Title: Evolution of behavioral resistance in host-pathogen systems

Authors: Caroline R. Amoroso, Janis Antonovics

Department of Biology, University of Virginia, Charlottesville, VA, 22902 USA

Correspondence

CRA: cra2z@virginia.edu

JA: ja8n@virginia.edu

Keywords: avoidance behavior, COVID-19, disgust, epidemics, genetic polymorphism, social distancing

Abstract

Behavioral resistance to parasites is widespread in animals, yet little is known about the evolutionary dynamics that have shaped these strategies. Theory developed for the evolution of physiological parasite resistance can only be applied to behavioral resistance under limited circumstances. We find that accounting explicitly for the behavioral processes, including the detectability of infected individuals, leads to novel dynamics that are strongly dependent on the nature of the costs and benefits of social interactions. As with physiological resistance, the evolutionary dynamics can also lead to mixed strategies that balance the costs of disease risk and the benefits of social interaction, with implications for understanding avoidance strategies in human disease outbreaks.

Introduction

Hosts resist parasites using diverse strategies, with broad implications for host-parasite coevolution [1–4]. Previous theoretical models of resistance evolution have largely focused on physiological or biochemical resistance [1,5–7]. Yet resistance against parasites can also take the form of behavioral traits [3,8,9] such as direct avoidance or "disgust" in response to diseased individuals [10,11] or general avoidance of interactions with other individuals, which in a human context is now termed "social distancing." Here, we ask whether the ecological and evolutionary dynamics of behavioral defenses against parasites operate according to similar principles as physiological defenses.

Host behavior is implicit in classical models of microparasite transmission as a component of the parameter β [12,13]. β is a composite of multiple factors [14], including, for directly transmitted parasites, the contact rate between hosts, which is a function of host behavior, and the per contact transmission probability, which is a function of host physiology [15]. Models of resistance evolution typically vary the per contact transmission probability, i.e. the physiological resistance [5,16]. Nevertheless, a high degree of variation in behavioral resistance to parasites has been reported across and within species: for example, avoidance of infected conspecifics in crustaceans [17], birds [18,19], and primates [20], including humans [10]. Despite the broad diversity of these behaviors [8,21,22], behavioral resistance has rarely been examined explicitly in theoretical contexts [23,24]. It remains unknown whether evolutionary dynamics of behavioral resistance follow the same patterns as physiological resistance. Previous theoretical research on physiological resistance has shown that susceptible and resistant individuals can coexist in the presence of a disease when resistance carries a direct

physiological cost [5,7,25], but such models have also not considered how behavioral costs might influence resistance evolution.

Here, we develop a theoretical model of a disease that is transmitted in a social context, through direct contact or aerosol, and investigate the evolution of behavioral resistance under several assumptions about behavioral processes and cost-benefit trade-offs. We show that behavioral resistance can result in evolutionary dynamics that are different from physiological resistance, depending on the specificity of behavioral responses to diseased conspecifics and the nature of the costs and benefits of sociality.

The Model

Social Behavior

We model the social behavior of the host in a population of individuals that enter into groups or remain singletons. Let S be the number of singletons and G the number of groups of size T, and total population size, $N = S + TG$.

The frequency of groups depends on the group encounter rate, ρ, and group dissociation rate, υ. We use the simplest case of pair formation ($T = 2$) to illustrate the dynamics. Pair formation in populations has been studied in the context of mating and marriage, and represents a complex problem of sampling without replacement [26,27]. Following previous work [28], we consider two forms of encounter. First, singletons can encounter one another at a constant frequency that is independent of their density, as would occur when individuals seek others out to form associations. Second, singletons can encounter others randomly, such that encounters occur at a higher rate at greater densities. These two types of group formation have parallels with

frequency-dependent and density-dependent disease transmission processes [28,29]. Throughout, the derivations of the equations are given in the Supplementary Materials (S1).

Equilibrium Group Formation

The number of groups at equilibrium under frequency-dependent encounter is

$$G = \left(\frac{\frac{\rho}{\upsilon}}{1 + \frac{\rho}{\upsilon}} \right) \left(\frac{N}{T} \right) \tag{1}$$

In the case of density dependent encounter, we assume the rate of group formation is a linear function of the number of singletons, πS, rather than the total population density. Then, the number of groups at equilibrium is

$$G = N - \frac{\left(-\upsilon + \sqrt{\upsilon^2 + 4T\rho\upsilon N} \right)}{2T^2\rho} \tag{2}$$

Behavioral Resistance

We compare two types of behavioral resistance: specific avoidance of diseased individuals and general avoidance of all associations. For specific avoidance, a healthy, avoiding individual can detect an infected individual, and avoid pairing with it, determined by a factor ϕ. For general avoidance, a healthy, avoiding individual encounters all other individuals, regardless of their infection status, at a reduced rate $(\rho - a)$, relative to the background rate of non-avoiding individuals ρ. We derive how R_0 depends on the equilibrium frequency of pairs.

Evolution of Behavioral Resistance

To understand the evolution of behavioral resistance we use the one-locus, two allele dynamical framework developed for physiological resistance evolution [5]. In this system, X_1 and X_2

87 represent two haploid genotypes that differ in their behavioral resistance to the disease, with X_2
88 being the avoider. X_1 and X_2 are equivalent in their transmission once infected, such that they
89 can be pooled into one class of diseased individuals, Y. Transmission occurs at rate δ from
90 infected (Y) individuals to X_1 or X_2 when they are in a pair. Individuals can enter into a pair with
91 their own type and the other types, the number of pairs of each type calculated from binomial
92 proportions. We use b and $(b - c)$ to refer to birth rate for X_1 and X_2 respectively, where c is the
93 cost of resistance (see below), and μ the background mortality rate. We assume the disease is
94 sterilizing, such that diseased individuals do not contribute to reproduction. We also impose
95 density dependence on birth rate of the healthy individuals because without a numerical or
96 ecological feedback, the system does not reach stable equilibrium [25]. These processes are
97 represented by

$$\frac{dX_1}{dt} = X_1(b - kN - \mu) - \delta\left(\frac{2GX_1Y}{N^2}\right) \tag{3}$$

$$\frac{dX_2}{dt} = X_2((b - c) - kN - \mu) - \delta\left(\frac{2GX_2Y}{N^2}\right) \tag{4}$$

$$\frac{dY}{dt} = \delta\left(\frac{2GY}{N^2}\right)(X_1 + X_2) - \mu Y \tag{5}$$

98 We simulated each model to equilibrium using an ordinary differential equation solver
99 (function "ode" Runge-Kutta "rk4" method) from the R package *deSolve* [29,30]. We explored a
100 range of values for each parameter (see results), and confirmed equilibria by perturbation.
101
102 *Resistance Costs*
103 Physiological resistance is usually assumed to carry some cost that results in reduced fitness in
104 the absence of the parasite [5,25]. Similarly, we assume X_2 individuals pay some reproductive
105 cost for avoiding others. First, avoidance may be costly regardless of whether it is instantiated;

for example, a less active genotype could have fewer encounters with others, but also have reduced food acquisition. Thus, the birth rate of X_2 is $(b - c)$.

Alternatively, costs of avoidance may only be instantiated when the individual avoids being in a group. This reflects a situation where sociality is beneficial. Thus, we examine the case in which the reproduction of both X_1 and X_2 increases as a function of the frequency at which it pairs. We model this benefit as a direct, linear function of the frequency of pairs within each genotype, such that birth rate for X_1 is calculated as $(1 + \frac{TG_{X1}}{X_1})b_1$ and for X_2 as $\left(1 + \frac{TG_{X2}}{X_2}\right) b_2$.

Results

Overall Dynamics

In basic models of physiological resistance, the transmission coefficient is a compound of per contact transmission rate and number of contacts. It can be shown that if all individuals are in pairs, i.e. in contact, then the dynamics of disease with pair formation are identical to the physiological resistance model.

If pair formation is incomplete, the basic reproductive number of the parasite, $R_0 = \frac{2\delta G}{N\mu}$, and equivalent to canonical formulations for R_0. We first examined the effect of the different pairing behaviors and avoidance strategies on the equilibrium frequency of individuals in pairs, prevalence of disease, and R_0 when only X_2, the avoiding genotype, was present (Fig. 1).

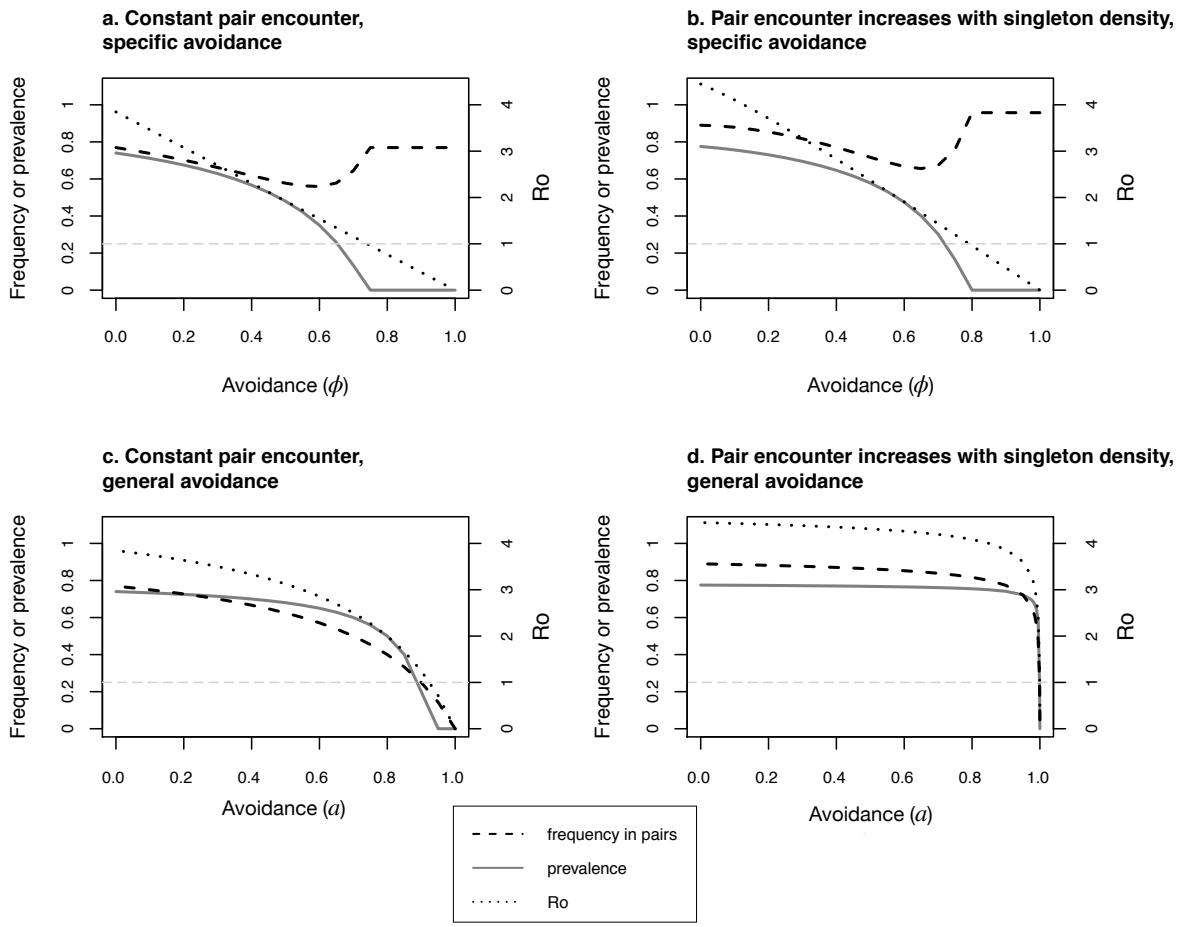

Figure 1. Pairing and disease dynamics at equilibrium when only the avoiding genotype (X_2) is present in the population, under different pairing processes and avoidance strategies. The light gray horizontal dotted line represents when the basic reproductive number, $R_0 = 1$, below which the disease cannot persist in the population, and above which sustained transmission is possible. $b = 1, \mu = 0.2, \delta = 1, \upsilon = 0.3, k = 0.01$.

Under both pair formation processes, increased specific avoidance of infected individuals (Figs. 1a and 1b) is highly effective at reducing prevalence of the disease, and as X_2 avoids Y it also results in a decrease in the frequency of individuals in pairs. However, the frequency of individuals in pairs increases again at high specific avoidance, because few infected individuals remain for the healthy X_2 individuals to encounter. With further avoidance, R_0 falls below 1,

prevalence drops to 0, and pair formation is only among healthy individuals. Thus, at high levels of specific avoidance, hosts can successfully extirpate the disease from the population while maintaining their social structure.

Contrarily, while general avoidance reduces R_0 and prevalence, as long as per contact transmission rate is high, avoidance of pairing must be nearly complete (Figs. 1c and 1d) to reduce R_0 below the threshold of 1. In other words, if hosts are not able to detect infection in conspecifics, behavioral avoidance effectively reduces disease risk, but possibly at levels where the hosts compromise their social structure.

Resistance Evolution

We next examined the evolutionary dynamics in a population with genetic variants that do (X_2) and do not (X_1) avoid disease when resistance carried a fixed cost. When behavioral resistance was through specific avoidance of infected individuals (ϕ), X_1 and X_2 could stably coexist across a range of avoidance levels, even at very high costs (>50% reduction in birth rate) when avoidance of infected individuals was highest (Fig. 2a). Varying behavioral resistance through general avoidance, ($\rho - a$), resulted in the same overall pattern, with polymorphism occurring across the broadest range of costs when avoidance was greatest (Fig. 2b). However, consistent with the results in Fig. 1, even high levels of general avoidance still resulted in some frequency of pairing with infected individuals. Thus, under the general avoidance strategy, X_2 could not tolerate as great a reduction in birth rate at intermediate levels of avoidance.

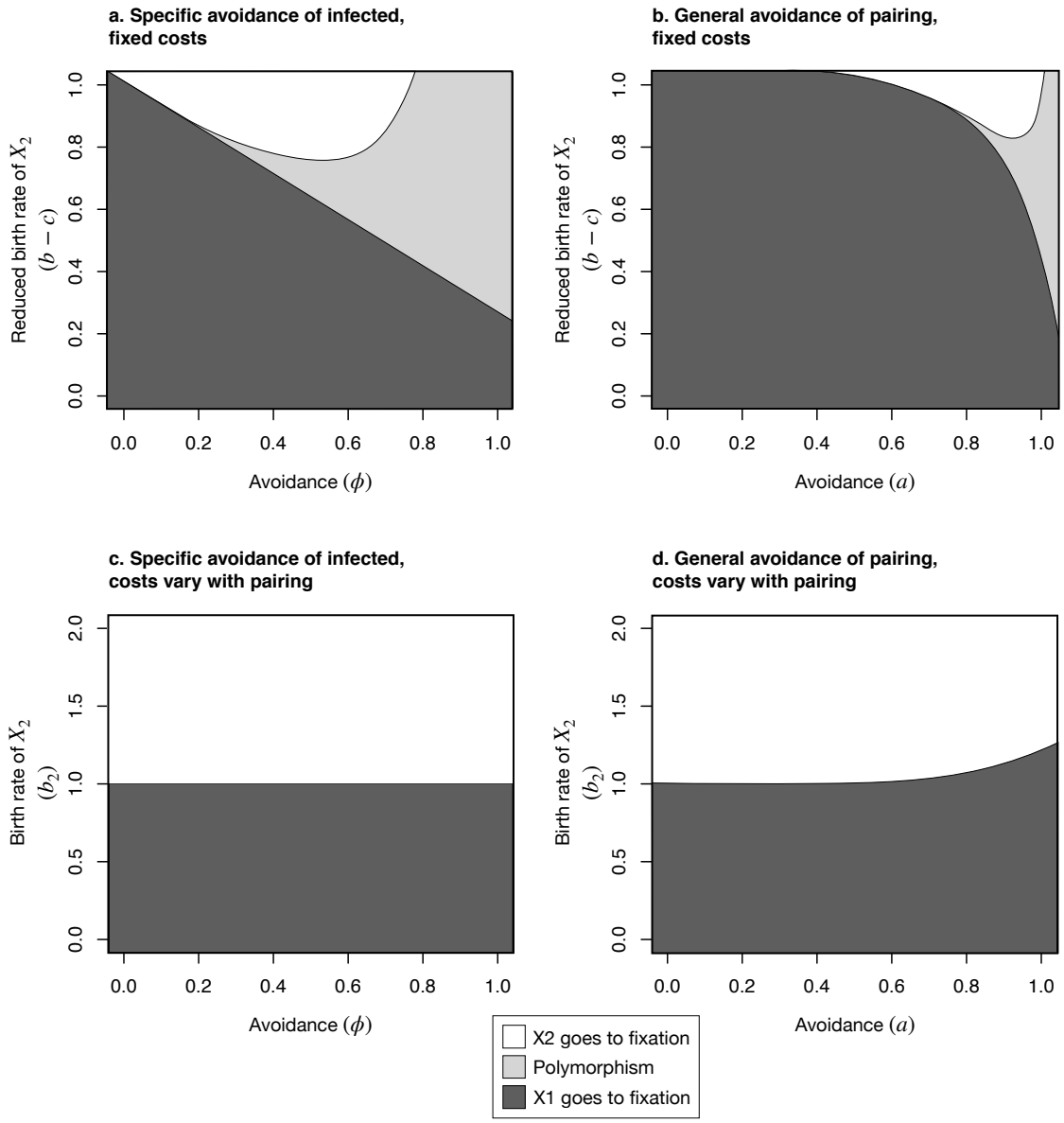

Figure 2: Shaded areas represent equilibrium gene frequency states for the models when the cost of X_2 and the avoidance strategy of X_2 are varied. Possible outcomes include X_1 or X_2 becoming fixed in the population, or X_1 and X_2 coexisting, i.e. polymorphism. All plots show results for constant rate of pair encounter. (Corresponding plots for density-dependent pair encounter rates can be found in Supplementary Materials S2). $b = 1, \mu = 0.2, \delta = 1, \upsilon = 0.3, k = 0.01$.

We next assumed that individuals receive a benefit as a function of social behavior relative to being alone, we found that in the case of specific avoidance the benefits of reduced

disease risk evenly balanced the costs of lost social interactions, such that X_2 only went to fixation when its fitness was relatively greater than X_1 (Fig. 2c). When avoidance was general, X_1 could even sometimes reach fixation when X_2 had a higher birth rate, because at high rates of general avoidance, reductions in disease risk are not substantial enough to compensate for the loss of social contacts (Fig. 2d). In both cases, when costs were linearly dependent on the frequency of individuals in pairs, polymorphism between X_1 and X_2 was not possible.

While we only present the results from models with a constant rate of pair encounter, the patterns of polymorphism were qualitatively similar when pair encounter rate depended on the density of singletons (Supplementary Materials S2).

Discussion

We present evidence here that the evolution of behavioral resistance can differ from physiological or biochemical resistance evolution depending on the costs and benefits of resistance and sociality. Similar to physiological resistance, polymorphism in behavioral resistance can be maintained across a broad range of fixed costs when the level of resistance is high [5,25]. When enough behaviorally resistant individuals are present in the population, behavioral avoidance strategies can effectively reduce the disease risk so that susceptible individuals can coexist.

However, such polymorphism is much less likely to occur when social interactions have benefits, as they do in many social organisms. In the case of specific avoidance, when infected individuals are detectable, social interactions are limited only in situations where avoidance will provide the benefit of reduced transmission. Thus specific avoidance reduces the negative impacts of lost social opportunities, and even allows for the full recuperation of social behavior

190 when avoidance is high enough to fully extirpate the disease through behavioral mechanisms.
191 Yet when avoidance is general and at a high level, the costs of lost social interactions are higher
192 than the benefits of reduced disease risk because of 'mistakes' in selection of diseased or healthy
193 social partners. This comparison highlights the challenge of controlling an outbreak of an
194 emergent disease, especially when asymptomatic transmission is possible, as in COVID-19 [31].
195 The maintenance of a polymorphic state under some conditions suggests that if avoidance
196 behavior could be performed flexibly, a mixed strategy of social distancing that allows for some
197 social interaction could strike a balance between the costs and benefits.

198 To dissect the basic differences between behavioral and physiological resistance we have
199 deliberately kept the models simple. Application to any specific host-pathogen context would
200 require more complexity in the temporal and social structure of the interactions. For example, in
201 nature individuals interact more fluidly, increasing opportunities for transmission. As groups
202 become larger, transmission within groups and movement between groups would be possible,
203 and behavioral resistance strategies could become more diverse. Consistent with previous
204 research, this simple model highlights trade-offs between the benefits of reducing disease risk
205 and the costs of foregoing other opportunities, whether nutritional [23], reproductive [24], or in
206 the case of our model, social.

207 Behavioral and physiological resistance are not separate phenomena but are likely to
208 interact, with behavioral effects being antecedent to physiological resistance, in a framework
209 similar to a two-step infection process [32]. In such situations, genetic associations can arise
210 between genes determining resistance, even though they may have no direct physiological
211 interaction. Physiological and behavioral defenses against parasites might therefore trade-off

with one another either directly or indirectly. For example, house finches that avoid sick conspecifics invest less in immune defenses [19].

A genetic basis for parasite avoidance behaviors has support from knockout experiments in laboratory mice [33] and selective breeding in livestock [34]. Direct evidence of genetic polymorphism in social behavior in natural populations has also begun to emerge [35]. Behavioral resistance can thus be innate, as we model it, or it can be learned through prior exposure [36–38], and how dynamics of learned resistance would differ from innate is a rich direction for future research. Together these innate and learned responses represent a suite of psychological and cognitive mechanisms that psychologists have termed the "behavioral immune system" [39]. Innate and acquired behavioral resistance are conceptually parallel to innate and adaptive immune responses, but whether this metaphor translates to equivalent dynamics merits further examination.

Funding

This work was funded by NIH R01GM122061, part of the joint NSF-NIH-USDA Ecology and Evolution of Infectious Diseases program.

Code and Supporting Materials

All code and derivations can be found in the Supplementary Materials.

Competing Interests

The authors have no competing interests to declare.

Authors' Contributions

CRA and JA conceived the project and derived the equations together. CRA carried out the simulations and drafted the manuscript. JA provided critical input on the simulations and revisions to the manuscript. All authors gave final approval for publication and agree to be held accountable for the work performed therein.

References

1. Boots M, Bowers RG. 1999 Three mechanisms of host resistance to microparasites - avoidance, recovery and tolerance - show different evolutionary dynamics. *J. Theor. Biol.* **201**, 13–23. (doi:10.1006/jtbi.1999.1009)
2. Hayward AD, Garnier R, Watt KA, Pilkington JG, Grenfell BT, Matthews JB, Pemberton JM, Nussey DH, Graham AL. 2014 Heritable, heterogeneous, and costly resistance of sheep against nematodes and potential feedbacks to epidemiological dynamics. *Am. Nat.* **184**. (doi:10.1086/676929)
3. Parker BJ, Barribeau SM, Laughton AM, Roode JC De, Gerardo NM. 2011 Non-immunological defense in an evolutionary framework. *Trends Ecol. Evol.* **26**, 242–248. (doi:10.1016/j.tree.2011.02.005)
4. Best A, White A, Boots M. 2009 The implications of coevolutionary dynamics to host-parasite interactions. *Am. Nat.* **173**, 779–791. (doi:10.1086/598494)
5. Antonovics J, Thrall PH. 1994 The cost of resistance and the maintenance of genetic polymorphism in host-pathogen systems. *Proc. R. Soc. B Biol. Sci.* **257**, 105–110.
6. Antonovics J, Boots M, Ebert D, Koskella B, Poss M, Sadd BM. 2013 The origin of specificity by means of natural selection: Evolved and nonhost resistance in host-pathogen interactions. *Evolution (N. Y).* **67**, 1–9. (doi:10.1111/j.1558-5646.2012.01793.x)
7. Boots M, Bowers RG. 2004 The evolution of resistance through costly acquired immunity. *Proc. R. Soc. B Biol. Sci.* **271**, 715–723. (doi:10.1098/rspb.2003.2655)
8. Hart BL. 2011 Behavioural defences in animals against pathogens and parasites: parallels with the pillars of medicine in humans. *Philos. Trans. R. Soc. B Biol. Sci.* **366**, 3406–3417. (doi:10.1098/rstb.2011.0092)
9. Roode JC De, Lefèvre T. 2012 Behavioral immunity in insects. *Insects* **3**, 789–820. (doi:10.3390/insects3030789)
10. Curtis V, de Barra M, Aunger R. 2011 Disgust as an adaptive system for disease avoidance behaviour. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **366**, 389–401. (doi:10.1098/rstb.2010.0117)
11. Tybur JM, Lieberman D. 2016 Human pathogen avoidance adaptations. *Curr. Opin. Psychol.* **7**, 6–11. (doi:10.1016/j.copsyc.2015.06.005)
12. Anderson RM, May RM. 1979 Population biology of infectious diseases: Part I. *Nature* **280**, 361–367. (doi:10.1038/280361a0)
13. May RM, Anderson RM. 1979 Population biology of infectious diseases: Part II. *Nature* **280**, 455–461. (doi:10.1038/280455a0)

14. Antonovics J, Iwasa Y, Hassell MP. 1995 A generalized model of parasitoid, venereal, and vector-based transmission processes. *Am. Nat.* **145**, 661–675.
15. McCallum H *et al.* 2017 Breaking beta: Deconstructing the parasite transmission function. *Philos. Trans. R. Soc. B Biol. Sci.* **372**. (doi:10.1098/rstb.2016.0084)
16. Boots M, Haraguchi Y. 1999 The evolution of costly resistance in host-parasite systems. *Am. Nat.* **153**, 359–370. (doi:10.1086/303181)
17. Behringer DC, Butler MJ, Shields JD. 2006 Avoidance of disease by social lobsters. *Nature* **441**, 421. (doi:10.1038/441421)
18. Bouwman KM, Hawley DM. 2010 Sickness behaviour acting as an evolutionary trap? Male house finches preferentially feed near diseased conspecifics. *Biol. Lett.* **6**, 462–465. (doi:10.1098/rsbl.2010.0020)
19. Zylberberg M, Klasing KC, Hahn TP. 2013 House finches (*Carpodacus mexicanus*) balance investment in behavioural and immunological defences against pathogens. *Biol. Lett.* **9**. (doi:10.1098/rsbl.2012.0856)
20. Poirotte C, Massol F, Herbert A, Willaume E, Bomo PM, Kappeler PM, Charpentier MJE. 2017 Mandrills use olfaction to socially avoid parasitized conspecifics. *Sci. Adv.* **3**, e1601721. (doi:10.1126/sciadv.1601721)
21. Curtis VA 2014 Infection-avoidance behaviour in humans and other animals. *Trends Immunol.* **35**, 457–64. (doi:10.1016/j.it.2014.08.006)
22. Buck JC, Weinstein SB, Young HS. 2018 Ecological and evolutionary consequences of parasite avoidance. *Trends Ecol. Evol.* **0**, 1–14. (doi:10.1016/j.tree.2018.05.001)
23. Fox NJ, Marion G, Davidson RS, White PCL, Hutchings MR. 2013 Modelling parasite transmission in a grazing system: The importance of host behaviour and immunity. *PLoS One* **8**. (doi:10.1371/journal.pone.0077996)
24. Theuer M, Berec L. 2018 Impacts of infection avoidance for populations affected by sexually transmitted infections. *J. Theor. Biol.* **455**, 64–74. (doi:10.1016/j.jtbi.2018.06.030)
25. Boots M, Best A, Miller MR, White A. 2009 The role of ecological feedbacks in the evolution of host defence: What does theory tell us? *Philos. Trans. R. Soc. B Biol. Sci.* **364**, 27–36. (doi:10.1098/rstb.2008.0160)
26. Hadeler KP. 1989 Pair formation in age-structured populations. *Acta Appl. Math.* **14**, 91–102. (doi:10.1017/CBO9781107415324.004)
27. Gimelfarb A. 1988 Processes of pair formation leading to assortative mating in biological populations: encounter-mating model. *Am. Nat.* **131**, 865–884.
28. Antonovics J, Bergmann J, Hempel S, Verbruggen E, Veresoglou S, Rillig M. 2015 The evolution of mutualism from reciprocal parasitism: more ecological clothes for the Prisoner's Dilemma. *Evol. Ecol.* **29**, 627–641. (doi:10.1007/s10682-015-9775-6)
29. Soetaert K, Petzoldt T, Setzer RW. 2010 Solving differential equations in R: Package deSolve. *J. Stat. Softw.* **33**, 1–25. (doi:10.18637/jss.v033.i09)
30. R Development Core Team R. 2011 R: A language and environment for statistical computing. *R Found. Stat. Comput.* **1**, 409. (doi:10.1007/978-3-540-74686-7)
31. Bai Y, Yao L, Wei T, Tian F, Jin D-Y, Chen L, Wang M. 2020 Presumed asymptomatic carrier transmission of COVID-19. *N. Engl. J. Med.* **323**, 1406–1407. (doi:10.1056/NEJMoa2001316)
32. Fenton A, Antonovics J, Brockhurst MA. 2012 Two-step infection processes can lead to coevolution between functionally independent infection and resistance pathways.

Evolution. **66**, 2030–2041. (doi:10.1111/j.1558-5646.2012.01578.x)

33. Kavaliers M, Choleris E, Ågmo A, Muglia LJ, Ogawa S, Pfaff DW. 2005 Involvement of the oxytocin gene in the recognition and avoidance of parasitized males by female mice. *Anim. Behav.* **70**, 693–702. (doi:10.1016/j.anbehav.2004.12.016)
34. Hutchings MR, Knowler KJ, McAnulty R, McEwan JC. 2007 Genetically resistant sheep avoid parasites to a greater extent than do susceptible sheep. *Proc. R. Soc. B Biol. Sci.* **274**, 1839–1844. (doi:10.1098/rspb.2007.0398)
35. Kocher SD, Mallarino R, Rubin BER, Yu DW, Hoekstra HE, Pierce NE. 2018 The genetic basis of a social polymorphism in halictid bees. *Nat. Commun.* **9**. (doi:10.1038/s41467-018-06824-8)
36. Klemme I, Karvonen A. 2016 Learned parasite avoidance is driven by host personality and resistance to infection in a fish-trematode interaction. *Proc. R. Soc. B Biol. Sci.* **283**. (doi:10.1098/rspb.2016.1148)
37. James CT, Noyes KJ, Stumbo AD, Wisenden BD, Goater CP. 2008 Cost of exposure to trematode cercariae and learned recognition and avoidance of parasitism risk by fathead minnows *Pimephales promelas*. *J. Fish Biol.* **73**, 2238–2248. (doi:10.1111/j.1095-8649.2008.02052.x)
38. Klemme I, Karvonen A. 2018 Experience and dominance in fish pairs jointly shape parasite avoidance behaviour. *Anim. Behav.* **146**, 165–172. (doi:10.1016/j.anbehav.2018.10.022)
39. Schaller M, Park JH. 2011 The behavioral immune system (and why it matters). *Curr. Dir. Psychol. Sci.* **20**, 99–103. (doi:10.1177/0963721411402596)

Supplementary Materials – S1: Equations
Equations are numbered as Supplementary Equations (SE) for ease of reference relative to the equations in the main text.

If encounter rate is at a constant frequency
The differential equations for number of groups and singletons are given as:

$$\frac{dG}{dt} = \rho S - \upsilon G \tag{SE1}$$

$$\frac{dS}{dt} = T(\upsilon G - \rho S) \tag{SE2}$$

By setting $\frac{dS}{dt}$ and $\frac{dG}{dt}$ to zero, we can calculate that at equilibrium, the ratio of groups to singletons, $\frac{G}{S} = \frac{\rho}{\upsilon}$. The frequency of individuals in groups, or $\frac{TG}{N}$, can be calculated from this equation as $\frac{\frac{\rho}{\upsilon}}{1+\frac{\rho}{\upsilon}}$. Thus, the number of groups at equilibrium is

Number of pairs of X1 (if all the individuals in the population were X1):

$$G_1 = \left(\frac{\frac{\rho}{\upsilon}}{1+\frac{\rho}{\upsilon}}\right)\left(\frac{N}{T}\right) \tag{SE3}$$

Number of pairs of X2 (if all individuals in the population were X2):

$$G_2 = \left(\frac{\frac{\rho - a}{\upsilon}}{1+\frac{\rho - a}{\upsilon}}\right)\left(\frac{N}{T}\right) \tag{SE4}$$

If encounter rate is dependent on the density of singletons
Such a scenario could be represented by a number of functions, but for the sake of simplicity, we calculate the rate at which groups encounter one another as a function of the number of singletons, ρS. Thus, as more singletons exist in the population, group formation increases.

This gives us the following differential equations:

$$\frac{dG}{dt} = \rho S^2 - \upsilon G \tag{SE5}$$

$$\frac{dS}{dt} = T(\upsilon G - \rho S^2) \qquad (SE6)$$

At equilibrium, $\frac{G}{S^2} = \frac{\rho}{\upsilon}$. We can substitute $G = \frac{N-S}{T}$ into this equation, which can be reduced to $T\rho S^2 + \upsilon S - \upsilon N = 0$. Using the quadratic formula, we can calculate that

$$S = \frac{-\mu + \sqrt{\mu^2 + 4T\rho\mu N}}{2T\rho} \qquad (SE7)$$

And the number of pairs at equilibrium can be calculated as follows.

$$G = \frac{N - S}{T} \qquad (SE8)$$

Thus, the number of pairs of X1 (if all the individuals in the population were X1) is

$$G_1 = N - \frac{-\upsilon + \sqrt{\upsilon^2 + 4T(\rho)\upsilon N}}{2T^2\rho} \qquad (SE9)$$

And the number of pairs of X2 (if all individuals in the population were X2) is

$$G_2 = N - \frac{-\upsilon + \sqrt{\upsilon^2 + 4T(\rho - a)\upsilon N}}{2T^2(\rho - a)} \qquad (SE10)$$

Where…
N = total population size
ρ = rate of pair encounter
υ = rate of unpairing
a = general avoidance parameter (=0 in case of specific avoidance)
T = group size (=2 henceforth)

Number of pairs of each type
Number of pairs of X1 and X2 with Y individuals, which provides the opportunity for transmission:

$$P_{X1Y} = 2G_1\left(\frac{X_1}{N}\right)\left(\frac{Y}{N}\right) = \left(\frac{2G_1X_1Y}{N^2}\right) \qquad (SE11)$$

$$P_{X2Y} = (1-\phi)\,2G_2\left(\frac{X_2}{N}\right)\left(\frac{Y}{N}\right) = (1-\phi)\left(\frac{2G_2X_2Y}{N^2}\right) \qquad (SE12)$$

Where ϕ = specific avoidance (=0 in case of general avoidance)

Total number of X1 and X2 in pairs:

$$P_{X1} = \frac{2G_1X_1}{N} \tag{SE13}$$

$$P_{X2} = \frac{2G_2X_2}{N} - (\phi)\, 2G_2\left(\frac{X_2}{N}\right)\left(\frac{Y}{N}\right) \tag{SE14}$$

where subtracting $(\phi)\, 2G_2\left(\frac{X_2}{N}\right)\left(\frac{Y}{N}\right)$ represents removing the pairs that were NOT formed as a result of specific avoidance of infected individuals.

Fixed costs

If costs are fixed, then the following equations define the rate of change of each type of individual:

$$\frac{dX_1}{dt} = X_1(b - kN - \mu) - \delta\left(\frac{2G_1X_1Y}{N^2}\right) \tag{SE15}$$

$$\frac{dX_2}{dt} = X_2((b - c) - kN - \mu) - \delta(1 - \phi)\left(\frac{2G_2X_2Y}{N^2}\right) \tag{SE16}$$

$$\frac{dY}{dt} = \delta\left(\frac{2G_1X_1Y}{N^2}\right) + \delta(1 - \phi)\left(\frac{2G_2X_2Y}{N^2}\right) - \mu Y \tag{SE17}$$

Where…

b = birth rate

c = fixed cost

δ = transmission given contact

μ = mortality

Costs depend on social structure

If costs depend on pairing, then the following equations define the rate of change of each type of individual:

$$\frac{dX_1}{dt} = X_1\left(b_1\left(1 + \frac{P_{X1}}{X_1}\right) - kN - \mu\right) - \delta\left(\frac{2G_1X_1Y}{N^2}\right) \tag{SE18}$$

$$\frac{dX_2}{dt} = X_2\left((b_2\left(1 + \frac{P_{X2}}{X_2}\right) - kN - \mu\right) - \delta(1 - \phi)\left(\frac{2G_2X_2Y}{N^2}\right) \tag{SE19}$$

$$\frac{dY}{dt} = \delta\left(\frac{2G_1X_1Y}{N^2}\right) + \delta(1 - \phi)\left(\frac{2G_2X_2Y}{N^2}\right) - \mu Y \tag{SE20}$$

Transmission term in behavioral vs. physiological resistance

When all individuals are in pairs, the model of behavioral processes of resistance is identical to a mass action model of mixing behavior. To illustrate this, using the X_1 genotype as an example,

the transmission term is classically represented by $\beta X_1 \left(\frac{Y}{N}\right)$. In the present behavioral model, when all individuals are in pairs, $G = \frac{N}{2}$. Substituting this fraction for G in the transmission term for X_1 above gives

$$2\delta \left(\frac{N}{2}\right)\left(\frac{X_1}{N}\right)\left(\frac{Y}{N}\right) \tag{SE21}$$

which simplifies to the equivalent $\delta X_1 \left(\frac{Y}{N}\right)$. The same follows for transmission to X_2.

Calculating R_0

R_0, or the basic reproductive number, is the condition that must be met for new infections to be produced in any time step of the model. In other words, the differential equation for Y must be greater than 0.

$$0 < \frac{dY}{dt} = \frac{2\delta GY}{N^2}(X_1 + X_2) - \mu Y \tag{SE22}$$

When Y is rare, $X_1 + X_2 \approx N$, which gives

$$0 < \frac{2\delta G}{N} - \mu \tag{SE23}$$

This can be further reduced to the formula for R_0:

$$1 < \frac{2\delta G}{N\mu} = R_0 \tag{SE24}$$

This formulation represents the frequency of pairs $\frac{2G}{N}$ multiplied by per contact transmission probability (δ), divided by the background mortality rate (μ).

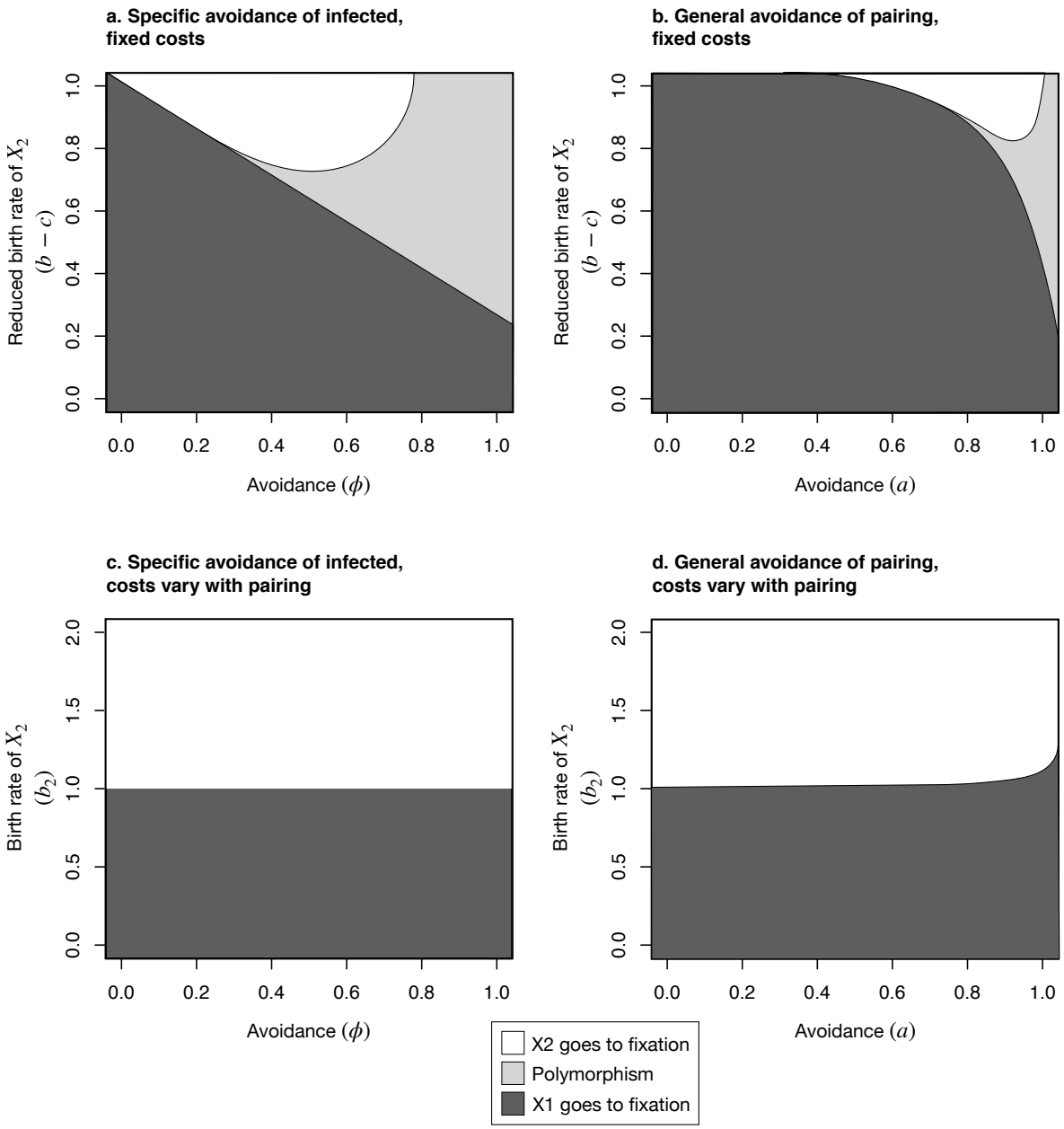

Figure S1: Shaded areas represent equilibrium gene frequency states for the models when the cost of X_2 and the avoidance strategy of X_2 are varied. Possible outcomes include X_1 or X_2 becoming fixed in the population, or X_1 and X_2 coexisting, i.e. polymorphism. All plots show results for density dependent encounter rate. $b = 1, \mu = 0.2, \delta = 1, \upsilon = 0.3, k = 0.01$.