Enriched pathogen diversity under host-type heterogeneity and immune-mediated competition

Pamela P. Martinez[1*]

Robert J. Woods[2]

Mercedes Pascual[1]

1. Department of Ecology and Evolution, University of Chicago, Chicago, Illinois 60637;

2. Division of Infectious Diseases, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan 48109;

∗ Corresponding author; e-mail: martinezp@uchicago.edu.

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Abstract

How pathogen diversity is maintained over time and how it influences epidemiological processes are active areas of research with relevance to control. Long-term coexistence of strains can emerge from host heterogeneity if strains become specialists for different host. This process can modify however competition for hosts on another dimension, that of cross-protection mediated by immune recognition. Motivated by empirical evidence that rotavirus utilizes different human blood group antigens for cell entry, we ask how frequency-dependent competition due to specific immunity affects the evolutionary outcome of diversity given differences in host-pathogen affinity. We further ask whether an association between differences in affinity and cross-immunity influences this outcome. With an adaptive dynamics framework, we analyze the long-term coexistence of multiple strains under these two kinds of competition typically considered separately. Our results show that when cross-immunity depends on host-pathogen affinity, diversity is magnified as long-term evolution allows for the coexistence of multiple semi-specialized strains, an outcome that is not observed when the degree of cross-immunity is independent from affinity distance among strains. These findings indicate the importance of considering the interplay of equalizing and stabilizing mechanisms related respectively to host heterogeneity and immunity, to understand diversity patterns in pathogens like rotavirus.

Introduction

In recent decades, the increased availability of molecular data has enhanced theoretical understanding of the role of epidemiological, immunological, and evolutionary processes in shaping pathogen diversity (Grenfell et al. 2004, Lipsitch and O'Hagan 2007, Volz et al. 2013). The mechanisms that underlie the phenotypic diversity of pathogens remain however an active area of research of relevance to epidemiology and responses to intervention.

Questions on strain diversity within pathogen populations exhibit clear similarity to those posed for species diversity within ecological communities. For the latter, two kinds of mechanisms for long-term species coexistence are distinguished: those known as 'stabilizing' which operate in a frequency-dependent manner as they confer an advantage to the rare; and those known as 'equalizing' because they minimize absolute fitness differences between species which would otherwise lead to dominance and exclusion (Chesson 2000). Equalizing effects reduce differences in fitness components such as growth rate, reproduction and survival. Given absolute fitness differences that promote exclusion, coexistence can also result from the existence of trade-offs as in the classical example provided by Tilman's R^* theory (Tilman 1982): multiple species that compete for the same resources can coexist if they have significantly different resource requirements and rely on the presence of a trade-off in the ability to consume these requirements.

In pathogens, frequency-dependent selection imposed by the immune system can result in different strains coexisting within a population (Gupta et al. 1996, Gupta et al. 1998, Gupta and Maiden 2001, Gog and Grenfell 2002, Gomes et al. 2002). The antigenic determinants that trigger the specific immune response are the phenotypic traits that underlie competition for hosts at the population level: once a host is protected against a given antigenic variant, it is no longer a resource for the growth of this specific type. Changes in antigenic sites allow the pathogen to escape immunity in the host population, so that strains that are sufficiently distant in antigenic space can coexist by limiting similarity (Macarthur and Levins 1967). Coexistence arises here

from purely stabilizing differences due to the frequency of given antigenic types, with no fixed fitness differences between individual pathogens.

Another aspect of strain diversity in viruses is associated with fixed fitness differences and follows from phenotypic variation in the host population itself (Shirato et al. 2008, Van Trang et al. 2014). In particular, host variation has the potential to promote strain diversity if strains differ in their ability to bind host receptors. This is the case for norovirus and rotavirus which recognize human histo-blood group antigens as receptors, with the ABO group and Lewis b antigen structures determining the strain's specificity for the host (Shirato et al. 2008, Van Trang et al. 2014).

We address here with an adaptive dynamics approach how differences in host-pathogen affinity (equalizing effect) interact with selection imposed by specific immunity (stabilizing effect) to influence strain diversity. Our results highlight the importance of considering the constraint imposed by a link between these two mechanisms when considering the stable coexistence of pathogen strains. We discuss the relevance of these findings in the context of epidemic control implementations.

Methods

Transmission model

We implemented an extended SIR transmission model that considers two types of hosts, A and B, which can differ in their binding affinity to two or more strains (fig 1A).

Within each host population, newly born individuals enter the susceptible class S. When hosts become infected, they move first to the infected (and infectious) class I_1, and then, to the first recovery class R_1 according to the recovery rate γ. Individuals within the R_1 class can be infected by a different strain with probability α denoting the degree of cross-immunity conferred by the first infection. Individuals can then transition to a second infected class I_2, followed by a second recovery class R_2, with the same recovery rate γ. At this point, individuals in the R_2

compartment are assumed to have acquired complete immunity and stay in this class until they die (the notation 1, 2 refers to the order of the events and not to the infection with a particular strain). Finally, P refers to the population size and μ to the birth/death rate. The complete set of differential equations is described in online appendix B.

The force of infection consists of the contact rate β and the probability of being infected after contact. Here, this probability specifically refers to host affinity, which defines the identity of each strain x_i and is characterized by the trait a_{x_i}. An increase in the affinity for one host is assumed to occur at the expense of a decreasing affinity for the other so that $a_{Ax_i}^{1/s} + a_{Bx_i}^{1/s} = 1$ (Egas et al. 2004). This trade-off means that each strain can be highly specialized for only one host (A or B). Its shape is determined by parameter s. Values of $s > 1$ result in a strong trade-off, while $s < 1$ generates a weak trade-off (fig 1B).

To compare the biological scenario where the degree of differences in host-binding affinity is independent from the intensity of cross-immunity, to one in which these two phenotypes are linked, we considered first a model with fixed values of α and then one in which α depends on the distance between the affinity values of the current and past infection (a_{x_i} and a_{x_j} respectively): $\alpha = 1 - e^{-(d(a_{x_i} - a_{x_j}))^2}$, where the parameter d determines how fast the immune protection decays as a function of the distance (Gog and Grenfell 2002, fig 1C). This assumption implies that changes in the protein that binds the host receptor have an effect in both the degree of cross-immunity (*i.e.* antigenic distance) and the affinity for the host.

Evolutionary dynamics

An adaptive dynamics framework was used to analyze the different strategies under which the system may evolve (Metz et al. 1996, Dieckmann and Law 1996, Geritz et al. 1997). This framework assumes that mutants have a small difference in the phenotype of interest with respect to the resident's individuals. Mutants can invade the system if the growth rate or 'invasion fitness' is positive. Changes in the invasion fitness associated with changes in the mutant phenotype determine the direction in which the population will evolve. For each combination of the

pathogen's trait, we estimated the endemic equilibrium numerically, which allowed us to obtain the selection gradient as well as the mutual invasibility plots. See online appendix B, for further details.

Results

We first analyzed the evolutionary dynamics of the system under a high degree of cross-immunity (for fixed $\alpha = 0.08$). Figure 2A-E shows the mutual invasibility plots for weak and strong trade-offs in the ability to bind the receptor of different hosts. When there is a weak trade-off in host utilization (values of $s < 1$), we observe that the system evolves towards a singular 'generalist' strategy. In contrast, for values of s greater than 1, the strains evolve to be 'specialists', either on different hosts (top left and bottom right), or on the same host (bottom left and top right of the mutual invasibility plot). The evolutionary outcome is dependent upon the initial values of the affinity trait a_{x_i}, which can lead the system in the direction of an evolutionary branching point (attractors that then allow branching toward specialization on different hosts), and/or away from an unstable repellor, which can trap the strains in regions where they both specialize on the same host. As we vary the strength of the affinity trade-off, the evolutionary outcomes are summarized in the bifurcation diagram (fig A1A), which shows that the system is dominated by a Continuously Stable Strategy (CSS, generalist strategy) for any value of $s < 1$. Likewise, for $s \geq 2$ the only possible outcome is a repellor, and thus a completely specialized trait. From high to low values of s, a bifurcation occurs at $s \approx 2$ where two repellors emerge together with a saddle node until s approaches 1. As we show next, $s < 1$ is a universal condition for the generalist strategy, while the value of s at which the bifurcation occurs depends on α and epidemiological parameters.

We then considered a model in which the strength of cross-immunity (α) depends on the host affinity distance between current and past infections (see Methods for detail). This can be the case when the receptor's binding site also functions as an antigen (*e.g.* Taylor et al. 1987,

Ruggeri and Greenberg 1991, Taylor and Dimmock 1994). This assumption implies that changes in binding affinity have a direct effect on antigenic distance, and that therefore, these changes affect the degree of specific immunity acquired from past infections. Figure 2F-J summarizes the findings from this analysis for a broad strain space ($d = 0.5$), for which the average probability α is 0.08. This result shows that the coexistence of semi-specialized strains is likely for a wide range of values of s, with the potential evolutionary outcomes shown in fig A1B. The area in the mutual invasibility plot under which two residents would coexist varies with the value of s in a nonlinear way (fig A2); this area refers to the percentage of possible trait combinations under which the invasion fitness (*i.e.* growth rate) is positive for both strains, showing that intermediate values of the affinity trade-off allow for greater coexistence. Interestingly, a model with fixed α exhibits more transient ecological coexistence than the one with a variable cross-immunity, but this coexistence does not last when considering evolutionary time scales.

For the above results, cross immunity was strong (as indicated by the low values of α and d). We now examine the effect of both an even higher and lower cross immunity. Not surprising based on our first analysis, the impact of cross-immunity is dependent upon the value of the host affinity trade-off when α is fixed and independent from host affinity. Under weak host affinity trade-offs ($s < 1$), the system evolves to a unique Evolutionarily Stable Strategy (ESS), which is also a CSS, over the full range of cross-immunity (fig 3A). In this situation, the strains have the same ability to infect both host types (*i.e.* same trait value), becoming neutral with respect to the binding affinity. When the trade-off is stronger ($s > 1$), evolutionary branching occurs under strong cross-immunity; that is, the population evolves to a dimorphic population and each strain becomes completely specialized for different hosts, avoiding competition. Finally, under a very strong trade-off ($s > 2$), the most likely scenario is one in which both strains become specialized for the same host (evolutionary repellors), this is because even very strong cross-immunity cannot push one of the populations to utilize the other host due to the steep trade-off. Stable coexistence of two specialized strains would be possible, however, if the evolutionary steps were larger, as is the case for zoonotic introductions. In summary, a weak trade-off favors the evolution of

generalist strains that are neutral with respect to their ability to bind the host receptor, while the evolutionary outcome for a strong trade-off is determined by initial conditions, where the two strains can become completely specialized for different hosts or for the same one (fig 3B).

In contrast to the fixed cross-immunity, the parameter space for the model with variable α in which the two phenotypes (differences in binding and immunity) are linked, is dominated by evolutionary branching points, followed by repellors and CSS (fig 3C). After the branching occurs, the population becomes polymorphic with completely or partially specialized pathogens (fig 3D, fig A3), where the coexistence of multiple strains is now evolutionarily stable. This result also indicates that higher values of d, and thus narrower cross-immunity width (fig 1C), amplify the coexistence of semi-specialized strains, which is consistent with observations in nature for pathogens like rotavirus, as we discuss next.

Discussion

We have presented a transmission model that ties together host-pathogen affinity with the frequency dependence selection caused by specific immune responses. Previous studies of pathogen diversity have considered these two aspects of competitive dynamics independently. Concordant with previous results, we show that a weak trade-off leads to generalists, while a strong trade-off leads to full specialists, when the degree of specific immunity is fixed (Egas et al. 2004). By contrast, if the strength of cross-immunity is functionally related to the difference in host affinity, the dynamics of the system do not follow from the simpler models. Our results show that coexistence of multiple semi-specialized strains able to infect both types of hosts is a common evolutionary scenario, favoring diversity. These results also suggest that populations need a weaker immune response to overcome the affinity trade-off (indicated by higher values of d, fig 3D) to maintain 2 or more phenotypes coexisting.

Two of the main assumptions of the adaptive dynamics framework are that the system initially consists of a monomorphic population (*i.e.* all pathogens have the same trait), and that most

mutations have a small effect. These assumptions highly constrain the outcome by repellors pushing the two types to specialize on the same host (trajectories along the diagonal in the Trait evolution plots). However, viruses like flu and rotavirus can experience zoonotic introduction of somewhat different types, pushing the system into the region where two strains have very different affinity values. The system under these conditions could lead to the utilization of multiple hosts, especially when cross immunity is dependent upon the affinity difference, with the evolution of semi-specialized strains, as commonly seen in rotavirus (*i.e.* many of the P types can bind multiple HBGAs) (Van Trang et al. 2014, Nordgren et al. 2014, Ayouni et al. 2015, Ma et al. 2015, Lui et al. 2016, Ramani et al. 2016, Sun et al. 2016a, Sun et al. 2016b, Sun et al. 2016c, Zhang et al. 2016).

Another important assumption of this work is the consideration of a trait that has an effect in both immune recognition as well as host entry. Several studies in viral pathogens have shown that the major antigenic sites or epitopes are located in the same subunits of the proteins responsible for binding the host-receptor (Taylor et al. 1987, Ruggeri and Greenberg 1991, Taylor and Dimmock 1994). For the case of rotavirus, the major antigenic sites of the VP4 protein are in the VP8 subunit (Larralde et al. 1991, Kirkwood et al. 1996), the same subunit responsible of cell attachment inside the host (Ruggeri and Greenberg 1991). Additionally, strong association between infection by the predominant rotavirus genotypes and histo-blood group antigens have been found in children (Van Trang et al. 2014), implying affinity differentiation and the presence of a trade-off in the way that the serotypes interact with the host receptor. Rotavirus' serotypes are defined based on the G and P genotypes that encode for the outer capsid protein (VP7) and the cell attachment protein (VP4) respectively. For human infections, around 11 P-types have been described (Matthijnssens et al. 2011), suggesting that strain diversity is higher than expected based solely on the number of blood types present in the population, and that therefore strains may not be completely specialized for a certain host type. The number of studies showing the association between histo-blood group types in the host and strain specificity has increased substantially in the last decade (*e.g.* Shirato et al. 2008, Van Trang et al. 2014, others). These studies

have only addressed however the affinity for the host, leaving open questions about the role of immunity in the observed diversity, especially when the distribution of rotavirus serotypes differs among different countries (Gentsch et al. 2005). Previous theoretical work has explored the relationship between the binding site and antigenic response (Ndifon et al. 2009). Inspired by the population dynamics of influenza, the authors showed that the presence of epitopes located far from the receptor-binding site may disrupt viral neutralization causing steric interference between antibodies. This consideration is of relevance as changes in the receptor binding site can also modify the recognition by the immune system, with epidemiological consequences that are still poorly understood. It would also be valuable to further investigate whether viruses with significant diversity tend to use a range of similar receptors, or if less diverse viruses have become fixed on a single receptor with no similar receptors, as a consequence of different degrees of cross-immunity and trade-off. These empirical studies could make possible the evaluation of predictions made by theoretical models like the one presented in this article, with potential contributions to more effective vaccine development, particularly in developing countries where vaccine efficacy has been limited (ZamanEtAl2010).

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Figure legends

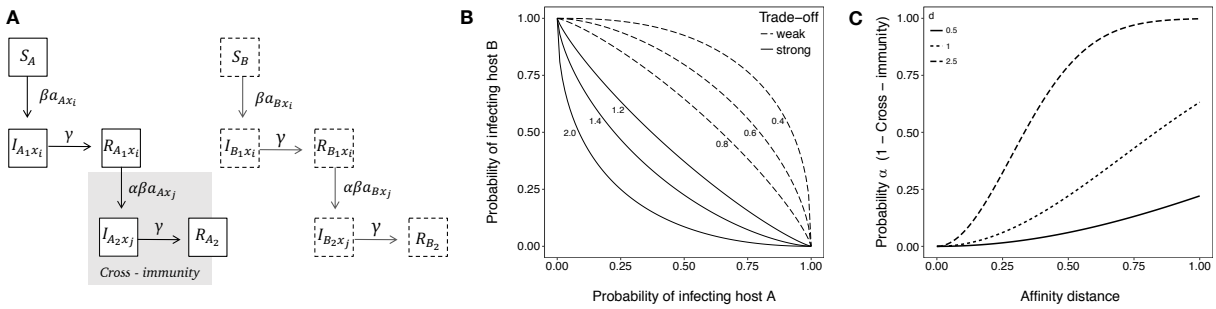

Figure 1: A) Transmission model. S, I, R refer respectively to the classes of Susceptible, Infected and Recovered individuals. The diagram on the left corresponds to host A, and the one on the right, to host B. B) Affinity trade-off. The trade-off can be strong ($s > 1$) or weak ($s < 1$). The different curves correspond to different values of s as indicated by the numbers next to each of them. C) Cross-immunity function. The probability α (1-cross-immunity) is plotted as a function of the affinity distance between current and previous infections, for different values of d.

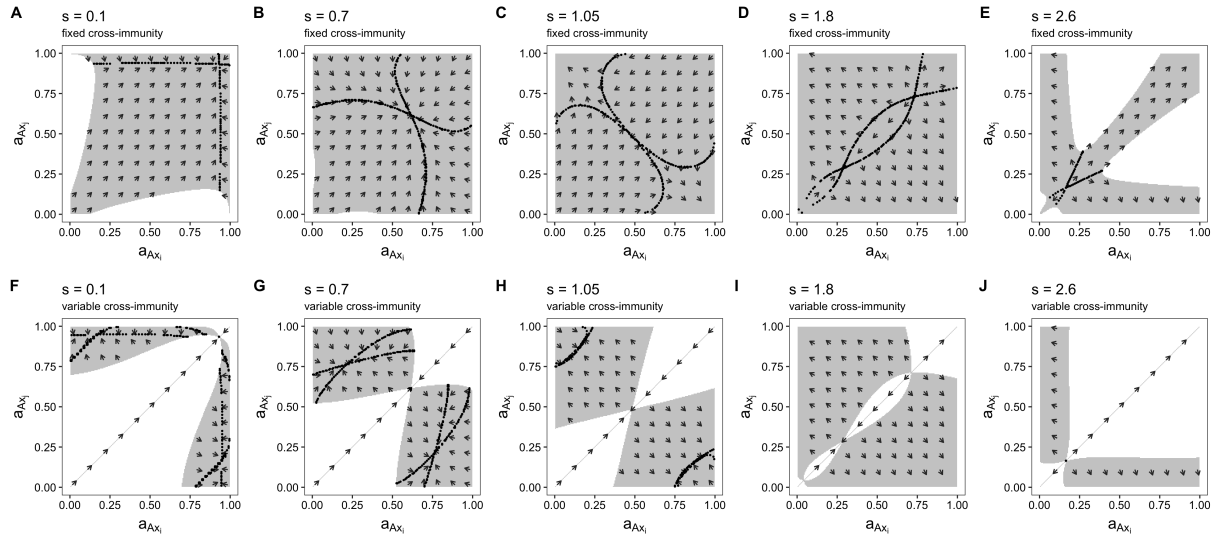

Figure 2: Trait evolution plots for the affinity for host A, for different values of trade-off strength s. Comparison of the evolutionary outcomes for the scenario in which α is fixed ($\alpha = 0.08$, A-E) and the one in which cross-immunity α depends on the binding affinity distance (between the traits a_{x_i} and a_{x_j}; $d = 0.5$, F-J). The arrows show the directions of evolution. The grey area indicates the region for which the pair of traits a_{x_i} and a_{x_j} can mutually invade and coexist (i.e. the invasion fitness is positive for both). The arrows indicate the direction of evolution as the result from successive invasion events. Dotted black lines refer to the adaptive isoclines, where the selection gradient vanishes. The intersection of these isoclines denotes singular strategies, which can be stable or unstable. If the strategy is stable, then the two traits that are given by this intersection stably coexist (*i.e.* they result in an evolutionary stable strategy).

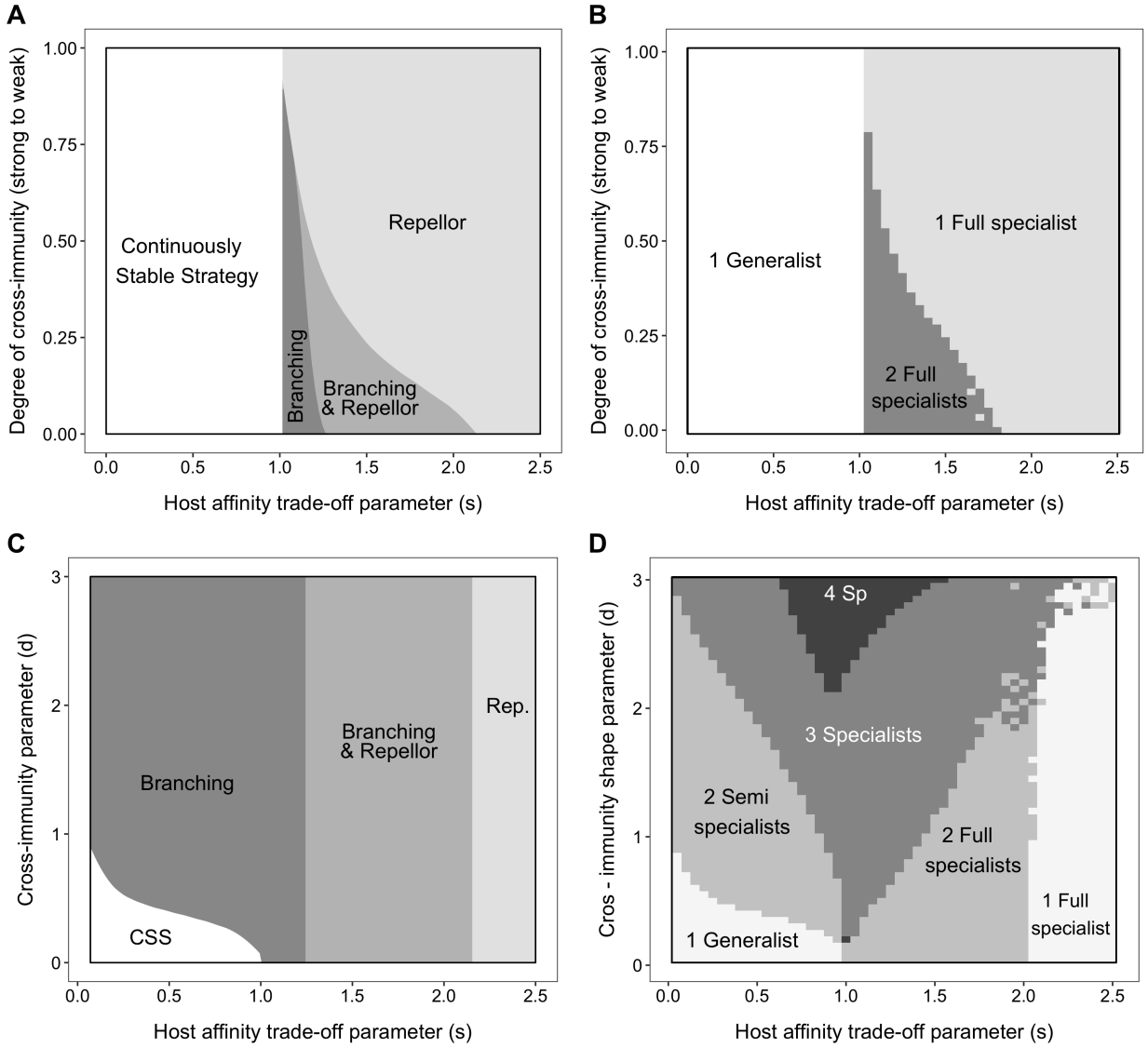

Figure 3: Long term behavior as a function of the strength of cross-immunity. Parameter space under which the system evolves to a CSS, Repellor and/or Evolutionary Branching strategy with their respective conversion into specialist or generalist. Complete cross-immunity is indicated by $\alpha = 0$ and $d = 0$. Figures A-B and C-D correspond to a fixed and variable α, respectively. Figures B and D were calculated from the output of numerical simulations (with an initial affinity value a_{Ax_i} of 0.5).

Online Appendix

A Supplementary Figures

Table A1: Epidemiological parameters*.

Description (parameter)	Value
Birth/death rate (μ)	0.067 (1/year)
Recovery rate (γ)	4 (1/year)
Contact rate (β)	20

* Parameter values where chosen based on the feasibility of steady states of the system for ecological time.

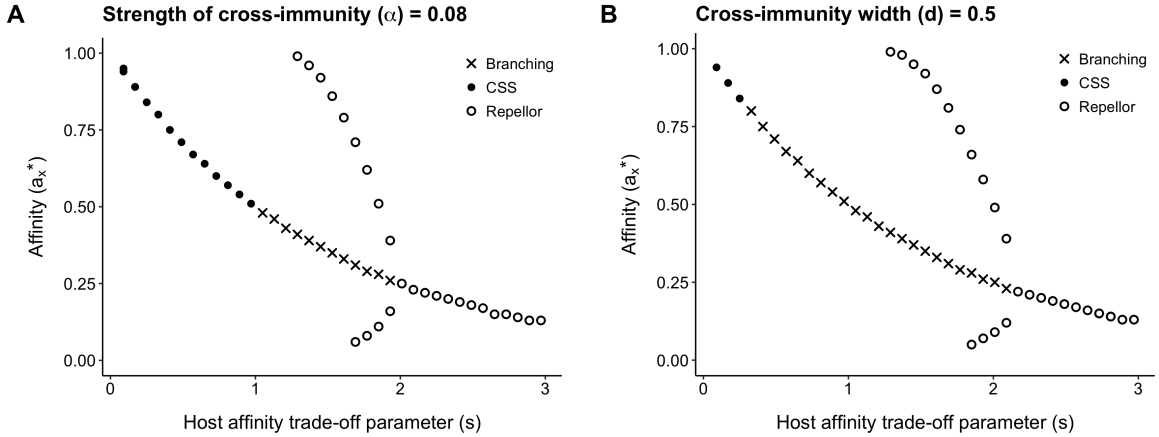

Figure A1: Bifurcation diagram. Evolutionary strategies as a function of the trade-off parameter s. The strategies under which the system may evolve are identified as: a Continuously Stable Strategy (CSS), a local evolutionarily stable strategy whose the affinity evolves until it reaches the CSS and cannot be invaded by a nearby mutant; an Evolutionary branching: the affinity trait evolves towards the branching point and once this point is reached, the traits diverge and the population becomes dimorphic; a Repellor: an evolutionary unstable strategy. The filled dots, open dots, and x symbols indicate CSS, repellors, and branching strategies, respectively, and the grey arrows denote the direction of monomorphic evolution.

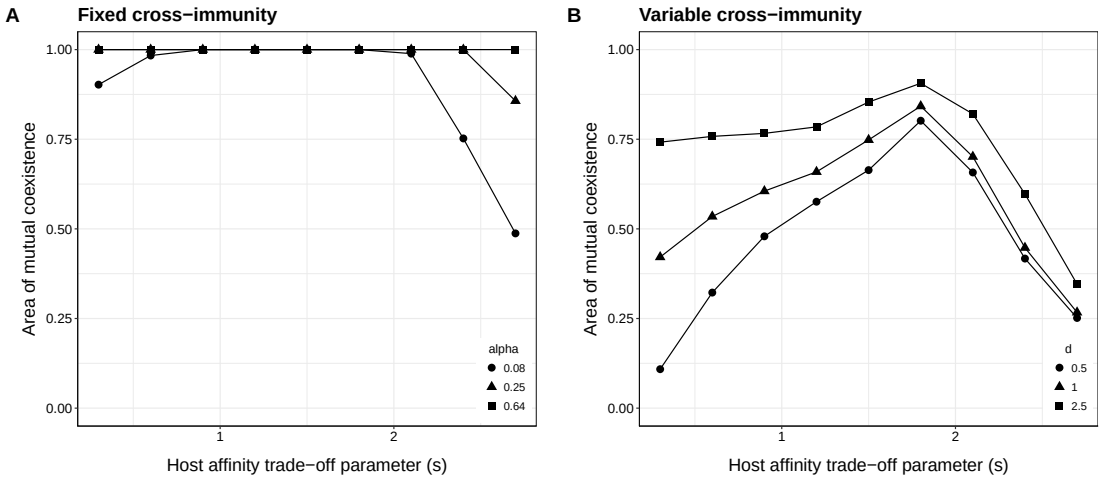

Figure A2: Percentage of all possible combinations of traits that allow for mutually invasion and coexistence as a function of s, for different values of fixed cross-immunity (A), and different values of d (variable cross-immunity, B).

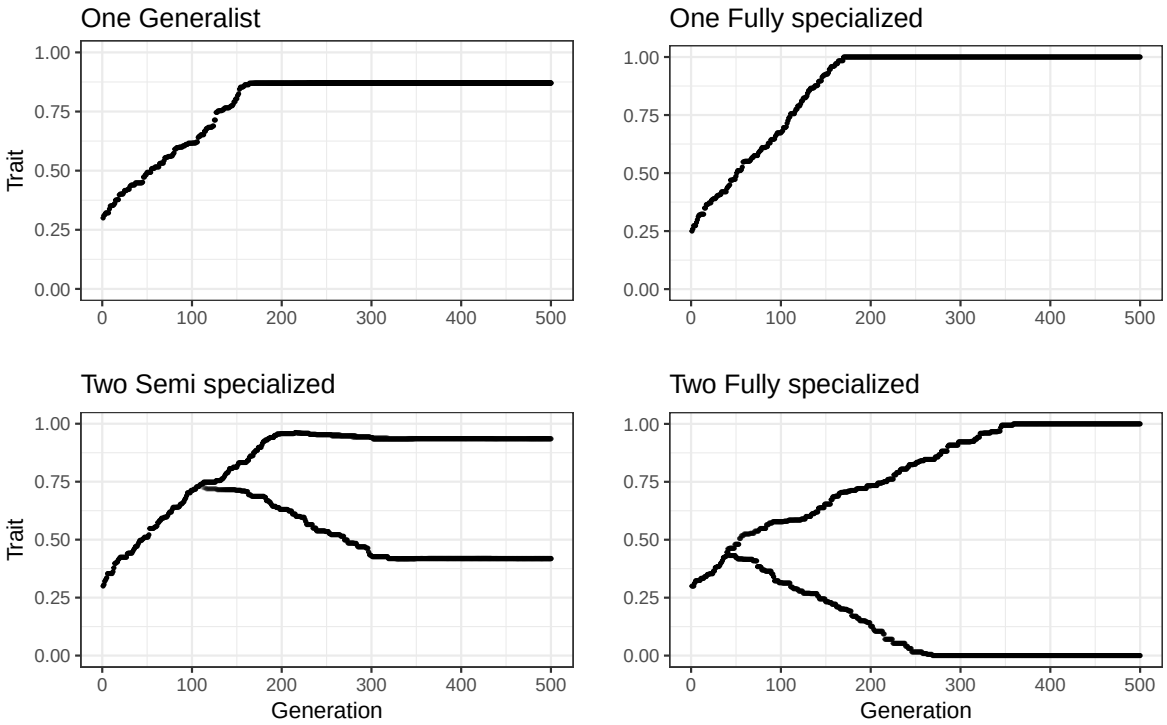

Figure A3: Representative evolutionary outcomes of affinity traits over time.

B Additional Methods

Transmission model

The population dynamics of the disease was represented with an SIR (Susceptive–Infected–Recovery) model that considers two populations of hosts (A and B) and multiple pathogen strains that differ in their affinity to bind the host receptor. The set of equations that describe the dynamics of the population A is given by

$$\begin{aligned}
\frac{dS_A}{dt} &= \mu P_A - \beta \frac{S_A}{P_A} \sum_{i=1}^{n} a_{Ax_i}(I_{A_1x_i} + I_{B_1x_i} + I_{A_2x_i} + I_{B_2x_i}) - \mu S_A \\
\frac{dI_{A_1x_i}}{dt} &= \beta \frac{S_A}{P_A} a_{Ax_i}(I_{A_1x_i} + I_{B_1x_i} + I_{A_2x_i} + I_{B_2x_i}) - \gamma I_{A_1x_i} - \mu I_{A_1x_i} \\
\frac{dR_{A_1x_i}}{dt} &= \gamma I_{A_1x_i} - \beta \frac{R_{A_1x_i}}{P_A} \sum_{j \neq i} \alpha_{ij}\, a_{Ax_j}(I_{A_1x_j} + I_{B_1x_j} + I_{A_2x_j} + I_{B_2x_j}) - \mu R_{A_1x_i} \\
\frac{dI_{A_2x_j}}{dt} &= \beta \sum_{i \neq j} \alpha_{ij} \frac{R_{A_1x_i}}{P_A} - \gamma I_{A_2x_j} - \mu I_{A_2x_j} \\
\frac{dR_A}{dt} &= \gamma \sum_{i=1}^{n} I_{A_2x_i} - \mu R_A
\end{aligned} \tag{1}$$

Similarly, the equations that characterize the population of host type B is given by:

$$\begin{aligned}
\frac{dS_B}{dt} &= \mu P_B - \beta \frac{S_B}{P_B} \sum_{i=1}^{n} a_{Bx_i}(I_{A_1x_i} + I_{B_1x_i} + I_{A_2x_i} + I_{B_2x_i}) - \mu S_B \\
\frac{dI_{B_1x_i}}{dt} &= \beta \frac{S_B}{P_B} a_{Bx_i}(I_{A_1x_i} + I_{B_1x_i} + I_{A_2x_i} + I_{B_2x_i}) - \gamma I_{B_1x_i} - \mu I_{B_1x_i} \\
\frac{dR_{B_1x_i}}{dt} &= \gamma I_{B_1x_i} - \beta \frac{R_{B_1x_i}}{P_B} \sum_{j \neq i} \alpha_{ij}\, a_{Bx_j}(I_{A_1x_j} + I_{B_1x_j} + I_{A_2x_j} + I_{B_2x_j}) - \mu R_{B_1x_i} \\
\frac{dI_{B_2x_j}}{dt} &= \beta \sum_{i \neq j} \alpha_{ij} \frac{R_{B_1x_i}}{P_B} - \gamma I_{B_2x_j} - \mu I_{B_2x_j} \\
\frac{dR_B}{dt} &= \gamma \sum_{i=1}^{n} I_{B_2x_i} - \mu R_B
\end{aligned} \tag{2}$$

The first infection is represented by the pathogen x_i and its respective affinity for hosts A

(a_{Ax_i}) and B (a_{Bx_i}). The second infection is then characterized by pathogen x_j. The identity of each strain is defined by its ability to bind the host, with affinity values between 0 and 1. After the second infection (by a different strain), the host becomes immune to all future infections. For the first part of our analyzes we have fixed the value of α (between 0 and 1), and therefore α_{ij} is independent from the identity of the strains. For the second part, α_{ij} is a function of the distance between a_{Ax_i} and a_{Bx_i}, as described in the Methods section and fig 1C. The epidemiological parameters that we have used are described in table A1.

Evolutionary dynamics

In order to determine the ability of a new mutant to invade the system, we first estimated the conditions under which the system goes to a stable endemic equilibrium. The equilibrium will be stable if the real part of the leading eigenvalue of the corresponding Jacobian matrix is negative. We then included the equations that involve the behavior of the mutant. The new Jacobian matrix has a block-triangular form, where the diagonal blocks correspond respectively to the Jacobian of the residents J_{res} (*i.e.* the system in the absence of the mutant) and the Jacobian of the mutant J_{mut}, as follows:

$$\begin{bmatrix} J_{res} & J \\ 0 & J_{mut} \end{bmatrix} \tag{3}$$

Therefore, the eigenvalues of the new system are those of these block-triangular matrix. Since the real part of the eigenvalue of J_{res} is negative, the stability of the new system is determined by the leading eigenvalue of J_{mut} (λ). If the real part of λ is positive, the equilibrium becomes unstable and thus the population of the mutant will increase over time, invading the system; conversely, if $\lambda < 0$, the mutant will not be able to invade and will go extinct. The invasion fitness of the mutant (x_k) is then defined by λ, and has the following form:

$$\lambda(x_i, x_j, x_k) = \frac{a_{Ax_k}\beta(\alpha_{ik}R^*_{A_1x_i} + \alpha_{jk}R^*_{A_1x_j} + S^*_A)}{P^*_A} + \frac{a_{Bx_k}\beta(\alpha_{ik}R^*_{B_1x_i} + \alpha_{jk}R^*_{B_1x_j} + S^*_B)}{P^*_B} - \gamma - \mu \tag{4}$$

where $a_{Bx_k} = (1 - a_{Ax_k}^{1/s})^s$ and α_{ik} can be a fixed value, or a function of the distance between a_{x_i} and a_{x_k}: $\alpha_{ik} = 1 - e^{-(d(a_{x_i} - a_{x_k}))^2}$. The direction of evolution as the result of successive invasions is determined by the selection gradient g, given by the first derivative of λ with respect to the trait of the mutant k and evaluated at the resident traits values i and j:

$$g_i(x_i, x_j) = \frac{\partial \lambda(x_i, x_j, x_k)}{\partial a_{Ax_k}}|_{k=i} \tag{5}$$

$$g_j(x_i, x_j) = \frac{\partial \lambda(x_i, x_j, x_k)}{\partial a_{Ax_k}}|_{k=j} \tag{6}$$

If the sign of the selection gradient is positive, mutants with traits higher than those of the residents will be successful, whereas if $g < 0$, mutants with traits lower than those of the residents will invade. The evolutionary singular strategy is characterized by the pair of traits a_{Ax_i} and a_{Ax_j} for which both values of selection gradients are zero.

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