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Impact of life stage specific immune priming on invertebrate disease dynamics

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The immune response of a host can have important impacts on host-pathogen interactions, but investment in immunity often changes dynamically across the life history of a host. One form of investment involves the induction of a primed immune response against previously encountered pathogens that protects the host from re-infection. In addition to providing immediate protective effects, immune priming can also provide two types of 'delayed' protection against pathogens: priming across life stages (ontogenic priming) and priming across generations (trans-generational priming). Consequently both types of immune priming have the potential to mediate life history variability in host–pathogen interactions, which could have important consequences for disease prevalence and dynamics as well as for the demographic structure of the host population. Here we develop a stage-structured SIRS model for an invertebrate host to explore the relative and combined impact of ontogenic priming and trans-generational priming on infection prevalence, host population size, and population age structure. Our model predicts that both types of immune priming can dramatically reduce disease prevalence at equilibrium, but their individual and combined effects on population size and age structure depend on the magnitude of tradeoffs between immune protection and reproduction as well as on the symmetry of infection parameters between life stages. This model underscores the potential importance of life-history based immune investment patterns for disease dynamics and highlights the need for wide-spread empirical estimation of parameters that represent the maintenance of immune priming in insects.

The immune response of a host to parasites or pathogens can alter host–pathogen interactions. In particular, priming of a host's immune system against a previously encountered pathogen reduces the risk and severity of future infections (Hamilton et al. 2008). Consequently, immune priming introduces heterogeneity in host susceptibility and disease transmission within the host population, with important implications for disease dynamics. Moreover, there is increasing recognition that factors like seasonality, resource availability, and life history tradeoffs can dictate a host's relative investment in immunity at any given time, altering a host's ability to respond to pathogenic insult (Moret and Schmid-Hempel 2009). The temporal heterogeneity of these within-host immune processes can directly affect between-host transmission dynamics and alter disease prevalence outcomes at the population level. Therefore, the coupling of immune investment with host life-history patterns can provide a powerful and currently underrated ecological point of view from which to consider the impact of disease on natural populations (Hawley and Altizer 2011).

Despite the lack of lymphocytes and other immune mechanisms traditionally associated with vertebrates (Kurtz and Armitage 2006, Schulenburg et al. 2007), invertebrates from many diverse taxa are capable of mounting a primed immune response against secondary pathogen exposure resulting in lower infectivity, higher survival rates, and less severe fecundity effects upon re-infection (Little et al. 2003, Schmid-Hempel 2005, Roth et al. 2009). Importantly, recent studies indicate that in addition to providing immediate protective effects, immune priming can influence the risk of infection across the life history of a host by providing two types of delayed protection against pathogens. First, immune priming can be retained across different life stages despite dramatic changes in the host's physiology (e.g. metamorphosis) (Thomas and Rudolf 2010). Second, immune priming can be transferred from one generation to the next from both maternal and paternal sources (Moret 2006, Sadd et al. 2005, Sadd and Schmid-Hempel 2007, Roth et al. 2010). Thus, immune priming results in stage-specific differences in host–pathogen interactions which could have important consequences for the population dynamics and stage-structure of the host. However, previous studies on immune priming have focused mostly at the individual level, and the implications of stage-specific immune priming for disease and host population dynamics are still poorly understood (Little and Kraaijeveld 2004, Schmid-Hempel 2005). Further investigation into the population-level effects of immune priming could substantially impact our understanding of processes as diverse as vector-borne disease transmission, pest bio-control, and the evolution of innate immunity.

The individual and relative importance of immune priming across developmental stages (ontogenic priming)

or from an adult to its larval offspring (trans-generational priming) likely depends on the stage-specific host–pathogen interaction. If larvae are the main drivers of infection, trans-generational priming would reduce the proportion of highly susceptible, and potentially highly infectious, larval individuals in the population. Immune priming from the larval to the adult stage might have more of an impact on disease dynamics if adults are more susceptible to a pathogen and more infectious if they do become infected. The manifestation of a disease in insects generally depends on the ontogenic stage of the host; different life stages occupy distinct ecological niches and have different rates of exposure, immune investment, disease-induced mortality and transmission potential for any given pathogen (Briggs and Godfray 1995a, Moerbeek and Van Den Bosch 1997, Milks et al. 1998, Zuk and Stoehr 2002, Jacot et al. 2005, Moret and Schmid-Hempel 2009, Thomas and Rudolf 2010). For instance, the larvae of the Indian meal moth *Plodia interpunctella* are highly susceptible to infection by a lethal granulosis virus, while adults do not appear to acquire infection (Sait et al. 1994, Boots 1998). In contrast, the fungus *Neozygites floridana*, a pathogen of cassava mites *Monoychellus tanajoa*, kills only adult females and spares other life stages (Elliot et al. 2002). In the confused flour beetle *Tribolium confusum* – protozoan parasite *Gregarina minuta* system, both larval and adult beetles can contract the parasites, but larvae support much higher parasite loads than adults, shed larger numbers of infectious protozoa, and suffer stage-specific development and mortality costs when infected (Detwiler and Janovy 2008, Thomas and Rudolf 2010). These cases highlight the need to account for stage-specific differences in host–pathogen interactions and indirect interactions between life stages (i.e. via immune priming) when estimating ecological and epidemiological parameters (Briggs and Godfray 1995b, Hartemink et al. 2008).

Here we examine the impact of ontogenic and trans-generational patterns of induced resistance for host–pathogen dynamics using a stage-structured SIRS model that is tailored to our own *Tribolium–Gregarine* host–pathogen system but has potential applicability to a wide variety of systems where investment in immunity varies across life history. We use this model to explore the relative impact of ontogenic and trans-generational immune priming on long term infection and population dynamics under a variety of virulence and life history trait scenarios. In particular, we ask how ontogenic and trans-generational immune priming 1) alters the equilibrium prevalence of endemic diseases, 2) influences population size and 3) affects the stage structure of an infected population. We incorporate ecological observations concerning the cost of immunity on insect development and fecundity (Jacot et al. 2005, Sadd and Siva-Jothy 2006, Sadd and Schmid-Hempel 2009) and identify the conditions that optimize and minimize the benefits of immune priming to a population. In general our results suggest that both types of immune priming can significantly alter the dynamics of host–pathogen systems. However, their relative impact depends on the stage-specific host–pathogen interactions. We discuss the implications of our results and offer suggestions for tailoring the model to specific applications.

The model

Our goal in designing the model was to investigate the contributions of ontogenic and trans-generational immune priming while also allowing different life-stages to contribute differently to infection and population dynamics (i.e. stage-specific host–pathogen interactions). The model consists of six coupled ordinary differential equations representing susceptible, infected and recovered/resistant classes for larval (L) and adult (A) life stages. To represent the retention of immune priming across developmental stages (Fig. 1), a proportion p of infected and resistant larvae retain their resistance across metamorphosis into adulthood instead of reverting to the susceptible adult class. To represent trans-generational immune priming, a proportion q of an infected or resistant parent's offspring enter the resistant larval class instead of being born into the susceptible class. The dynamics of the system are given by:

$$\frac{dS_L}{dt} = b_S e^{-yN} S_A + (1-q)e^{-yN}(b_I I_A + b_R R_A) - \beta_{LL} S_L I_L - \beta_{AL} S_L I_A - (\varepsilon_S + \delta_L) S_L + \omega_L R_L$$

$$\frac{dI_L}{dt} = \beta_{LL} S_L I_L + \beta_{AL} S_L I_A - (\varepsilon_I + \delta_L + \gamma_L + \alpha_L) I_L$$

$$\frac{dR_L}{dt} = q e^{-yN}(b_I I_A + b_R R_A) + \gamma_L I_L - (\varepsilon_R + \delta_L + \omega_L) R_L$$

$$\frac{dS_A}{dt} = \varepsilon_S S_L + (1-p)(\varepsilon_R R_L + \varepsilon_I I_L) - \beta_{AA} S_A I_A - \beta_{LA} S_A I_L - \delta_A S_A + \omega_A R_A$$

$$\frac{dI_A}{dt} = \beta_{AA} S_A I_A + \beta_{LA} S_A I_L - (\gamma_A + \delta_A + \alpha_A) I_A$$

$$\frac{dR_A}{dt} = p(\varepsilon_R R_L + \varepsilon_I I_L) + \gamma_A I_A - (\delta_A + \omega_A) R_A$$

Parameters $b_{S,I,R}$ are the birth rates from the indicated adult infection class, $\delta_{L,A}$ are the background death rates of larvae or adults, and $\varepsilon_{S,I,R}$ are the rates of larval development in each infection class. The parameter β_{ij} represents the transmission coefficient of infection from stage i to stage j, $\alpha_{L,A}$ indicates the disease-induced mortality rate for each life stage, $\gamma_{L,A}$ represents the recovery rate from infected to resistant, and $\omega_{L,A}$ indicates the rate of reversion, or waning of immunity. The population size (N) is the sum of individuals from all larval and adult compartments, and y is a coefficient that imposes a density-dependent decline in birth rate as N increases due to cannibalism by larvae and adults (Dennis et al. 1995).

In order to keep the model as simple and general as possible, we make the assumptions that resistant individuals are not infectious, that infection parameters are independent of pathogen load, that infected individuals are instantly infectious, and that there is no vertical transmission of infection. Furthermore, we lump all larval stadia/instars into one class, and we assume that infected larvae lose infection during metamorphosis to emerge as uninfected adults. This assumption allows us to isolate the consequences of immune priming

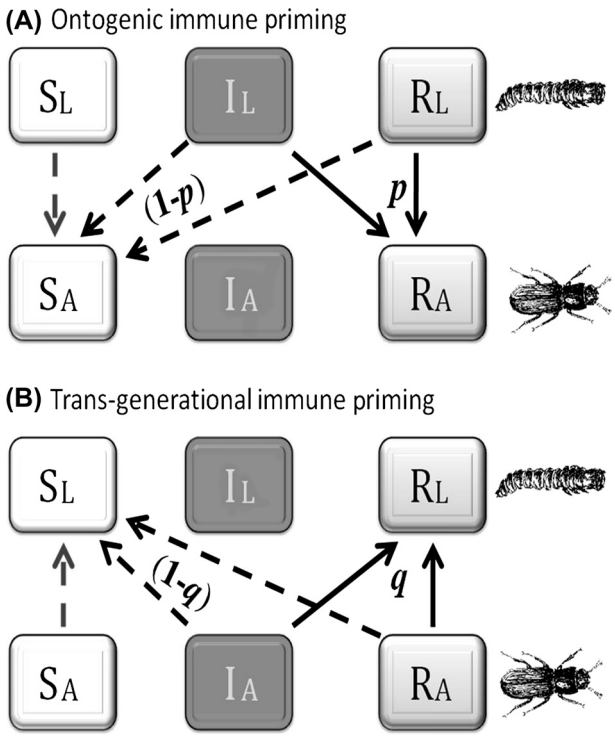

Figure 1. Potential immune priming scenarios across stages and generations. Susceptible (S), larvae (L) and adults (A) can become infected (I) by a pathogen. The population is capable of resistance if infected individuals can recover into the resistant (R) class and avoid re-infection. If an infected or resistant larva can maintain resistance (A, solid arrow) into the adult stage as opposed to reverting to the susceptible adult class (dashed arrow), ontogenic immune priming occurs, and the proportion, from zero to one, of infected or resistant larvae that accomplish ontogenic priming is represented by (p) in the model. Susceptible larvae always become susceptible adults (gray dash). The proportion (q) of infected or resistant adults that can give birth to resistant (solid arrow), as opposed to susceptible (dashed arrow), offspring determines the level of trans-generational immune priming (B). Susceptible adults always give birth to susceptible larvae.

across life-stages and applies to a variety of host–pathogen systems where the duration of an infection is shorter than a life-stage, or where metamorphosis of the host results in the loss of the infection (Boots 1998, Thomas and Rudolf 2010).

Parameter estimation

We parameterized the model (Table 1) to mimic dynamics of flour beetle *Tribolium* spp. host systems (Park and Marian Burton 1948, 1950, Leslie and Park 1949, Roth et al. 2009, 2010) because they are capable of ontogenic (Thomas and Rudolf 2010) and trans-generational (Roth et al. 2010) immune priming, the biology of this model system is well understood, and it is representative of many other host–pathogen life cycles. In all simulations, parameter values were kept within biologically plausible ranges relative to other parameters. All numerical simulations were run using the ode45 solver (ver. 5.74.4) in MATLAB (ver. 7.9.0).

Results

Disease free dynamics

To obtain a general understanding of the basic dynamics of the model in the absence of infection, we ran numerical simulations to explore the stability of the disease-free ($I_L = I_A = 0$) population over time and found that the population size and age structure generally stabilized to an equilibrium value well before the 600-day time point used as the equilibrium level in subsequent simulations. We repeated this process for simulations in the presence of infection to ensure that the numerical equilibrium values retained stability. Numerical simulations indicate that at the disease-free equilibrium the ratio of larvae to adults is driven by the background death rate of adults (δ_A) and the development rate of the larvae (ε_S), as suggested by an analytical examination of the susceptible adult equation. Upon application of the *Tribolium* parameter values (Table 1), the model produces a stable equilibrium ratio of one larva for every three adults.

We also derived a next-generation matrix for our model representing the basic reproductive number of a pathogen (R_0, Appendix 1) (McCormack and Allen 2007) and confirmed its predictions about persistence or extinction of infection at a given host equilibrium with numerical simulations using parameter values that produced a dominant eigenvalue

Table 1. Parameter explanation and estimation for a two life-stage model of immune priming in insects.

Parameter (rates are per individual per day)	Symbol	Value	Selected sources
Expressivity of ontogenic priming	p	0 to 1	allowed to vary
Expressivity of trans-generational priming	q	0 to 1	allowed to vary
Reproductive rate of susceptible adults	b_S	1.2	Park and Burton 1948
Reproductive rate of infected adults	b_I	0.8	Kang and Rudolf, unpubl. data.
Reproductive rate of resistant adults	b_R	1	Park and Burton 1948
Natural death rate*	δ_i	0.02	Pearl et al. 1941
Developmental rate for susceptible larvae	ε_S	0.06	Thomas and Rudolf 2010
Developmental rate for infected larvae	ε_I	0.04	Thomas and Rudolf 2010
Developmental rate for resistant larvae	ε_R	0.05	Thomas and Rudolf 2010
Disease-induced mortality rate*	α_i	0.2	Anderson and May 1981
Disease recovery rate from I to R*	γ_i	0.1	estimated based on R_0
Reversion rate from R to S*	ω_i	0.005	estimated based on R_0
Transmission coefficient from i to j*	β_{ij}	0.003	estimated based on R_0
Density dependence coefficient	y	0.01	estimated

Notes: An asterisk (*) indicates that the parameter was divided into separate larval (L) and adult (A) values when appropriate as indicated in the text. The index i can take the form L or A. The values for estimated parameters are based on a combination of preliminary sensitivity analysis results, *Tribolium* biology plausibility, and the assumption that reversion happens more slowly than recovery.

around the $R_0 = 1$ threshold. Because the incidence of the disease is assumed to be zero prior to invasion, immune priming across stages has no impact on R_0 (Appendix 1). Solving for the dominant eigenvalue of our next-generation matrix indicates that $R_0 = 3.5$ under our chosen parameter values (Table 1).

Immune priming across stages and generations – consequences for endemic patterns

To explore the effects of immune priming on the endemic presence of a disease in a population, we created five scenarios. Two scenarios are bereft of immune priming across life stages: the first prohibits any kind of increased protection from previously encountered pathogens (no resistance), while the second allows for recovery into a resistant class but does not allow its retention across stages or generations (no priming). Three scenarios have the benefit of immune priming across life history stages. One allows for ontogenic priming through the transfer of an infected or resistant larva into the resistant adult class (ontogenetic priming only), while another allows for the transfer of offspring of infected or resistant adults into the resistant larval class in order to represent trans-generational immune priming (trans-generational priming only). The last scenario allows for both ontogenic and trans-generational priming.

When a pathogen with an R_0 of 3.5 (Fig. 2) was allowed to invade a population without the ability to mount any kind of primed immune resistance ($p = q = \gamma = 0$), the endemic infection prevalence reached a stable non-zero equilibrium. In addition, the population size at equilibrium was dramatically smaller than a disease free population. Allowing for the ability to acquire resistance ($p = q = 0$, $\gamma = 0.1$), even in the absence of immune priming across life stages, cut the endemic prevalence at equilibrium in half (Fig. 2A), and brought the equilibrium population size much closer to disease-free equilibrium (DFE) levels (Fig. 2B). Allowing for ontogenic retention of immune priming ($p = 1$, $q = 0$, $\gamma = 0.1$) further reduced endemic infection prevalence and increased population size to a small extent. Trans-generational priming ($p = 0$, $q = 1$, $\gamma = 0.1$) produced similar trends, most likely due to symmetry between life stages arising from the one to one larva to adult ratio created in the population under both of these scenarios. Finally, allowing for both trans-generational

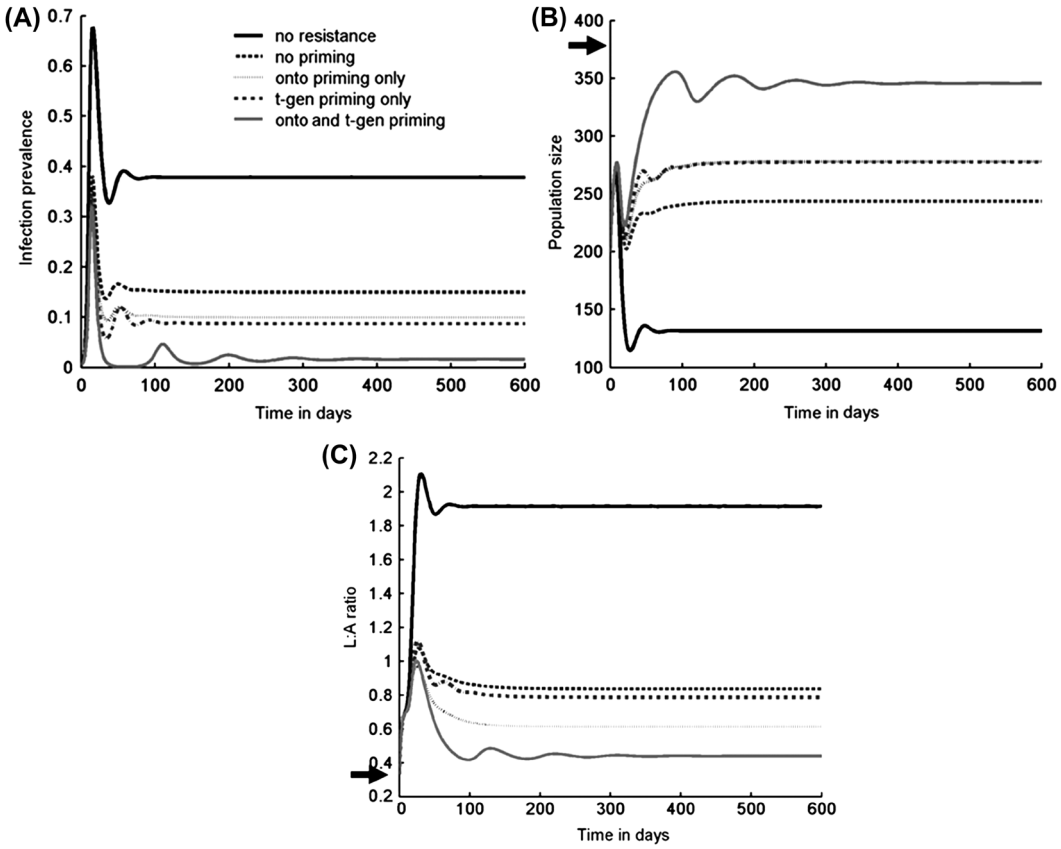

Figure 2. Population level effects of resistance, ontogenic priming, and trans-generational immune priming. When insects are allowed to recover ('no priming', $p = q = 0$, $\gamma = 0.1$) from an infection ($R_0 = 3.5$) into a resistant class as opposed to reverting into the susceptible class ('no resistance', $p = q = \gamma = 0$), the equilibrium infection prevalence decreases (A). Adding resistance and one type of priming ('onto priming only', $p = 1$, $q = 0$, $\gamma = 0.1$, or 't-gen priming only', $p = 0$, $q = 1$, $\gamma = 0.1$) further reduces the endemic prevalence of an infection, while combining ontogenic and trans-generational priming ('onto and t-gen priming', $p = q = 1$, $\gamma = 0.1$) can force a pathogen to near – zero endemic levels. Similarly, in the presence of resistance ($\gamma > 0$) the population density (B) achieves a higher equilibrium value, and immune priming across life stages or to the next host generation enhances this buffering effect. Adding both trans-generational and ontogenic priming ($p, q > 0$) results in an even greater buffering effect. The addition of ontogenic and trans-generational immune priming also returns age structure to pre-infection larva-to-adult ratios (C), whereas larvae dominate in an infected population incapable of resistance. DFE population size and age ratios are represented by an arrow on the y axis.

priming and ontogenic priming ($p = q = 1$, $\gamma = 0.1$) reduced equilibrium infection prevalence as dramatically as the initial addition of resistance to the model. Furthermore, the equilibrium population size hovered around disease-free levels (Fig. 2B). The effect of immune priming on age structure echoed these patterns (Fig. 2C), as the addition of ontogenic and trans-generational immune priming nearly restored the DFE larva-to-adult ratios compared to a population without resistance, where larvae dominate. Although intuition dictates that resistance in a population will decrease infection prevalence, it is much harder to estimate the additional impact of extending acquired resistance across stages and generations. These results indicate that, using biologically realistic parameters, the addition of ontogenic and trans-generational priming can reduce infection prevalence and buffer population size as profoundly as the initial inclusion of recovery into an SIS model.

Immune priming and reproductive costs

While the above scenarios assume that there is some individual cost of resistance on larval development and adult fecundity, they also assume that infected individuals pay a still greater cost (Boots and Begon 1993, Rolff and Siva-Jothy 2003). To investigate the effects of mounting and maintaining a primed immune response when the costs of resistance are greater than the costs of infection, as in the case of a response to commensal gut microbiota (Freitak et al. 2007), we co-varied disease-induced mortality (low to high) against the fecundity (from sterile to equaling susceptible levels) of resistant adults. We then examined the consequences for population infection prevalence, population size, and age structure across the full parameter space for scenarios with and without ontogenic and trans-generational immune priming (Fig. 3).

When individuals are allowed to recover from infection but not retain immune priming across life stages, infection prevalence is relatively independent of any fecundity cost associated with resistance and is highest at low disease-induced mortality values presumably because infected individuals live to spread the pathogen (Fig. 3A). In contrast, ontogenic coupled with trans-generational immune priming (Fig. 3B) always decreases infection prevalence, and when there is no fecundity cost to resistance, prevalence is only a fraction of the unprimed population infection prevalence at low disease-induced mortality levels. However, decreasing the reproductive rate of resistant adults under the priming scenario quickly decreases the benefits of priming in reducing disease prevalence. The concurrent change in population size without priming comes closer than the primed population to matching the DFE population size (Fig. 3C–D) at very low mortality levels and high fecundity costs. A low resistant adult fecundity also results in a slightly inflated larva to adult ratio in the presence (Fig. 3F) but not in the absence (Fig. 3E) of priming, where it actually slightly decreases the proportion of larvae in the population. These results suggest that immune priming across metamorphosis and generations does not always mitigate the impact of a disease on a population, but can actually exacerbate it when immune priming imposes a cost to reproductive individuals within an population.

The relative contributions of ontogenic and trans-generational immune priming

During development, an invertebrate may go through several distinct life stages that require a shift in metabolism, physiology, and even habitat. Therefore some life stages have a greater probability of encountering and harboring certain pathogens (Briggs and Godfray 1995a, Moerbeek and Van Den Bosch 1997, Milks et al. 1998). We investigated such stage-specific differences in host–pathogen interactions by allowing one stage to contribute more than the other to the dynamics of an infection. When larvae and adults acquire, transmit, and suffer infection equally, the contributions of increasing ontogenic or trans-generational priming are nearly symmetrical, although trans-generational priming has a slightly greater impact on disease prevalence (Fig. 4A), while ontogenic priming has a more pronounced effect on mitigating shifts in age structure (Fig. 4G). To put the emphasis on larval contribution (i.e. larvae are disproportionally affected by pathogens), we increased the larval transmission coefficients (β_{LL}, $\beta_{LA} = 0.006$) to six times the level of adult transmission (β_{LA}, $\beta_{AA} = 0.001$), mirroring the relative infectiousness of *Tribolium confusum* life stages parasitized by protozoa (Thomas and Rudolf 2010). We also made larvae five times ($\alpha_{\perp}L = 0.5$) more likely than adults ($\alpha_{\perp}A = 0.1$) to die when infected. To create the opposite situation for adults driving infection, we switched the parameter values between larvae and adults. We then applied these scenarios across different proportions of ontogenic and trans-generational priming to look at the relative importance of each type of priming under asymmetrical infection conditions (Fig. 4).

Under a larval infection bias, trans-generational priming resulted in a stronger reduction in infection prevalence and increase in population size than similar levels of ontogenic priming, although the benefits of priming were maximized when both trans-generational and ontogenic priming are present at high levels (Fig. 4B, E). When adults drive infection, ontogenic priming alone reduces infection prevalence and protects the size of a population more effectively than trans-generational priming alone, although again both must be present at high levels to allow the population to reach DFE levels (Fig. 4C, F). Trans-generational priming always favors the dominance of larvae over DFE levels in the age structure of an infected population (Fig. 4G–I), although when larvae are drivers of infection (Fig. 4H) the shift in the larva to adult ratio from the DFE ratio is much more modest than when adults drive infection even in the absence of priming (Fig. 4I). However, ontogenic priming has a much more pronounced effect in reducing the larva to adult ratio compared to trans-generational priming, especially when adults are drivers of infection. In general, this suggests that ontogenic and trans-generational immune priming differ in how they influence host–pathogen dynamics, that the impact of one type of priming may depend on the degree of expression of the other, and that we cannot dismiss one version of priming as being universally less interesting or important than the other in natural host–pathogen systems because influence depends on the context of infection.

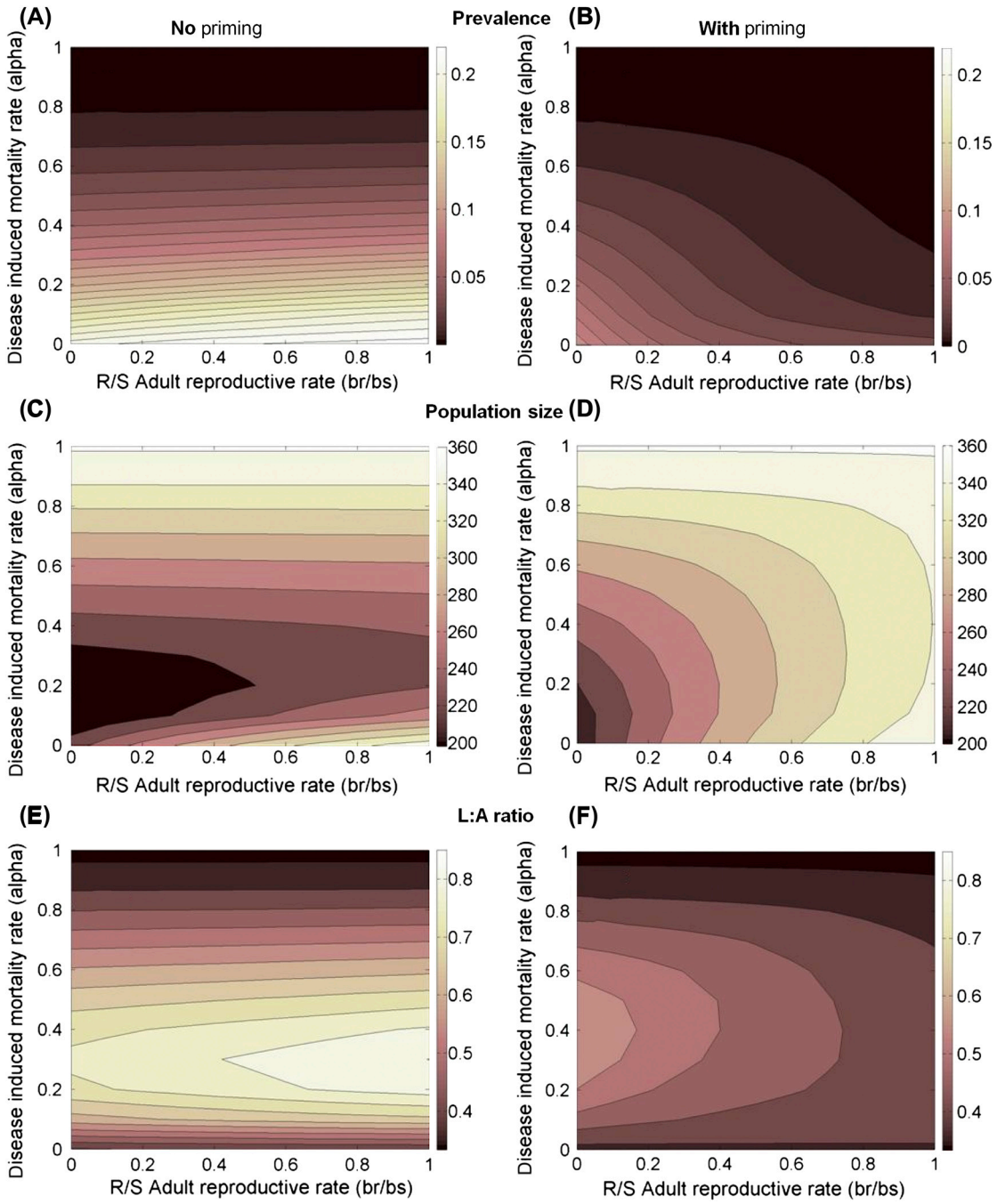

Figure 3. Effects of disease-induced mortality and reproductive (adult fecundity) costs with (A, C, E) and without (B, D, F) ontogenic and trans-generational immune priming. Over a certain disease-induced mortality threshold (here, $\alpha \approx 1$), R_0 is less than one and infection prevalence is negligible in a population at equilibrium. In a population where recovery is possible ($\gamma = 0.1$) but resistance cannot be transferred across life stages or generations ($p = 0$, $q = 0$), infection prevalence (A) is independent of resistant adult fecundity rates, while a reproductive cost to resistance has a negative impact on infection prevalence (B) when individuals who acquire resistance maintain it into adulthood ($p = 1$, $q = 1$). There is a similar effect of immune priming on population size (D), especially when a pathogen exerts very low mortality but resistance demands a high reproductive cost, compared to the recovery of population size at low mortality rates in a population that does not transfer immunity to the next life stage (C). The equilibrium age structure of an unprimed population (E) only depends on the fecundity of resistant adults at intermediate mortality values, while imposing a cost to resistance on adult fecundity in a population capable of immune priming (F) results in an increased contribution of resistant adult fecundity to population age structure.

Discussion

Linking the effects of stage-specific immune priming is important to understand how immune priming influences the ecological dynamics of host–pathogen systems. Our model predicts that ontogenic and trans-generational immune priming in an insect system can dramatically reduce disease prevalence, buffer the size of a population against pathogen-induced declines, and dampen the shift toward larval dominance in the age structure of a population. However, the nature and magnitude of these shifts depend on processes specific to the two life stages, including the

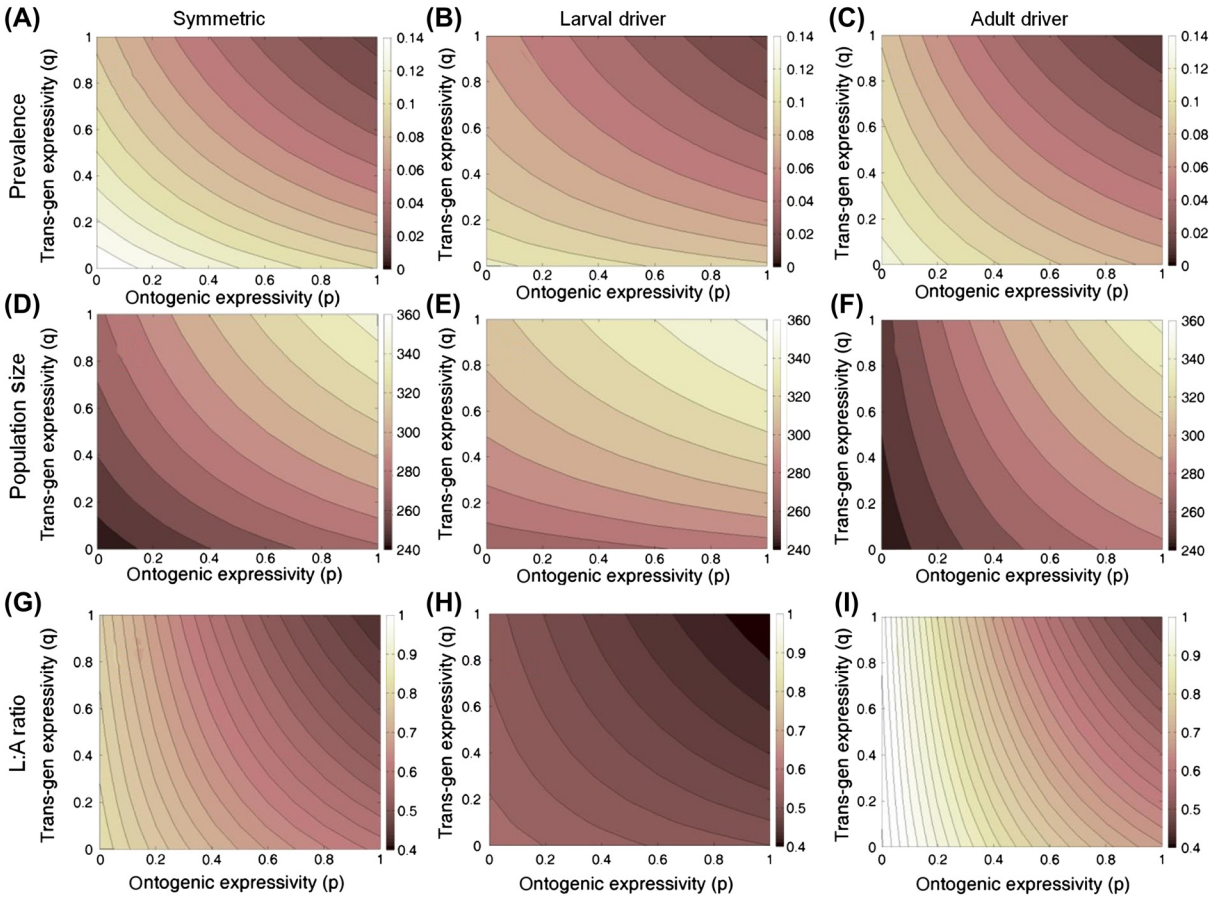

Figure 4. The relative contributions of ontogenic and trans-generational immune priming to infection dynamics driven by larvae or adults. When larvae and adults contribute equally to infection dynamics (A, D, G), trans-generational priming (0 is absent, 1 is fully present) reduces infection prevalence slightly more efficiently, and ontogenic priming pushes the larva to adult ratio toward D, F, E levels more substantially. When larvae (B, E, H) or adults (C, F, I) experience asymmetrical transmission and disease-induced mortality when compared to the other age class, the relative importance of ontogenic and trans-generational priming to infection prevalence, population size, and age structure depends on the age class driving the infection.

symmetry of infection parameters and the tradeoffs of inducing resistance. In addition, we show that both types of immune priming vary in their impact on host–pathogen systems.

Immune priming across stages and generations – consequences for endemic patterns

One of the most basic functions of our model is to allow for investigation of the dynamics of a pathogen as it settles into an invertebrate population capable of immunological priming. Previous models of insect–pathogen systems have incorporated stage-structured transmission dynamics (Anderson and May 1980, Briggs and Godfray 1995a, b, Goulson et al. 1995, Hartemink et al. 2008) but to the best of our knowledge none have allowed for recovery into a resistant class or allowed for primed resistance over multiple life stages or generations. We found that allowing individuals in a population to acquire resistance as the consequence of recovery from an infection, even with a forced reversion to susceptibility after metamorphosis, resulted in a dramatic decrease in the endemic prevalence of a pathogen after several host generations. Allowing individuals to retain any resistance they acquired across a life stage (ontogenic or trans-generational priming) further reduced the endemic disease prevalence at equilibrium, and when individuals who had experienced infection were allowed to maintain resistance across metamorphosis and pass on immunological protection to their offspring, infection prevalence could be driven to negligible levels. This suggests that immune priming in insects has the potential to significantly impact the persistence of a pathogen in a population above and beyond the influence of transient recovery.

Immune priming and reproductive costs

Investment in immunity is not always cheap, however, and tradeoffs between inducing resistance and channeling resources to other essential life history processes, like development and reproduction, may alter the advantages of immune priming (Jacot et al. 2005). Immune priming to one pathogen can divert immune processes and indirectly facilitate the establishment of a different, but equally troublesome, pathogen (Sadd and Schmid-Hempel 2009). Furthermore, the same immune effector molecules that clear infection can also cause substantial collateral damage to host tissue (Sadd and Siva-Jothy 2006), and it is not in the best interests of a host to maintain them in an active state when no infection exists. The population level consequences of tradeoffs between

immune investment and other components of fitness may depend on the context, as susceptible individuals may benefit from herd immunity initially, but the risk of infection rises as the frequency of susceptible individuals increases.

In our simulations, populations with individuals forced to mount, maintain and pass on primed resistance in response to an infection had a much lower equilibrium infection prevalence regardless of any reproductive cost or disease-induced mortality rate compared to populations that could recover but not maintain a primed immune response across life stages. The comparative effect on total population size, however, was not as straightforward. Both populations reached the greatest size when the fecundity of resistant adults was close to the fecundity of susceptible adults. At intermediate mortality rates, the population without immune priming across stages and generations decreased in size more rapidly than the primed population even as resistant adult fecundity decreased, but at very low mortality rates the population without extended immune priming recovered its size more rapidly under high fecundity cost conditions. In the presence of priming, resistant adult fecundity provides offspring that contribute to herd immunity in the population, and so reducing their input of resistant offspring decreases the ratio of R:(S + I) and creates a scenario that begins to resemble the state of affairs in a population incapable of priming (i.e. higher prevalence, lower population size, inflated larval presence). By the same logic, in a population that can recover but not transfer resistance to the next generation, resistant adults keep producing susceptible larvae that subsequently can get infected, suffer developmental delays, and linger in the population longer, inflating the ratio. While we cannot use our model to evaluate the evolutionary success of particular immune strategies or genotypes, the model does suggest that the ability of immune priming to mitigate disease dynamics in a population may be influenced by specific tradeoffs at the individual level. Therefore, the empirical use of population-level measures like head count and age structure to detect immune priming in natural invertebrate populations may result in the underestimation of priming expressivity if individuals are paying underlying costs while mounting immune responses. This model underscores the necessity of investigating potential reproductive and developmental tradeoffs to immune priming in the specific model system before attempting any empirical survey of the expressivity and consequences of priming in the population.

The relative contributions of ontogenic and trans-generational immune priming

We built age structure into the model because many diseases of invertebrates attack, through mortality, development, fecundity, or transmission effects, one life stage disproportionately over another (Moerbeek and Van Den Bosch 1997). Since trans-generational priming results in an increased proportion of resistant larvae whereas ontogenic priming serves to protect adults, the relative contributions of these types of priming may depend on the life stage that drives infection. Our results indicate that adult-driven infections, defined by higher transmission and mortality among adults than larvae, have a more drastic effect on population size and age structure regardless of any immune priming profile applied. Nevertheless, the relative effects of ontogenic and trans-generational priming are consistent with our predictions. When adults drive infection, increasing the proportion of resistant or infected larvae that experience ontogenic priming results in a buffering of the reproductive class against the effects of disease-induced mortality, and translates into a more pronounced positive effect on population size than trans-generational priming. In a similar vein, trans-generational priming increases the proportion of resistant larvae and has more of an impact on prevalence and population size if larvae are the primary transmission agents. Ontogenic priming always restored the low ratio of larvae to adults more efficiently, regardless of infection symmetry, because trans-generational priming protects larvae from disease, and protected larvae can accumulate, inflating the proportion of larvae in the population.

Based on these patterns, we can make predictions about the relative importance of ontogenic and trans-generational priming in real host–pathogen systems. In the case of flour beetles and their protozoan parasites, for example, the infection is driven by larvae, but both larvae and adults can contract the parasites (Thomas and Rudolf 2010). Our model predicts that in this case, either type of priming alone would be sufficient to dampen the effects of the parasite on the population, although trans-generational immunity would have a greater impact on infection prevalence and population size. However, in other species like the Indian meal moth adults cannot contract the virus that kills their larvae (Boots and Begon 1993). Trans-generational priming should therefore still have a greater positive impact than ontogenic priming on infection prevalence and population size, but without ontogenic priming from sublethal exposure as larvae, there would be no primed adults to transfer immunity to the next generation. Therefore, for moth populations to gain any advantage through immune priming, both ontogenic and trans-generational priming should be present, and recent empirical evidence supports this prediction (Tidbury et al. 2010).

Implications and future directions

Our model was developed to create a general theoretical framework to examine the consequences of stage-specific differences in host–pathogen interactions and types of immune priming for population and disease dynamics. As every host–pathogen system presents unique characteristics in the process of infection and recovery, we hope that future extension of our basic model will be developed to examine how such factors influence other host–pathogen systems. For example, in some systems, larval instars may differ in their susceptibility to infection and disease-induced mortality (Boots 1998, 2004, Hartemink et al. 2008). While small differences are unlikely to change the general patterns, large differences may alter the stage-structure and dynamics, and extending the model to account for different instars would make the model more intensive for such systems. Furthermore, for the sake of simplicity we assumed that the transition between stages is very short relative to the duration of each stage. In some systems these transitions can be relatively long and influence dynamics of insect populations (Briggs and Godfray 1995a). Incorporating these delays may be important to fully

understand the impact of immune priming in such systems. While we focused on systems where immune priming involves only increased resistance, it is possible that some systems show an up-regulation of tolerance mechanisms as an alternative strategy that may be employed by insects, and which would presumably create very different trends of infection prevalence and induce very different long term consequences for host–parasite coevolution (Schneider and Ayres 2008, Råberg et al. 2009). Other factors that might be ecologically important in the context of infection and immune priming and could be added to the model includes sex-specific differences (Zuk and Stoehr 2002) or host density and aggregation effects on disease dynamics (Rolff and Siva-Jothy 2003).

We recommend that biologists interested in the epidemiological or immunological aspects of an invertebrate host–pathogen system check for immune priming in their study organism, as it could have substantial consequences for population-level phenomena that could be misinterpreted if immune priming is not considered. Furthermore, there were a few parameters for which we could not find reliable empirical data, most notably the transmission coefficients, which are notoriously difficult to define, measure and model (McCallum et al. 2001). Although there are some estimates of increased survival and changes in the rates of reproduction under immune priming scenarios, there have been no rigorous empirical estimates for the waning of immunity, or for precise rates of recovery into the resistant class. Similarly little is known about the variation in the expression of immune priming, i.e. whether immune priming is only either present or absent, or if variation among individuals or environmental conditions result in partial, incomplete expressivity of priming on the population level. Further work on immune priming in insects should begin to quantify these parameters, as they all have the potential to impact population dynamics. Finally, recent work has begun to hone in on the mechanisms governing immune priming in insects (Pham et al. 2007, Schulenburg et al. 2007, Freitak et al. 2009, Riddell et al. 2009), and these may be relevant to ecologists as well as immunologists because the costs of resistance, the rate of recovery, and the rate of reversion to susceptibility are all most likely dependent on the mechanisms involved in primed immunity.

Conclusions

There is increasing evidence that immune priming occurs frequently in insect populations, but the implications for host–pathogen systems are still not well understood (Little and Kraaijeveld 2004). We predict, based on the results of our model, that immune priming can have significant consequences for host populations and parasite dynamics, but there is little empirical data for comparison, and the evolutionary consequences are still unexplored. For now, we have established that the population-level consequences of immune priming likely depend largely on stage-specific host–pathogen interactions, as well as on the degree of ontogenic and trans-generational immune priming present in a specific system. The results indicate that shifting the focus from the identification of the presence of immune priming in different taxa to a focus on its broader mechanistic, ecological and evolutionary significance will provide a fruitful new avenue for understanding the larger implications of invertebrate immune priming.

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Appendix A

Basic Reproductive Number R_0

To derive an expression for the basic reproductive number (R_0) of a pathogen applied to this model, we recognized two stages of host (larvae and adults) and that intrastage and interstage transmission parameters were not necessarily equivalent (McCormack and Allen 2007). For each type of transmission event, we created an expression for the infectiousness of the host, defined as the transmission rate (β) divided by the rate at which a host leaves the infectious stage through recovery (γ), background mortality (δ), disease-induced mortality (α), and metamorphosis (ε), in the case of larvae. This gives us a two-by-two form of the next-generation matrix representing infection dynamics between hosts,

$$\begin{bmatrix} \dfrac{\beta_{LL}\widehat{S_L}}{\gamma_L+\alpha_L+\varepsilon_I+\delta_L} & \dfrac{\beta_{AL}\widehat{S_L}}{\gamma_A+\alpha_A+\delta_A} \\ \dfrac{\beta_{LA}\widehat{S_A}}{\gamma_L+\alpha_L+\varepsilon_I+\delta_L} & \dfrac{\beta_{AA}\widehat{S_A}}{\gamma_A+\alpha_A+\delta_A} \end{bmatrix}$$

where $\widehat{S_A}$ and $\widehat{S_L}$ are the DFE equilibrium values for larval and adult life stages. Finally, the dominant eigenvalue of the matrix gives the overall R_0 for a pathogen in the population.