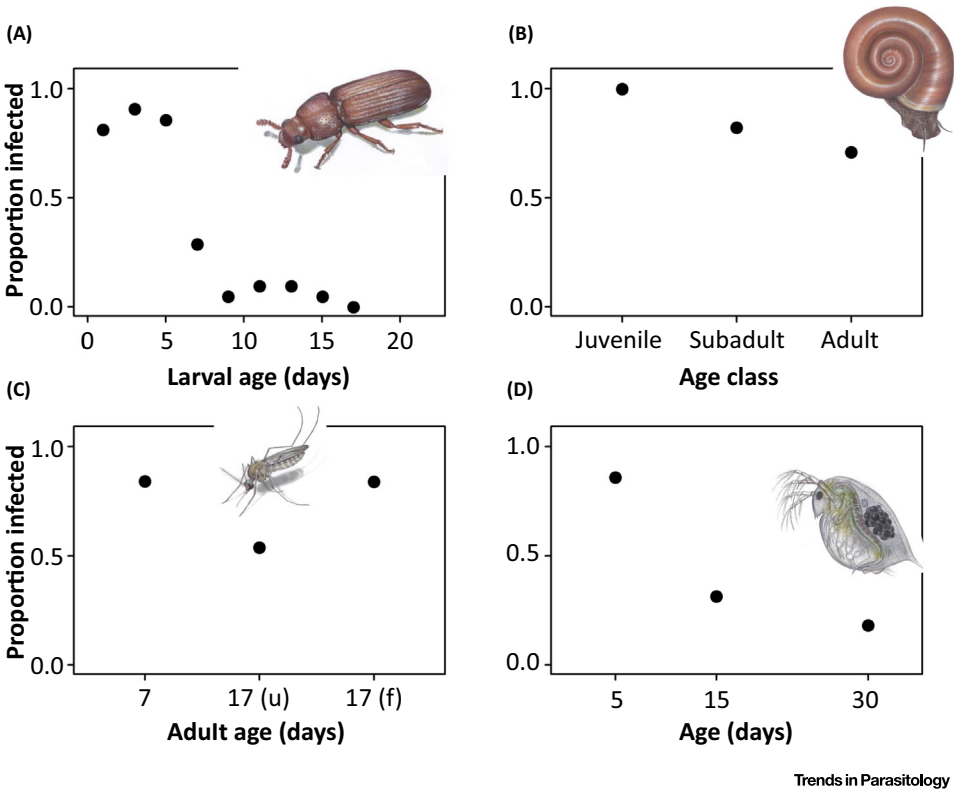

Figure 1. Examples of Host–Parasite Systems in Which Individual-level Age Effects Have Been Observed. (A) Only young larvae of the red flour beetle, *Tribolium castaneum*, were susceptible to the microsporidian parasite *Nosema whitei* [103]. (B) Infection rates of *Biomphalaria glabrata* by the trematode *Schistosoma mansoni* were higher in juveniles and subadult snails than in adult snails [39]. (C) Older, unfed (u) mosquitoes (*Culex pipiens*) were more resistant to malaria infection by *Plasmodium relictum* than were their younger counterparts, though blood-fed (f) mosquitoes were not [43]. (D) Younger *Daphnia magna* were more susceptible to the bacterial parasite *Pasteuria ramosa* than were older ones [47]. Drawings by Tuvia Kurz.

cohorts. Yet other populations have variable degrees of mixtures of age classes (e.g., species with overlapping generations). Invertebrates possess an array of developmental strategies and discrete life stages. For example, development in insects can be ametabolic (slight or no metamorphosis, only a gradual increase in size), hemimetabolic (egg, nymph, adult) or holometabolic (egg, larva, pupa, adult) [30]. In social bees and other members of the Hymenoptera, the pupa further diverges into three distinct adult roles (queen, drone, worker). Nematodes pass through an embryonic stage, four juvenile stages, and an adult stage. Many mollusks are benthic, but have planktonic veliger larva. In some species, not all life stages share the same habitat and thus are not exposed to the same parasites. Given that invertebrates represent 97% of animal diversity [26], it is important to employ a holistic approach when studying age effects in invertebrates.

Individual-level Age Effects

Interest in studying individual-level age effects in invertebrates aroused already more than half a century ago [31,32]. Studying bacterial infections of honey bees and a variety of moths infected by granulosis and nucleopolyhedrosis viruses, several authors found that older larval stages (instars) were more resistant and had lower mortality than younger ones (Table 1). In

Table 1. Studies of Individual-level Host Age Effects in Invertebrates

Invertebrate host (type, class or order for insects)	Parasite (type)	Host development strategy	Traits examined and main findings	Refs
Meloidogyne spp. (root-knot nematode, Secernentea)	*Pasteuria penetrans* (bacterium)	Holometabolic	Only the second larval stage of the root-knot nematode is susceptible to infection	[62]
Enallagma boreale (damselfly, Odonata)	Lipopolysaccharide (endotoxin found in the outer membrane of Gram-negative bacteria)	Hemimetabolic	Sexually mature individuals had lowered survivorship than newly emerged damselflies	[45]
Forficula auricularia (earwig, Dermaptera)	*Metarhizium brunneum* (fungus)	Hemimetabolic	Higher mortality of nymphs to the 2nd and 3rd instars in comparison to 4th instars and adults	[44]
Tribolium castaneum (beetle, Coleoptera)	*Nosema whitei* (microsporidium)	Holometabolic	Only young larvae were susceptible, infected larvae had a prolonged life span and did not pupate	[103]
Anoplophora glabripennis (beetle, Coleoptera)	*Metarhizium brunneum* (fungus)	Holometabolic	Young unmated males were more susceptible than mature unmated males, while there was no effect of age on susceptibility of unmated females	[104]
Glossina morsitans morsitans (fly, Diptera)	*Trypanosoma congolense* and *T. brucei* (kinetoplastid)	Holometabolic	Newly emerged flies were more susceptible than adult flies	[40]
			Prevalence of congolense-type, vivax-type and immature infections increased with age	[105]
Culex pipiens (mosquito, Diptera)	*Plasmodium relictum* (protist)	Holometabolic	Older hosts were more resistant	[43]
Acromyrmex octospinosus (ant, Hymenoptera)	Chymotrypsin (enzyme, no infection)	Eusocial, holometabolic	Older ant workers increased phenoloxidase (PO) activity relative to young ones, no differences in PO levels between solitary living and nestmate groups	[106]
Apis mellifera (honey bee, Hymenoptera)	*Paenibacillus larvae larvae* and *Bacillus larvae* (bacterium)	Eusocial, holometabolic	Older larvae were more resistant than younger ones	[32,107–109]
	Nosema ceranae (microsporidium)		Older hosts were more resistant, but had more intense infections and lower baseline immunocompetence	[42]
Bombus terrestris (bumblebee, Hymenoptera)	*Nosema bombi* (microsporidian)	Eusocial, holometabolic	2-day-old bees were twice as susceptible as their 10-day-old sisters	[41]
Heliothis zea, *Heliothis virescens* (moth, Lepidoptera)	Nucleopolyhedrosis (virus)	Holometabolic	Mortality of young larvae was higher than larvae approaching pupation	[31,110]
Hyphantria cunea (moth, Lepidoptera)	Granulosis and nucleopolyhedrosis (virus)	Holometabolic	Older larvae were more resistant and had lower mortality than younger ones	[111]
Laspeyresia pomonella (moth, Lepidoptera)	Granulosis (virus)	Holometabolic	Fifth-instar larvae were resistant to a wider range of virus dosages than first-instar larvae	[112]
Mamestra brassicae (moth, Lepidoptera)	Nucleopolyhedrosis (virus)	Holometabolic	Older larvae were more resistant than younger ones, and suffered little mortality even at high doses	[113]
Mamestra configurata (moth, Lepidoptera)	Nucleopolyhedrosis (virus)	Holometabolic	Older larvae were more resistant and had lower mortality than younger ones	[114]

Table 1. (continued)

Invertebrate host (type, class or order for insects)	Parasite (type)	Host development strategy	Traits examined and main findings	Refs
Spodoptera exigua (moth, Lepidoptera)	Nucleopolyhedrosis (virus)	Holometabolic	Older larvae were more resistant than younger ones	[115]
Orgyia pseudotsugata (moth, Lepidoptera)	Nucleopolyhedrosis (virus)	Holometabolic	Late instars are more infectious than early instars; transmission to healthy early instars decreases with increasing patchiness of infected hosts, but transmission to healthy late instars is unaffected by patchiness	[56]
Plodia interpunctella (moth, Lepidoptera)	Granulosis (virus)	Holometabolic	Older larvae had lower mortality than younger ones	[116]
Helicoverpa armigera (moth, Lepidoptera)	Lipopolysaccharide (endotoxin found in the outer membrane of Gram-negative bacteria)	Holometabolic	Age-dependent trade-off between juvenile immune function and adult male (but not female) reproductive investment	[117]
Daphnia magna (water flea, Branchiopoda)	*Pasteuria ramosa* (bacterium)	Direct development	Younger hosts were more susceptible, older hosts were more resistant	[46,47]
			Offspring born to young mothers were more susceptible and smaller than those born to older mothers	[51,52]
			Increased mortality of young males, but no age-dependent mortality of females	[48]
			Within-host parasite competition in young, multiply-exposed hosts was weak, allowing coexistence and transmission of both parasite clones, whereas in older, multiply-exposed hosts, competitive exclusion was observed	[49]
Biomphalaria glabrata (freshwater snail, Gastropoda)	*Schistosoma mansoni* (trematode)	Direct development	Host susceptibility was more negatively correlated with snail size rather than snail age	[33,35]
			Infection rates and intensity were higher for subadult snails than for juvenile and adult snails; atrial amebocytic accumulations, typically appearing at onset of egg-laying, result in transient adult nonsusceptibility	[38,39]
Stagnicola elodes, *Lymnaea stagnalis*, *Gyraulus parvus*, *Gyraulus circumstriatus*, *Promenetus exacuous*, *Armiger crista* (freshwater snails, Gastropoda)	*Cyclocoelum* spp. (trematode)	Direct development	In six highly susceptible species, snail size was negatively related to susceptibility; no such relation was found in three species with low susceptibility	[34]
Stagnicola elrodi (freshwater snail, Gastropoda)	*Trichobilharzia ocellata* (trematode)	Direct development	Age/size did not affect host susceptibility, but infection intensity was highest in adult snails	[36]
Biomphalaria alexandrina (freshwater snail, Gastropoda)	*Schistosoma mansoni* (trematode)	Direct development	Younger snails were more susceptible, with the genetic background of their parents (resistant vs. susceptible) influencing infection rates	[37]

the early 1980s, research included freshwater snails and their castrating trematodes, particularly those of veterinary and medical importance [33]. Here, diverse patterns were described. For example, studies on several gastropods reported size (a proxy of age) to be negatively correlated with susceptibility [33–35], whereas in other studies the inverse or no relationship was found [36,37]. Furthermore, in *B. glabrata* infected by *S. mansoni*, infection intensity was higher for subadult snails than for juvenile and adult snails, while in *Stagnicola elrodi* infected by *Trichobilharzia ocellata*, infection intensity was highest in adult snails [36,38,39].

The past decade has seen a renewed interest in studying individual-level age effects, and a corresponding increase in the number of taxa being investigated and traits being measured. Mostly consistent with earlier studies, older (adult) hosts were found to be more resistant to infection than younger ones in studies involving tsetse flies [40], bumblebees [41], western honey bees [42], and common house mosquitoes [43]. Age-dependent mortality, similar to that observed in moths, was also found in common earwigs, where nymphs to the second and third instars suffered from higher parasite-induced mortality in comparison to fourth instars and adults [44], but not in damselflies, where sexually mature adults had lowered survivorship than newly emerged ones [45]. The only crustacean system so far investigated is *Daphnia magna* and its bacterial parasite *Pasteuria ramosa*. Young *Daphnia* were found to be more susceptible to infection than older individuals [46,47]. However, increased mortality was only associated with young infected males, not with infected females [47,48]. When hosts were exposed to two parasite clones together, young *Daphnia* allowed coexistence and transmission of both parasite clones, whereas in older individuals competitive exclusion was observed [49].

Transgenerational-level age effects, whereby the age at which parents produced offspring affects their offspring's susceptibility, are a further form of individual-level age effects. These effects, which constitute a special case of transgenerational immune priming [50], have rarely been examined. In the *Daphnia–Pasteuria* system, offspring born to young mothers were more susceptible and smaller than those born to older mothers [51–53]. Given the costs associated with 'early parenting', the maintenance and evolution of transgenerational-level age effects is dependent on the predictability of host and parasite environments across generations and the fitness-related costs and benefits to both parents and offspring.

Besides examples where host age determines the susceptibility to, or expression of, disease, there are many cases where age determines the exposure risk to diseases. For example, differences in foraging activity and feeding regime among hosts of different ages can result in differential exposure to parasites [54–56]. Social interactions among hosts can further influence the exposure risk [57]. Sexually transmitted diseases typically infect only the sexually active part of a population, while juveniles and old hosts may not be exposed, even though they could have become infected if exposure had occurred. Likewise, vertically transmitted parasites infect only eggs and the newborn. For example, older hosts are known to be susceptible to the cytoplasmic parasite *Wolbachia*, albeit their exposure to the parasite seems extremely rare [58].

Studies on individual-level age effects typically correct for life span, by appropriate experimental design. For example, animals of different age are exposed in the same environment and over the same time span to a standardized dose of the parasite [47]. In studies of natural (uncontrolled) populations, the age of individuals may be assessed by various proxies (e.g., body size), but age is confounded with the individual's experience. Thus, even if older individuals are less susceptible to infection than younger individuals, they may show a higher

prevalence of chronic infections in the population, because they had a longer lifetime exposure to parasites than did younger individuals. For example, a survey of the duck mussel *Anodonta anatine* in 18 lakes from northeastern Poland found that infection prevalence of trematodes was higher in older and female mussels [59]. While the authors suggest that the risk of infection increases with the amount of water processed by filter-feeding hosts (i.e., longer duration of exposure), it is not possible to distinguish between individual-level age effects and the effect of lifetime exposure.

In summary, current evidence suggests that individual-level age effects are frequently observed and may be even universal. Although there is not always a clear pattern, it seems that a decline in susceptibility with increasing age is more often observed than other age-susceptibility relationships. Furthermore, these effects can influence additional host and parasite traits, such as host mortality, within-host parasite development, and competition.

Individual-level Stage Effects

Most studies presented in the previous section tested for age effects by comparing either larvae or adults of different ages with each other (Table 1). Typically, the age classes considered in these studies occur in the same habitat, under the same environmental conditions, with similar levels of exposure to parasites and similar encounter rates of different parasite species. This is often not the case when different life stages are compared. Different stages have different life styles, often live in different habitats and ecologies, and may therefore experience different parasite exposure risks. This situation almost corresponds to having different host species, for example, terrestrial insects with aquatic larval stages. The link between stage and ecology may select for specific associations, where stage, rather than age *per se*, is the determining factor. For example, larvae of social insects live in the same ecology, but under different conditions (e.g., feeding regime, social interactions) than the pupae and the caretakers [60]. Certain waterborne microsporidian parasites of mosquitoes are only transmitted to larvae [61]. Early larval stages are usually sessile, while the adults or later larval stages are motile, for example, in the root-knot nematode, *Meloidogyne incognita*, only the second larval stage, which is free living, can be infected by its bacterial parasite *Pasteuria penetrans* [62]. The existence of such differences among stages is one of the reasons why pest control is often stage-specific [61,62]. Ultimately, studies of individual-level age effects should strive to decouple stage-specific effects before making age-specific inferences.

Host Senescence and the Evolution of Individual-level Age Effects

In contrast to our limited knowledge about the evolution of individual-level age effects, the study of senescence is deeply rooted in evolutionary research and is still actively debated [63,64]. It is generally agreed that senescence evolved because the force of selection declines with age, that is, after maturity is reached, and due to the existence of genes with pleiotropic effects on survival, such that increased survival at one age is accompanied by decreased survival at another [65,66]. Deleterious mutations that arise late in life and differences between male and female reproductive strategies (e.g., sexual selection, sexual conflict) can further contribute to the evolution of senescence [67,68]. Thus, it is a powerful concept to analyze patterns seen among adult age classes. The theory of aging predicts a decline in body function with adult age, and with regard to immune defense, a decline in resistance with increasing adult age is predicted [69]. Consistent with the prediction, young adult damselflies had higher survivorship when infected than did older adults [45]. Similarly, young adult beetles were less susceptible to infection than older adults [70]. These studies do not contradict the results presented in the section on Individual-level Age Effects, because the comparison here is between reproductive and nonreproductive adults (i.e., approaching senescence).

The theory of aging helps to explain why we see age-specific patterns in general. Thus, it seems plausible that individual-level age effects are caused by differences in the host's immunological development through age. For example, elevated juvenile susceptibility is expected to evolve over a wide range of conditions (including for invertebrates), but should be lowest when hosts have moderate life spans and an intermediate probability of reaching the adult stage [71]. However, this may not explain all of the variation, as it ignores the complexity of host–parasite interactions, insofar that age-specific effects depend on the host, the parasite, and their interactions. It is possible that the observed effects are due to parasite adaptation to the host age class they infect predominantly. For example, parasites of larval insects may not be adapted to cope with the immune system of adult hosts. The parasite may either phenotypically adjust its exploitation strategy to a specific host age class or evolve a level of host exploitation that takes into account the average host age it encounters [47]. This hypothesis still requires differences in parasite performance among hosts of different age, but parasite adaptation may exaggerate these differences.

In species with distinct life stages, where often a stage-specific ecological difference in the habitat is seen and where different stages may have strikingly different body architecture, physiology, behavior, resource demands and food consumption, a single host exploitation strategy may not be optimal for the parasite. Even in species with direct development, but with a seasonal, strongly changing age structure and variable forces of infection over time, it is likely that the average age at infection changes seasonally. This will undoubtedly have an influence on the evolution of individual-level age effects. In summary, we know little about the evolution of individual-level age effects, in both vertebrates and invertebrates. The epidemiological feedbacks inherent in the evolutionary ecology of host–parasite interactions make this a difficult topic, and it is questionable whether it will be possible to reach general conclusions.

Population-level Age Effects

With individual-level age effects being omnipresent, host populations with different age structures will experience epidemics by infectious diseases differently (e.g., a different proportion of susceptible hosts or force of infection). In the absence of parasites, variation in age structure is often observed with strong temporal changes (e.g., more juveniles following the breeding season), developing age cohorts or mixtures of age classes with relative abundances varying over time. Such differences in age structure might interact with individual-level age effects and influence disease expression, outbreak dynamics and spread. For example, in cohorts of same-age individuals, if a certain age is particularly sensitive to attack by parasites, the disease may spread rapidly when the cohort reaches this age. Thus, same-age cohorts may be similar to **monocultures** in their sensitivity to infectious diseases. In contrast, in mixed-age populations disease would spread slower, or might not even reach the necessary force of infection to spread. In the case of human diseases, cohort effects have been widely documented. For example, yearly measles epidemics are often triggered by the arrival of immunologically-naïve same-age cohorts of children in primary schools [72,73]. Even in a population that was substantially immune following the 2009 swine-origin influenza A(H1N1) pandemic, the addition of a few cohorts of susceptible children might have been sufficient to tip the epidemic threshold, enabling the resurgence of the same influenza strain 4 years later [74]. In invertebrates, empirical evidence for population-level age effects that influence disease dynamics are scarce [55,56]. For example, a field experiment using populations of the tussock moth, *Orgyia pseudotsugata*, showed that late instars were both more infectious and more likely to become infected by nucleopolyhedrosis virus than were early instars, even though laboratory experiments showed that the physiological resistance of larvae increases with age [56]. The discrepancy with laboratory results has been attributed to the higher mobility of late instars, which puts

them at greater risk of contracting an infectious dose [56]. In an *in situ* (lake enclosure) experiment using *Daphnia dentifera*, fungal epidemics resulted in less stable host dynamics with more synchronized juveniles and adults (i.e., juveniles and adults cycle in-phase) [55]. Such dynamics apparently occurred because competitively superior adults tend to depress their foraging rates more than juveniles when exposed to spores, and infected adults tend to reduce their foraging rates even further [55].

In many populations of invertebrates, the potential threat posed to hosts by their parasites changes as a function of population density (i.e., density-dependent transmission [1,2]). Changes in host density are often accompanied by changes in the age structure of the population [68], and they are widespread in social insects and invertebrates living in dense aggregation [57]. As host density rises, the risk of infection also rises, and thus host populations are expected to experience elevated levels of parasitism and more frequent epidemics [1,2]. Consequently, investment in disease resistance mechanisms will increase, because high density is predicted to favor hosts that increase resource allocation in immune defense [**density-dependent prophylaxis (DDP) hypothesis** [75]]. A major assumption of the DDP hypothesis is that potential hosts can alter their phenotype (e.g., physiology, behavior, development, morphology, feeding ecology) in response to cues associated with population density [75]. If hosts of different stage or age differ in their phenotypic response to high density, then the age structure of the host population could influence disease dynamics. For example, in Mormon crickets subjected to crowding, the immune response of young adults was weaker than that of older adults nearing reproductive maturity [76]. Such differences in the phenotypic response could affect the time delay between the change in population density and the subsequent phenotypic response, which in return can determine whether DDP stabilizes or destabilizes disease dynamics [77].

While empirical support for the DDP hypothesis has been found in several invertebrate species, it has been suggested that connectivity within and between host populations may be a more appropriate population parameter to use when considering disease-associated risks in social insects [78]. This is because parasite transmission in social insects can occur both from mother to daughter colony and between neighboring colonies. Furthermore, besides having individual behavioral and physiological immune defenses, social insects have evolved collective immune defenses (social immunity [79]). These defenses are a consequence of cooperation among group members to combat the increased risk of disease transmission that is inherent in sociality and group living [79]. Although social insects feature an array of age/stage classes, including **age polyethism**, the influence of age structure on disease spread in colonies of social insects has rarely been studied. For example, age polyethism in a honeybee colony has been shown to impede the spread of infection within the colony, thereby suggesting that disturbance in the natural age structure may increase the severity of an infection [80]. These results highlight the importance of age effects on the population level, but emphasize the need to carry out more population-level experiments with varying age structures.

To better understand population-level effects in invertebrates, several authors developed epidemiological models to explain **age–prevalence curves** derived from field and laboratory datasets. For example, Anderson and Crombie analyzed the results of experimental studies of *S. mansoni* infections in laboratory populations of *B. glabrata* of varying sizes and age structures [81]. They showed that the net force of infection is linearly dependent on the rate at which miracidia are introduced into the host population, and that, for individual snails, the per capita force of infection is related to snail age and size [81]. However, such a relationship between the force of infection and snail age was not found by Woolhouse, who attempted to

explain the decline in prevalence among older snails in natural populations of *Bulinus globusus* infected by *Schistosoma haematobium* in Zimbabwe [82]. He suggested instead that seasonal variation in the force of infection and snail fecundity are responsible for this decline [82]. Inconclusive evidence of the relationship between the force of infection and age was also found in *Trypanosoma* infections of the tsetse fly *Glossina pallidipes*. While age–prevalence data of *Trypanosoma vivax*-type infections can be explained by an epidemiological model which incorporates only a constant rate of infection, *T. congolense*-type infections can only be explained by a model which assumes a declining rate of infection with age and that the fraction of susceptible flies varies among sites [83]. Taken together, these results indicate that age effects can have – at least in some systems – a profound influence on disease epidemiology.

The difficulties in understanding age effects are demonstrated when asking whether human childhood diseases are a consequence of higher innate resistance of adults or because of higher acquired resistance of adults due to exposure during childhood. With both herd immunity present and higher innate susceptibility in young age, children have a higher chance of contracting disease, hence the term 'childhood disease'. For many human childhood diseases, both factors seem to contribute to the phenomenon [1]. In invertebrates, however, the term 'childhood disease' would be misleading, that is, individuals that became infected as juveniles will not necessarily acquire resistance as adults [84,85]. Instead, chronic diseases will accumulate over their life span, resulting in higher prevalence in older animals, unless this is counteracted by disease-induced mortality. Thus, we may see very different age–prevalence curves in invertebrates, whereby chronic diseases that infect only juveniles might still have a high prevalence in adults (Box 1).

Towards a Unified Age Structure Theory for Disease

Age-structured populations are of interest to both evolutionary geneticists and epidemiologists. In the absence of ecological interactions (e.g., competition, predation, parasitism), an age-structured population is expected to remain in genetic equilibrium only if it is demographically stable, that is, if the population is stationary in size or growing at a constant rate, and has a constant age structure [68]. It follows that populations subject to ecological interactions such as parasitism may show fluctuations in their composition at loci undergoing selection [68]. Parasite-driven demographic shifts, which can tilt the age structure of the population in favor or against a certain age class, will thus influence relative genotypic fitnesses, and thereby alter the population's genetic composition [68]. Surprisingly, our knowledge of the consequences of host age effects and host age structure on the evolution of disease, particularly in invertebrates, is limited. Epidemiological models of disease dynamics in humans have long recognized the importance of incorporating host age effects and host age structure [86–89]. The models, which rely on herd immunity, assisted in the design of effective control programs based on mass immunization of a disease-dependent proportion of each cohort of the population at a certain age [1,86,90]. Insights from these models have also been applied in vaccination programs of invertebrate populations, primarily in the aquaculture industry [91,92]. However, epidemiological models of age-structured populations of invertebrates are practically inexistent. For example, Iritani *et al*. [93] examined the evolutionary outcomes of stage-specific virulence using a stage-structured epidemiological model. Their findings suggest that higher juvenile virulence will be selected either when transmission is assortative within age classes and maturation is slow, or if transmission is disassortative (occurring between age classes) and maturation is relatively fast [93]. These results emphasize the need to incorporate realistic invertebrate-specific features into epidemiological and evolutionary models, such as social and stage structure, host life span, and the duration of immune memory, and host clearance versus chronic diseases.

Box 1. Age–Prevalence Curves for Different Disease Scenarios

An age–prevalence curve shows the proportion of individuals of a certain age (or stage) that are infected. Figure I shows three age–prevalence curves for a disease. Panel A corresponds to a population where prevalence peaks in juveniles, but occurs in adults of all ages. The disease can be either chronic or nonchronic (i.e., the parasite can clear infection), and from the curve alone it is not possible to differentiate between the two. Panel B shows a pattern seen for childhood diseases. Prevalence peaks in juveniles, and adults are hardly infected. Such a curve may result from a disease that kills the host and/or a disease that is cleared by the host. In panel C, a monotonic increase in prevalence is seen. This scenario corresponds to a population with a chronic disease (no clearance), and where the parasite affects host survival. With a high force of infection, prevalence can be high already in juveniles, but with a lower force of infection the curve plateaus off. It should be emphasized that sudden high-impact events, such as the arrival of a large cohort of young individuals or the death of a specific age class, can hinder the interpretation of the curve. To avoid such misinterpretations, it may be necessary to prepare several age–prevalence curves from different sampling points.

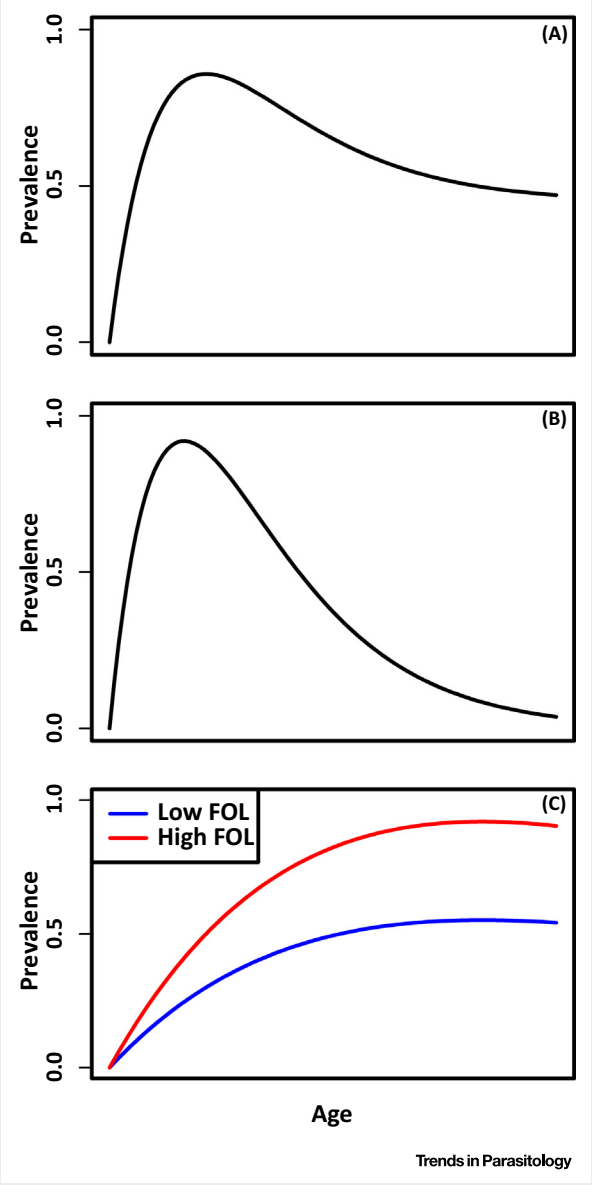

Figure I. Three Possible Age–prevalence Curves for a Disease in Which All Hosts Are Equally Exposed to the Disease, But Young Hosts Are More Susceptible Than Older Hosts. (A) Prevalence peaks in juveniles, but occurs in adults of all ages. (B) Prevalence peaks in juveniles, and adults are hardly infected, that is, childhood disease. (C) Monotonic increase in prevalence. Abbreviation: FOI, force of infection.

An alternative approach for studying population-level age effects stems from models of consumer-resource interactions in stage-structured populations. Such models are especially suited for modeling the relationship between individual life history components and populations dynamics, where there are big differences in feeding, growth, reproduction, and mortality among individuals of different stages, but little difference among individuals within the same stage [94]. Without disease, theory on single-species dynamics suggests that competition for shared resources between juvenile and adult consumers can lead to population fluctuations in natural systems and feedback on demographic rates [95]. Parasitism can further destabilize these stage-structured interactions, because parasites may potentially reduce the asymmetry of competition between life stages by, for example, inflicting stronger virulent effects on otherwise competitively dominant adults [55,96–98]. Castrating parasites in particular are known to impact host populations strongly [1,99]. Faster parasitic castration of young hosts (e.g., trematodes) will, by contrast, slow down juvenile production and thus increase the frequency of low-amplitude cycles at the expense of fewer high-amplitude cycles [47]. This is in part because castration happens with a time delay after infection and therefore affects virulence: hosts castrated as adults will still produce offspring before reproduction ceases, while juveniles will likely never produce any offspring. In summary, mathematical models are a powerful way forward in understanding complex disease dynamics in systems that include individual- and population-level effects of host age.

Host Age at Exposure in Experiments

Host age at exposure is rarely taken into consideration in studies of host–parasite interactions (e.g., infection assays) and experimental evolution. In humans, we know a great deal about age differences in susceptibility and morbidity, because age is an easy and commonly collected statistic in clinical studies. In contrast, in experiments using invertebrates, host age is usually controlled for, and experimental hosts are chosen to be of the age when the infection treatment is most likely to succeed [100]. This practice reduces unwanted variation caused by age effects among hosts. Such experimental designs nevertheless, assume that the results are representative for the entire population, disregarding their age structure. With strong individual-level age effects often observed (Figure 1), this assumption may introduce a profound bias in the experimental results and may lead to their misinterpretation.

Concluding Remarks and Future Perspectives

Individual-level age effects are possibly universal, but differ in shape and direction, with a tendency that lower susceptibility is observed in older hosts (see Outstanding Questions). However, we still lack knowledge on how individual-level age effects influence different steps of the infection process, including within-host competition among parasite strains/species and between-host parasite transmission. Our understanding on how to study and quantify individual-level age effects in natural populations is also limited. A special case of individual-level age effects are stage effects. They differ strongly from age effects, because different stages often live in different environmental conditions and may differ profoundly in body architecture, physiology, behavior, resource demands, and food consumption, and thus disease exposure risk. Individual-level age effects are so far not well explained by evolutionary reasoning. We do not know if individual-level age and stage effects are a consequence of parasite adaptation to the host age class it infects predominantly, and if a targeted host age class can evolve reduced susceptibility in return. Profound differences in age structure across space and time can cause variation within populations over time and among populations. Yet identifying age-related aspects of disease in age- and stage-structured populations and deriving parameters from experimental work in order to incorporate them into models of disease dynamics can be challenging. Ultimately, evolutionary models related to development, senescence, life history, and immune-related trade-offs may be helpful in explaining age effects.

Outstanding Questions

Individual-level Age Effects:

- Are individual-level age effects universal?
- How do individual-level age effects influence different steps of the infection process, from encounter to within-host parasite development?
- How do individual-level age effects influence multiple infections by several parasite strains or species?
- How do individual-level age effects influence parasite transmission?
- Do the parasite's life history and transmission mode influence individual-level age effects?
- Can individual-level age effects be seen in invertebrates collected from natural populations? How can we quantify these effects?
- Are individual-level age effects a consequence of parasite adaptation to the host age class it infects predominantly? Can a targeted host age class evolve reduced susceptibility in return?
- Can we explain why susceptibility seems to decline with age in many systems?
- How do we measure the costs and benefits associated with transgenerational-level age effects, whilst considering the predictability of host and parasite environments across generations?
- How do individual-level age effects influence senescence in different age classes (e.g., newly born, juveniles, early adulthood)?

Population-level Age Effects:

- How do we identify age-related aspects of disease in stage-structured populations, where age and environmental conditions are strongly confounded?
- How do differences in age-specific infection rates influence age–prevalence curves for chronic and nonchronic diseases?
- Which parameters should be derived from experimental work in order to incorporate host age structure into models of disease dynamics?
- How do differences in the age or stage structure of a population influence density-dependent prophylaxis?

Acknowledgments

I am grateful to P. Kong and three anonymous reviewers for valuable comments on the manuscript. This work was supported by grant #938/16 from the Israel Science Foundation (ISF).

References

1. Anderson, R.M. and May, R.M. (1991) *Infectious Diseases of Humans: Dynamics and Control,* Oxford University Press
2. Anderson, R.M. and May, R.M. (1979) Population biology of infectious diseases: part I. *Nature* 280, 361–367
3. Hill, A.V.S. (2012) Evolution, revolution and heresy in the genetics of infectious disease susceptibility. *Philos. Trans. R. Soc. B* 367, 840–849
4. Cressler, C.E. *et al.* (2016) The adaptive evolution of virulence: a review of theoretical predictions and empirical tests. *Parasitology* 143, 915–930
5. Lewis, F.I. *et al.* (2014) Dynamics of the force of infection: insights from *Echinococcus multilocularis* Infection in foxes. *PLoS Negl. Trop. Dis.* 8, e2731
6. Papkou, A. *et al.* (2016) Host–parasite coevolution: why changing population size matters. *Zoology* 119, 330–338
7. Geard, N. *et al.* (2015) The effects of demographic change on disease transmission and vaccine impact in a household structured population. *Epidemics* 13, 56–64
8. Benton, T.G. *et al.* (2006) Complex population dynamics and complex causation: devils, details and demography. *Proc. R. Soc. B* 273, 1173–1181
9. Woolhouse, M.E. (2011) How to make predictions about future infectious disease risks. *Philos. Trans. R. Soc. B* 366, 2045–2054
10. Metcalf, C.J.E. and Pavard, S. (2007) Why evolutionary biologists should be demographers. *Trends Ecol. Evol.* 22, 205–212
11. Benton, T.G. (2012) Individual variation and population dynamics: lessons from a simple system. *Philos. Trans. R. Soc. B* 367, 200–210
12. Felizardo, A.A. *et al.* (2018) Could age and aging change the host response to systemic parasitic infections? A systematic review of preclinical evidence. *Exp. Gerontol.* 104, 17–27
13. Müller, L. *et al.* (2013) Immunosenescence in vertebrates and invertebrates. *Immun. Ageing* 10, 12
14. Coustau, C. *et al.* (2015) Advances in gastropod immunity from the study of the interaction between the snail *Biomphalaria glabrata* and its parasites: a review of research progress over the last decade. *Fish. Shellfish Immunol.* 46, 5–16
15. Allan, E.R.O. *et al.* (2018) Clearance of schistosome parasites by resistant genotypes at a single genomic region in *Biomphalaria glabrata* snails involves cellular components of the hemolymph. *Int. J. Parasitol.* 48, 387–393
16. Pila, E.A. *et al.* (2017) Schistosomiasis from a snail's perspective: advances in snail immunity. *Trends Parasitol.* 33, 845–857
17. Sadd, B.M. and Schmid-Hempel, P. (2006) Insect immunity shows specificity in protection upon secondary pathogen exposure. *Curr. Biol.* 16, 1206–1210
18. Osta, M.A. *et al.* (2004) Effects of mosquito genes on *Plasmodium* development. *Science* 303, 2030–2032
19. Buchon, N. *et al.* (2014) Immunity in *Drosophila melanogaster* – from microbial recognition to whole-organism physiology. *Nat. Rev. Immunol.* 14, 796–810
20. Pan, G. *et al.* (2018) Invertebrate host responses to microsporidia infections. *Dev. Comp. Immunol.* 83, 104–113
21. Ebert, D. and Weisser, W.W. (1997) Optimal killing for obligate killers: the evolution of life histories and virulence of semelparous parasites. *Proc. R. Soc. B* 264, 985–991
22. Lafferty, K.D. and Kuris, A.M. (2009) Parasitic castration: the evolution and ecology of body snatchers. *Trends Parasitol.* 25, 564–572
23. Mondotte, J.A. *et al.* (2018) Immune priming and clearance of orally acquired RNA viruses in *Drosophila*. *Nat. Microbiol.* 3, 1394–1403
24. Pradeu, T. and Du Pasquier, L. (2018) Immunological memory: what's in a name. *Immunol. Rev.* 283, 7–20
25. Milutinović, B. and Kurtz, J. (2016) Immune memory in invertebrates. *Semin. Immunol.* 28, 328–342
26. Melillo, D. *et al.* (2018) Innate immune memory in invertebrate metazoans: a critical appraisal. *Front. Immunol.* 9, 1915
27. Nyholm, S.V. and Graf, J. (2012) Knowing your friends: invertebrate innate immunity fosters beneficial bacterial symbioses. *Nat. Rev. Microbiol.* 10, 815–827
28. Little, T.J. and Kraaijeveld, A.R. (2004) Ecological and evolutionary implications of immunological priming in invertebrates. *Trends Parasitol.* 19, 58–60
29. Miller, M.R. *et al.* (2007) Host life span and the evolution of resistance characteristics. *Evolution* 61, 2–14
30. McGavin, G.C. (2001) *Essential Entomology: An Order-by-Order Introduction,* Oxford University Press
31. Ignoffo, C.M. (1966) Effects of age on mortality of *Heliothis zera* and *Heliothis virescens* larvae exposed to a nuclear-polyhedrosis virus. *J. Invertebr. Pathol.* 8, 279–282
32. Woodrow, A.W. and Gochnauer, T.A. (1941) Susceptibility of honey bee larvae to American foulbrood. *Glean. Bee Cult.* 69, 148–151 190
33. Anderson, R.M. *et al.* (1982) Transmission of *Schistosoma mansoni* from man to snail: experimental studies of miracidial survival and infectivity in relation to larval age, water temperature, host size and host age. *Parasitology* 85, 339–360
34. McKindsey, C.W. and McLaughlin, J.D. (1995) Species- and size-specific infection of snails by *Cyclocoelum mutabile* (Digenea: Cyclocoelidae). *J. Parasitol.* 8, 513–519
35. Niemann, G.M. and Lewis, F.A. (1990) *Schistosoma mansoni*: influence of *Biomphalaria glabrata* size on susceptibility to infection and resultant cercarial production. *Exp. Parasitol.* 70, 286–292
36. Graham, A.L. (2003) Effects of snail size and age on the prevalence and intensity of avian schistosome infection: relating laboratory to field studies. *J. Parasitol.* 89, 458–463
37. Abou-El-Naga, I.F. *et al.* (2015) Impact of the age of *Biomphalaria alexandrina* snails on *Schistosoma mansoni* transmission: modulation of the genetic outcome and the internal defence system of the snail. *Mem. Inst. Oswaldo Cruz* 110, 585–595
38. Richards, C.S. and Minchella, D.J. (1987) Transient non-susceptibility to *Schistosoma mansoni* associated with atrial amoebocytic accumulations in the snail host *Biomphalaria glabrata*. *Parasitology* 95, 499–505
39. Théron, A. *et al.* (1998) Host choice by larval parasites: a study of *Biomphalaria glabrata* snails and *Schistosoma mansoni* miracidia related to host size. *Parasitol. Res.* 84, 727–732
40. Kubi, C. *et al.* (2006) The effect of starvation on the susceptibility of teneral and non-teneral tsetse flies to trypanosome infection. *Med. Vet. Entomol.* 20, 388–392
41. Rutrecht, S.T. *et al.* (2007) Horizontal transmission success of *Nosema bombi* to its adult bumble bee hosts: effects of dosage, spore source and host age. *Parasitology* 134, 1719–1726
42. Roberts, K.E. and Hughes, W.O.H. (2014) Immunosenescence and resistance to parasite infection in the honey bee, *Apis mellifera*. *J. Invertebr. Pathol.* 121, 1–6
43. Pigeault, R. *et al.* (2015) Mosquito age and avian malaria infection. *Malaria J.* 14, 383
44. Vogelweith, F. *et al.* (2017) Age, pathogen exposure, but not maternal care shape offspring immunity in an insect with facultative family life. *BMC Evol. Biol.* 17, 69

45. Robb, T. and Forbes, M.R. (2006) Age-dependent induction of immunity and subsequent survival costs in males and females of a temperate damselfly. *BMC Ecol.* 6, 15
46. Garbutt, J.S. *et al.* (2014) The development of pathogen resistance in *Daphnia magna*: implications for disease spread in age-structured populations. *J. Exp. Biol.* 217, 3929–3934
47. Izhar, R. and Ben-Ami, F. (2015) Host age modulates parasite infectivity, virulence and reproduction. *J. Anim. Ecol.* 84, 1018–1028
48. Gipson, S.A.Y. and Hall, M.D. (2018) Interactions between host sex and age of exposure modify the virulence-transmission trade-off. *J. Evol. Biol.* 31, 428–437
49. Izhar, R. *et al.* (2015) Host age modulates within-host parasite competition. *Biol. Lett.* 11, 20150131
50. Roth, O. *et al.* (2018) Recent advances in vertebrate and invertebrate transgenerational immunity in the light of ecology and evolution. *Heredity* 121, 225–238
51. Clark, J. *et al.* (2017) Disease spread in age structured populations with maternal age effects. *Ecol. Lett.* 20, 445–451
52. Coakley, C.M. *et al.* (2018) Testing hypotheses for maternal effects in *Daphnia magna*. *J. Evol. Biol.* 31, 211–216
53. Garbutt, J.S. and Little, T.J. (2017) Bigger is better: changes in body size explain a maternal effect of food on offspring disease resistance. *Ecol. Evol.* 7, 1403–1409
54. Siva-Jothy, J.A. *et al.* (2018) Navigating infection risk during oviposition and cannibalistic foraging in a holometabolous insect. *Behav. Ecol.* 29, 1426–1435
55. Hite, J.L. *et al.* (2016) Parasites destabilize host populations by shifting stage-structured interactions. *Ecology* 97, 439–449
56. Dwyer, G. (1991) The roles of density, stage, and patchiness in the transmission of an insect virus. *Ecology* 72, 559–574
57. Schmid-Hempel, P. (1998) *Parasites in Social Insects,* Princeton University Press
58. Werren, J.H. *et al.* (2008) *Wolbachia*: master manipulators of invertebrate biology. *Nat. Rev. Microbiol.* 6, 741–751
59. Müller, T. *et al.* (2015) Factors affecting trematode infection rates in freshwater mussels. *Hydrobiologia* 742, 59–70
60. Fürst, M.A. *et al.* (2014) Disease associations between honeybees and bumblebees as a threat to wild pollinators. *Nature* 506, 364–366
61. Koella, J.C. *et al.* (2009) Microsporidians as evolution-proof agents of malaria control? *Adv. Parasitol.* 68, 315–327
62. Davies, K.G. (2009) Understanding the interaction between an obligate hyperparasitic bacterium, *Pasteuria penetrans* and its obligate plant-parasitic nematode host, *Meloidogyne* spp. *Adv. Parasitol.* 68, 211–245
63. Maklakov, A.A. *et al.* (2015) Why organisms age: evolution of senescence under positive pleiotropy? *Bioessays* 37, 802–807
64. Flatt, T. and Partridge, L. (2018) Horizons in the evolution of aging. *BMC Biol.* 16, 93
65. Williams, G.C. (1957) Pleiotropy, natural selection, and the evolution of senescence. *Evolution* 11, 398–411
66. Hamilton, W.D. (1966) The moulding of senescence by natural selection. *J. Theor. Biol.* 12, 12–45
67. Bonduriansky, R. *et al.* (2008) Sexual selection, sexual conflict and the evolution of ageing and life span. *Funct. Ecol.* 22, 443–453
68. Charlesworth, B. (1994) *Evolution in Age-Structured Populations,* Cambridge University Press
69. Simon, A.K. *et al.* (2015) Evolution of the immune system in humans from infancy to old age. *Proc. R. Soc. B* 282, 20143085
70. Khan, I. *et al.* (2016) Immunosenescence and the ability to survive bacterial infection in the red flour beetle *Tribolium castaneum*. *J. Anim. Ecol.* 85, 291–301
71. Ashby, B. and Bruns, E. (2018) The evolution of juvenile susceptibility to infectious disease. *Proc. R. Soc. B* 285, 20180844
72. Bolker, B.M. and Grenfell, B.T. (1996) Impact of vaccination on the spatial correlation and persistence of measles dynamics. *Proc. Natl. Acad. Sci. U. S. A.* 93, 12648–12653
73. Earn, D.J.D. *et al.* (2000) A simple model for complex dynamical transitions in epidemics. *Science* 287, 667–670
74. Skowronski, D.M. *et al.* (2015) Pre- and postpandemic estimates of 2009 pandemic influenza A(H1N1) seroprotection to Inform surveillance-based incidence, by age, during the 2013–2014 epidemic in Canada. *J. Infect. Dis.* 211, 109–114
75. Wilson, K. and Reeson, A.F. (1998) Density-dependent prophylaxis: evidence from Lepidoptera-baculovirus interactions? *Ecol. Entomol.* 23, 100–101
76. Srygley, R.B. (2012) Age- and density-dependent prophylaxis in the migratory, cannibalistic Mormon cricket *Anabrus simplex* (Orthoptera: Tettigoniidae). *Environ. Entomol.* 41, 166–171
77. Reynolds, J.J. *et al.* (2011) The population dynamical consequences of density-dependent prophylaxis. *J. Theor. Biol.* 288, 1–8
78. Elliot, S.L. and Hart, A.G. (2010) Density-dependent prophylactic immunity reconsidered in the light of host group living and social behavior. *Ecology* 91, 65–72
79. Cremer, S. *et al.* (2007) Social immunity. *Curr. Biol.* 17, R693–R702
80. Betti, M.I. *et al.* (2016) Age structure is critical to the population dynamics and survival of honeybee colonies. *R. Soc. Open Sci.* 3, 160444
81. Anderson, R.M. and Crombie, J. (1984) Experimental studies of age-prevalence curves for *Schistosoma mansoni* infections in populations of *Biomphalaria glabrata*. *Parasitology* 89, 79–105
82. Woolhouse, M.E. (1989) On the interpretation of age-prevalence curves for schistosome infections of host snails. *Parasitology* 99, 47–56
83. Woolhouse, M.E. and Hargrove, J.W. (1998) On the interpretation of age-prevalence curves for trypanosome infections of tsetse flies. *Parasitology* 116, 149–156
84. Duneau, D. *et al.* (2016) Infections by *Pasteuria* do not protect its natural host *Daphnia magna* from subsequent infections. *Dev. Comp. Immunol.* 57, 120–125
85. Thomas, A.M. and Rudolf, V.H.W. (2010) Challenges of metamorphosis in invertebrate hosts: maintaining parasite resistance across life-history stages. *Ecol. Entomol.* 35, 200–205
86. Anderson, R.M. and May, R.M. (1985) Vaccination and herd immunity to infectious diseases. *Nature* 318, 323–329
87. Castillo-Chavez, C. *et al.* (1989) Epidemiological models with age structure, proportionate mixing, and cross-immunity. *J. Math. Biol.* 27, 233–258
88. Galvani, A.P. (2005) Age-dependent epidemiological patterns and strain diversity in helminth parasites. *J. Parasitol.* 91, 24–30
89. Pitzera, V.E. and Lipsitch, M. (2009) Exploring the relationship between incidence and the average age of infection during seasonal epidemics. *J. Theor. Biol.* 260, 175–185
90. Fine, P.E. (1993) Herd immunity: history, theory, practice. *Epidemiol. Rev.* 15, 265–302
91. Syed Musthaq, S.K. and Kwang, J. (2014) Evolution of specific immunity in shrimp – a vaccination perspective against white spot syndrome virus. *Dev. Comp. Immunol.* 46, 279–290
92. Rowley, A.F. and Pope, E.C. (2012) Vaccines and crustacean aquaculture – a mechanistic exploration. *Aquaculture* 334–337, 1–11
93. Iritani, R. *et al.* (2019) The evolution of stage-specific virulence: differential selection of parasites in juveniles. *Evol. Lett.* Published online February 27, 2019. http://dx.doi.org/10.1002/ev13.105
94. de Roos, A.M. *et al.* (2003) The influence of size-dependent life-history traits on the structure and dynamics of populations and communities. *Ecol. Lett.* 6, 473–487
95. Murdoch, W.W. *et al.* (2003) *Consumer-Resource Dynamics,* Princeton University Press
96. de Roos, A.M. and Persson, L. (2013) *Population and Community Ecology of Ontogenetic Development,* Princeton University Press

97. McCauley, E. *et al.* (1999) Large-amplitude cycles of *Daphnia* and its algal prey in enriched environments. *Nature* 402, 653–656

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

99. Ebert, D. *et al.* (2004) The evolution of virulence when parasites cause host castration and gigantism. *Am. Nat.* 164, S19–S32

100. van der Staay, F.J. *et al.* (2010) The standardization-generalization dilemma: a way out. *Genes Brain Behav.* 9, 849–855

101. Tarsi, K. and Tuff, T. (2012) Introduction to population demographics. *Nat. Educat. Knowledge* 3, 3

102. John, T.J. and Samuel, R. (2000) Herd immunity and herd effect: new insights and definitions. *Eur. J. Epidemiol.* 16, 601–606

103. Blaser, M. and Schmid-Hempel, P. (2005) Determinants of virulence for the parasite *Nosema whitei* in its host *Tribolium castaneum*. *J. Invertebr. Pathol.* 89, 251–257

104. Fisher, J.J. and Hajek, A.E. (2016) Influence of mating and age on susceptibility of the beetle *Anoplophora glabripennis* to the fungal pathogen *Metarhizium brunneum*. *J. Invertebr. Pathol.* 136, 142–148

105. Kubi, C. *et al.* (2007) Age prevalence of trypanosomal infections in female *Glossina morsitans morsitans* (Diptera: Glossinidae) on the plateau area of eastern Zambia. *Onderstepoort J. Vet. Res.* 74, a125

106. Armitage, S.A.O. and Boomsma, J.J. (2010) The effects of age and social interactions on innate immunity in a leafcutting ant. *J. Insect Physiol.* 56, 780–787

107. Brødsgaard, C.J. *et al.* (1998) Response of in vitro reared honey bee larvae to various doses of *Paenibacillus larvae larvae* spores. *Apidologie* 29, 569–578

108. Woodrow, A.W. (1942) Susceptibility of honey bee larvae to individual inoculations with spores of *Bacillus larvae*. *J. Econ. Entomol.* 35, 892–895

109. Hoage, T.R. and Rothenbuhler, W.C. (1966) Larval honey bee response to various doses of *Bacillus larvae* spores. *J. Econ. Entomol.* 59, 42–45

110. Allen, G.E. and Ignoffo, C.M. (1969) The nucleopolyhedrosis virus of *Heliothis*: Quantitative *in vivo* estimates of virulence. *J. Invertebr. Pathol.* 13, 378–381

111. Boucias, D.G. and Nordin, G.L. (1977) Interinstar susceptibility of the fall webworm, *Hyphantria cunea*, to its nucleopolyhedrosis and granulosis viruses. *J. Invertebr. Pathol.* 30, 68–75

112. Sheppard, R.F. and Stairs, G.R. (1977) Dosage-mortality and time-mortality studies of a granulosis virus in a laboratory strain of the codling moth, *Laspeyresia pomonella*. *J. Invertebr. Pathol.* 29, 216–221

113. Evans, H.F. (1981) Quantitative assessment of the relationships between dosage and response of the nuclear polyhedrosis virus of *Mamestra brassicae*. *J. Invertebr. Pathol.* 37, 101–109

114. Bucher, G.E. and Turnock, W.J. (1983) Dosage responses of the larval instars of the bertha armyworm, *Mamestra configurata* (Lepidoptera: Noctuidae), to a native nuclear polyhedrosis. *Can. Entomol.* 115, 341–349

115. Smits, P.H. and Vlak, J.M. (1988) Biological activity of *Spodoptera exigua* nuclear polyhedrosis virus against *S. exigua* larvae. *J. Invertebr. Pathol.* 51, 107–114

116. Sait, S.M. *et al.* (1994) The influence of larval age on the response of *Plodia interpunctella* to a granulosis virus. *J. Invertebr. Pathol.* 63, 107–110

117. McNamara, K.B. *et al.* (2013) Age-dependent trade-offs between immunity and male, but not female, reproduction. *J. Anim. Ecol.* 82, 235–244