doi:10.1111/evo.136

Evolution of transmission mode in conditional mutualisms with spatial variation in symbiont quality

Alexandra Brown[1,2] **and Erol Akçay**[1]

[1] *Department of Biology, University of Pennsylvania, Philadelphia Pennsylvania 19104*

[2] *E-mail: alexabr@sas.upenn.edu*

Received May 4, 2018

Accepted October 23, 2018

Many symbioses have costs and benefits to their hosts that vary with the environmental context, which itself may vary in space. The same symbiont may be a mutualist in one location and a parasite in another. Such spatially conditional mutualisms pose a dilemma for hosts, who might evolve (higher or lower) horizontal or vertical transmission to increase their chances of being infected only where the symbiont is beneficial. To determine how transmission in hosts might evolve, we modeled transmission evolution where the symbiont had a spatially conditional effect on either host lifespan or fecundity. We found that over ecological time, symbionts that affected lifespan but not fecundity led to high frequencies of infected hosts in areas where the symbiont was beneficial and low frequencies elsewhere. In response, hosts evolved increased horizontal transmission only when the symbiont affected lifespan. We also modeled transmission evolution in symbionts, which evolved high horizontal and vertical transmission, indicating a possible host–symbiont conflict over transmission mode. Our results suggest an eco-evolutionary feedback where the component of host fitness affected by a conditionally mutualistic symbiont in turn determines its distribution in the population, and, through this, the transmission mode that evolves.

KEY WORDS: **Conditional mutualism, context-dependent, symbiosis, spatial variation, transmission mode.**

Most, if not all, multicellular organisms live in symbiosis with other species. While some symbioses are always mutualistic or always parasitic, many others have costs and benefits that are context-dependent (Thomas et al. 2000; Daskin and Alford 2012; Chamberlain et al. 2014). We call these interactions conditional mutualisms. Symbiont effects may vary based on abiotic factors (e.g., nutrient availability (Cheplick et al. 1989) or temperature (Baker et al. 2013)) or biotic factors (e.g., the presence of a third species that parasitizes the host (Smith 1968)). The abiotic or biotic context may in turn vary in space. In some cases, the symbiont may change from a mutualist to a parasite depending on the location. For example, the endophytic fungus *Epichloë coenophiala* increases the biomass of tall fescue (*Festuca arundinacea*) seedlings in nutrient-rich soil, while decreasing host biomass in nutrient-poor soils (Cheplick et al. 1989). Variation with temperature in the nutrients provided by *Symbiodinium* endosymbionts of corals produces a similar pattern. Clade D members of *Symbiodinium* provide less nitrogen than Clade C symbionts except at high temperatures, where they provide equivalent nitrogen and more carbon (Baker et al. 2013). Even unicellular organisms can have conditionally mutualistic symbionts, as many plasmids are beneficial only in the presence of specific environmental factors (such as antibiotics or a particular nutrient source) and harmful otherwise (Carroll and Wong 2018).

Such spatially conditional mutualisms pose a dilemma for hosts with regard to how to acquire their symbionts. In general, assuming no correlation between horizontal and vertical transmission, hosts are predicted to evolve reduced vertical (parent-to-offspring) transmission of parasites and increased vertical transmission of mutualists (Yamamura 1993). In spatially structured populations, hosts may also evolve decreased horizontal transmission of parasites, either by preventing their own infection (Best et al. 2011) or by reducing their rates of transmission to others (Débarre et al. 2012). However, hosts in spatially conditional

mutualisms have to deal with a symbiont that is both a mutualist and a parasite, and it is not clear whether horizontal transmission, vertical transmission, both, or neither will evolve in conditional mutualisms. Furthermore, symbionts as well as hosts may show genetic variation that affects the two rates of transmission (Ebert 2013). There may thus be host–symbiont conflict over transmission mode, which may also influence transmission evolution.

Which transmission mode evolves is an important question, because transmission mode itself, regardless of whether it arises through host or symbiont evolution, influences how symbionts spread and the evolution of symbiont costs and benefits. Horizontal transmission is predicted to select for more parasitic symbionts, and vertical transmission for more mutualistic ones (Ewald 1987; Alizon et al. 2009), in the absence of other feedbacks (Werren et al. 2008; Shapiro and Turner 2014; Akçay 2015). Furthermore, research on the impact of spatial variation on parasitism shows that spatial heterogeneity in various factors can have a large influence on the virulence and spread of parasites (Hochberg et al. 2000; Thrall and Burdon 2000; Krist et al. 2004; Lively 2006; Real and Biek 2007; Tellier and Brown 2011; Jousimo et al. 2014; Penczykowski et al. 2014; Carlsson-Granér and Thrall 2015; Gibson et al. 2016; Saeki and Sasaki 2018). Understanding transmission mode evolution in hosts and symbionts in spatially conditional mutualisms may thus give insight into both potential host–symbiont conflict as well the future distribution and virulence of the symbiont.

We model transmission mode evolution in a spatially conditional mutualism over a range of newborn host dispersal rates. We consider two different types of spatially conditional mutualisms that affect different components of host fitness. In the first conditional mutualism, the symbiont affects host lifespan, and in the second the symbiont affects host fecundity (modeled as chance of reproduction per unit time). We split symbiont effects into these components partly because they lead to significantly different evolutionary predictions, and partly because symbionts may affect lifespan and fecundity differently. For example, symbionts may affect only one component of host fitness. Symbioses that are involved only with reproduction, like plant-pollinator/seed parasite relationships will influence host fecundity without affecting lifespan. On the other hand, symbioses involved with, for example, juvenile survival (as in the interaction between jellyfish and the juvenile scads they protect from predators) affect lifespan without having any influence on the reproductive output of hosts who survive to adulthood (Bonaldo et al. 2004). Furthermore, symbionts may affect both lifespan and fecundity but in opposite directions. For example, fungal endophyte infection was found to decrease fecundity and increase survival for the grass *Poa alsodes* (Chung et al. 2015), while fungal endophytes increased fecundity at the expense of survival in the grass *Agrostis hyemalis* (Yule et al. 2013). These trade-offs between survival and fecundity have been shown theoretically to determine the persistence of infection in non-context-dependent symbioses (Rudgers et al. 2012; Yule et al. 2013; Chung et al. 2015; Bibian et al. 2016), suggesting it may be useful and informative to separate lifespan and fecundity effects for conditional mutualisms as well.

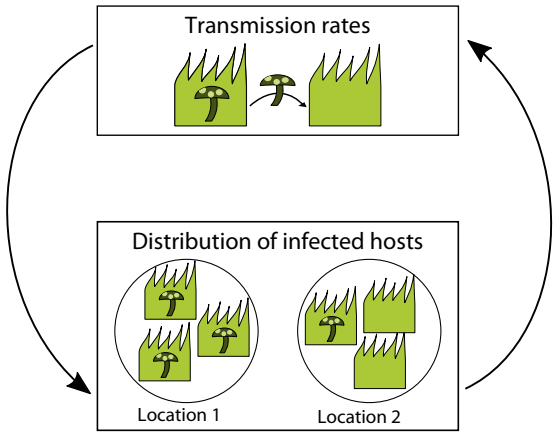

Figure 1. The evolution of transmission is governed by an eco-evolutionary feedback. The spatial distribution of infected hosts (bottom) affects the selective advantage of a mutant host or symbiont with a different transmission rate. As a mutant spreads, its transmission rates in turn influence the spatial distribution of infected hosts. The feedback from the spatial distribution to the transmission rates is influenced by the dispersal rate and the component of host fitness the symbiont affects. Similarly, the selective advantage of a mutant with new transmission rates is influenced by whether selection acts on the host or the symbiont, as different distributions of infected hosts are beneficial to each.

Intuitively, we may predict that when a host is likely to stay in the same location as its parent, vertical transmission may be a good strategy to ensure an advantageous infection status (i.e., infection where the symbiont is beneficial and lack of infection where the symbiont is harmful). Conversely, when hosts often disperse from their natal patch, they might instead rely on horizontal transmission from their new neighbors to acquire the symbiont where it is beneficial. However, horizontal transmission will only confer the "right" infection status when a host's neighbors are infected where the symbiont is a mutualist and uninfected where the symbiont is a parasite. Thus, hosts should only evolve horizontal transmission when the distribution of infected hosts matches the spatial distribution of symbiont effects. As the distribution of infected hosts is itself influenced by the transmission rates, the evolution of the transmission mode is fundamentally governed by an eco-evolutionary feedback (see Fig. 1).

This eco-evolutionary feedback suggests that the evolution of transmission mode might ultimately depend on which life history stage is affected by the symbiont through the fitness component's influence on the distribution of infected hosts. Accordingly, we find that when the symbiont affects host lifespan,

ecological conditions allow hosts to evolve high horizontal transmission. In contrast, when the symbiont affects host fecundity, high horizontal transmission leads to high levels of parasitism. Regardless of the type of symbiont effect, hosts can evolve high vertical transmission at low but not high dispersal rates.

Finally, to determine whether there is host–symbiont conflict over transmission, we model transmission mode evolution under host and symbiont control separately. We infer the possibility of conflict if hosts evolve one transmission rate and symbionts evolve another.

Our results highlight how ecological feedback from the fraction of infected hosts generated by the current transmission rates affects the selective advantage of mutant transmission rates, determining the course of evolution. This suggests that the manner in which the symbiont affects host life history and ecology ultimately influences host evolution and the ecological dynamics hosts evolve toward.

Methods

We first describe the model in general, then discuss the methods for the analytical and simulation models.

THE MODEL

We model a patch-structured population where the symbiont is beneficial in half the patches (M-patches) and harmful in the other half (P-patches). We consider two types of conditional mutualism: one where the symbiont affects host fecundity and the other where it affects host lifespan. In the main text, we have shown results from the case where the symbiont affects host lifespan through adult host mortality. This is almost identical to the case where the symbiont affects lifespan through newborn hosts' establishment probability, which we have shown in Fig. S2.

We analytically model the case where there are two patches of infinite size. For tractability in our analytical model, the ecological and evolutionary dynamics occurr on separate timescales. It is possible that evolution may proceed differently if ecological and evolutionary changes can happen concurrently or if populations are finite. To investigate this, we also simulated transmission evolution on the same time scale as ecological changes and in finite populations. In both the analytical model and the simulations, we assume all patches are of constant and equal size. We track the fraction of infected hosts in each patch (given by i_q for patch q) and the horizontal and vertical transmission probabilities of the resident and mutant, (h and v for the resident and h^* and v^* for the mutant; see Table 1 for list of variables). We assume that neither multiple infection nor loss of the symbiont once infected is possible. When hosts control transmission, we assume that a host's transmission probabilities determine its probability of infection. When symbionts control transmission, uninfected hosts cannot be said to have a transmission probability. Instead we model the potentially infecting symbiont as determining the transmission probability. Conflict over transmission mode might then occur between the host receiving the symbiont and the incoming symbiont.

Table 1. Variables used in the analytical and simulation models.

Variable	Definition
i_q	Fraction of infected hosts in patch q
q and q'	Focal patch and the other patch, respectively
h	Resident horizontal transmission probability
v	Resident vertical transmission probability
h^*	Mutant horizontal transmission probability
v^*	Mutant vertical transmission probability
d	Probability a newborn disperses to the other patch
N	Size of host population
$\overline{f}$	Average fecundity
$\overline{m_q}$	Average mortality in patch q
$f_{q,U}$	Fecundity of uninfected hosts in patch q
$f_{q,I}$	Fecundity of infected hosts in patch q
$s_{q,U}$	Establishment probability of uninfected hosts in patch q
$s_{q,I}$	Establishment probability of infected hosts in patch q
$m_{q,U}$	Mortality of uninfected hosts in patch q
$m_{q,I}$	Mortality of infected hosts in patch q
M	Patch where symbiont is a mutualist
P	Patch where symbiont is a parasite
t	Time in units of host births
τ	Time in units of tN
X	Matrix giving mutant growth rates
A	Matrix giving mutant birth rates
B	Matrix giving mutant death rates
A', B'	Mutant birth and death rates multiplied by N
A_v, A_h	Mutant symbiont births due to vertical and horizontal transmission

We model overlapping host generations in discrete time. Each time step a host is chosen to reproduce, with the probability of reproduction determined by the host's patch and infection status. A host in patch q has fecundity $f_{q,I}$ if it is infected or $f_{q,U}$ if uninfected. The probability that a host with fecundity f reproduces is $\frac{f}{N\overline{f}}$, where N is the population size and $\overline{f}$ is the average fecundity.

$$\overline{f} = \frac{1}{\#\text{patches}} \sum_{q \in \text{Patches}} (1 - i_q) f_{q,U} + i_q f_{q,I}$$

When the symbiont affects host fecundity, we assume infected hosts have higher fecundity than uninfected hosts in M-patches, and that the reverse is true in P-patches. When the

symbiont affects host lifespan, we assume all hosts have equal fecundity.

If the parent host is infected, its offspring has a chance to acquire the symbiont via vertical transmission. For a vertical transmission probability v, the probability that a host in patch q gives birth to an uninfected or infected offspring is

$$\begin{aligned}&\Pr(\text{Produces offspring born uninfected})\\&= \begin{cases} f_{q,U}/(N\overline{f}), & \text{if parent is uninfected}\\ (1-v)f_{q,I}/(N\overline{f}), & \text{if parent is infected}\end{cases}\\&\Pr(\text{Produces offspring born infected})\\&= \begin{cases} 0, & \text{if parent is uninfected}\\ vf_{q,I}/(N\overline{f}), & \text{if parent is infected}\end{cases}\end{aligned} \tag{1}$$

After birth, newborns disperse to a new patch with probability d or stay in their natal patch with probability $1-d$. We assume that newborns must mature somewhat before they become susceptible to horizontal infection, such that there is a window of time after dispersal and before establishment where newborns might acquire the symbiont horizontally, as is the case for many horizontally transmitted symbioses (Bright and Bulgheresi 2010). For simplicity, we assume that when newborns arrive in the patch, they make contact with a single neighbor, who, if infected, might infect the newborn with probability h. (We assume that only newborns are capable of becoming infected, so contact between an infected newborn and an uninfected adult neighbor does not lead to the adult's infection.)

Once newborns have dispersed and became infected (or not), they must establish in their patch. Uninfected and infected newborns in patch q have establishment probabilities $s_{q,U}$ and $s_{q,I}$, respectively. When the conditional mutualism affects host establishment, infected hosts are more likely to establish than uninfected in M-patches. The reverse is true in P-patches. When the symbiont affects fecundity or mortality, we set all establishment probabilities to 1, so that newborns always established. (Assuming all newborns had an establishment probability less than 1 made the simulations slower without changing the results.)

For a newborn arriving in patch q, its chance of establishing as an uninfected (or infected) adult is

$$\begin{aligned}&\Pr(\text{Establishes as uninfected adult})\\&= \begin{cases} (1-hi_q)s_{q,U}, & \text{if born uninfected}\\ 0, & \text{if born infected}\end{cases}\\&\Pr(\text{Establishes as infected adult})\\&= \begin{cases} hi_q s_{q,I}, & \text{if born uninfected}\\ s_{q,I}, & \text{if born infected}\end{cases}\end{aligned} \tag{2}$$

Finally, we assume patch sizes are constant, so if the newborn successfully establishes, an adult host in the patch is then chosen to die. Given that a newborn establishes in patch q, the probability that a particular adult host in q with mortality m dies is

$$\begin{aligned}&\Pr(\text{A given adult in patch } q \text{ dies}|\text{Newborn establishes in } q)\\&= \frac{m}{\overline{m_q}\left(\frac{N}{\#\text{patches}}\right)}\end{aligned} \tag{3}$$

where N is the population size and $\overline{m_q}$ is the average mortality in patch q.

$$\overline{m_q} = (1-i_q)m_{q,U} + i_q m_{q,I}$$

Because an adult in q is guaranteed to die if a newborn establishes in the patch,

$$\sum_{j\in\text{adults in patch } q} \Pr(\text{adult } j \text{ dies}|\text{Newborn establishes in patch } q) = 1$$

ANALYTICAL MODEL

Before we can determine the fitness of a mutant host or symbiont, we must know what fraction of hosts are currently infected in each patch. To determine the ecological equilibrium fraction of infected hosts in a monomorphic population, we find the point where the rate of change of the fraction of infected hosts in each patch vanishes. (The ecological equilibrium is not affected by whether hosts or symbionts control transmission evolution.) Assuming all fecundities and mortalities are nonzero, the rate of change of the fraction of infected hosts in patch q is

$$\begin{aligned}\frac{di_q}{d\tau} = \frac{1}{\overline{f}\,\overline{m_q}} \cdot \{&[((1-d)(f_{q,U}(1-i_q) + f_{q,I}(1-v)i_q)\\&+ d(f_{q',U}(1-i_{q'}) + f_{q',I}(1-v)i_{q'}))hi_q\\&+ ((1-d)f_{q,I}vi_q + df_{q',I}vi_{q'})] \cdot s_{I,q}m_{q,U}(1-i_q)\\&-[(1-d)(f_{q,U}(1-i_q)+f_{q,I}(1-v)i_q)+d(f_{q',U}(1-i_{q'})\\&+ f_{q',I}(1-v)i_{q'})](1-hi_q)\cdot s_{U,q}m_{q,I}i_q\}\end{aligned} \tag{4}$$

where τ is the time in units of hosts birth times population size, $\tau = tN$, where t is time measured in host births, and the population size goes to infinity (see Appendix for derivation).

We used Mathematica version 11 (Wolfram Research Inc. 2017) to solve for the values of i_M and i_P where $\frac{di_M}{d\tau}$ and $\frac{di_P}{\Delta\tau}$ were equal to 0 (code given in Supporting Information). While there might be multiple (i_M, i_P) pairs that satisfiy the equation (for example, $(i_M = 0, i_P = 0)$ is always a solution), not all of them are stable in response to small perturbations in the fraction of infected hosts. We considered stable equilibria only (see Appendix). In most cases, there is only one stable ecological equilibrium. In

cases where there is more than one ecological equilibrium, we have shown one equilibrium in the main text and the other in the Supporting Information. In all cases that we investigated, multiple ecological equilibria for a given pair of transmission probabilities do not have qualitatively different effects on the overall pattern of transmission evolution.

To determine in which direction transmission probabilities evolve, we found the invasion fitness of a mutant with slightly different horizontal and vertical transmission probabilities than the resident. Because mutants in different patches (and, for mutant hosts, mutants with different infection statuses) differ in their chances of producing offspring, we model the growth of the mutant when rare as a multitype branching process (Lehmann et al. 2016). We write a matrix X_τ that gives the expected number of mutants produced by a mutant in each patch (or, for host control, an uninfected or infected mutant in each patch) at every time step, measuring time in units of host births times population size, $\tau = tN$ as the population size goes to infinity. The leading eigenvalue of X_τ then gives the growth rate of the mutant when rare. The derivation of X_τ for host and symbiont control follows straightforwardly from equations 1 and 2 and is given in detail in the Appendix.

Once we have X_τ, we can calculate the derivative of the mutant growth rate in terms of the mutant transmission probabilities. We can then use these derivatives to trace the path of transmission evolution. We found the derivatives of the leading eigenvalue of X_τ numerically and then numerically calculated the path of the evolutionary trajectories in Mathematica (see Appendix).

SIMULATIONS

Transmission evolution could possibly be affected by the analytical model assumptions that the population is infinite and that evolution happens only once the fraction of infected hosts has equilibrated. To test whether this is the case, we simulated transmission evolution in finite populations and where ecological and evolutionary changes occur on the same time scale.

We simulated transmission mode evolution in Julia version 0.5.1 (Bezanson et al. 2017, the simulation code is available as Supporting Information). Each time step, a single host was selected to give birth, with the probability of selection determined by its patch and infection status. After a host was born, if hosts control transmission, we allowed the newborn's transmission probabilities to mutate. In the case of host control, the newborn host's possibly mutated new transmission probability determined its probability of infection. When symbionts controlled transmission, the parent's symbiont determined the vertical transmission probability, and then if infection was successful, the newborn's symbiont was allowed to mutate.

The newborn then dispersed to a new patch with probability d and remained in its natal patch with probability $1 - d$. If the newborn dispersed, it was equally likely to end up in any patch except its natal one. If the newborn was so far uninfected, a random adult host in the newborn's patch was then selected to be its potentially infectious contact. If this adult was infected, horizontal transmission occurs with probability given by the newborn's horizontal transmission probability (host control case) or the neighbor's symbiont's horizontal transmission probability (symbiont control case). If the newborn became infected and the symbiont controlled transmission, the newborn's symbiont might then mutate. Finally, the newborn's establishment in the patch was determined by its infection status and location. If the newborn successfully established, a random adult host was chosen to die.

Before allowing transmission mode to evolve, we ran the simulation for 4000 time steps to allow the resident population to equilibrate. We started the simulations from an 11x11 grid of starting points evenly spaced over the space of all possible transmission probabilities. After the equilibration period, we ran each simulation for 10^7 time steps. We used a mutation rate of 0.02, with mutations normally distributed with a mean of the original transmission probability and SD of 0.05. For the host control case, we also had a 0.5% chance that an uninfected newborn would be spontaneously infected. We did this to prevent the infection from being lost by chance leading transmission to evolve neutrally for the rest of the simulation. We analyzed the simulations by finding the average transmission rates and fraction of infected hosts in M- and P-patches at the last time step using the pandas package version 0.23.4 (McKinney 2010) in Python 2.7.15 (Rossum 1995).

Results

HOST CONTROL OF TRANSMISSION

Analytical model

Symbiont affects lifespan

When the symbiont affects host lifespan, the ecological equilibrium fraction of infected hosts is generally higher in M-patches than P-patches (Fig. 2 A–F), except when both transmission probabilities are too low and the infection dies out (white regions in Fig. 2) or when both transmission probabilities are 1 and all hosts in both patches are infected. In both cases, transmission evolves neutrally, because changes in transmission do not affect a host's chances of becoming infected.

Aside from the above cases, host evolutionary trajectories lead to either complete horizontal and no vertical transmission, i.e., ($h = 1, v = 0$); or they lead to complete vertical transmission and no horizontal transmission, ($h = 0, v = 1$). At low dispersal rates, the basins of attraction of the two endpoints are very similar in size (Fig 2 A, D). As the dispersal rate increases, more

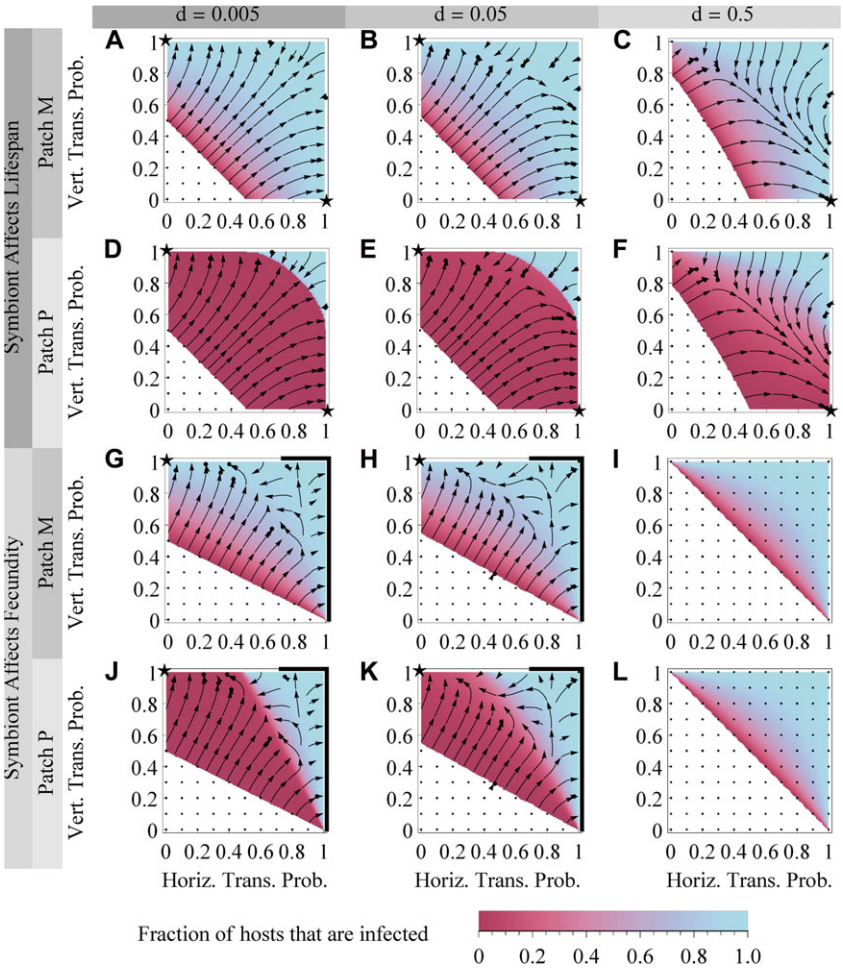

Figure 2. **Ecological equilibria and host evolutionary trajectories for an infinite population. Panels A–F: Symbiont affects host lifespan; panels G–L: Symbiont affects host fecundity. Columns indicate dispersal rates. The upper and lower pairs of panels in a column each represent a single metapopulation, with the upper panel indicating the fraction of infected hosts in Patch M, and the lower the fraction of infected hosts in Patch P (e.g., panels A and D represent a single population). For each plot, colors indicate the fraction of infected hosts in the patch when the population is monomorphic for a given pair of horizontal and vertical transmission rates. Arrows indicate hosts evolutionary trajectories, with dots where transmission evolves neutrally. Stars and thick black lines on the edges of the plot mark evolutionary stable strategies. Panels from the same metapopulation show the same trajectories, as the entire population evolves together. Parameters, panels A–F: $m_{M,I} = m_{P,U} = 0.5$, $f_{M,U} = f_{P,I} = f_{M,I} = f_{P,U} = m_{M,U} = m_{P,I} = 1$; panels G–L: $f_{M,U} = f_{P,I} = 0.5$, $f_{M,I} = f_{P,U} = m_{M,U} = m_{M,I} = m_{P,U} = m_{P,I} = 1$.**

trajectories lead to the point ($h = 1$, $v = 0$). This corresponds to changes in the transmission probabilities that lead to high fractions of parasitized hosts. As dispersal increases, even intermediate values of horizontal and vertical transmission paired with high levels of the other lead to a large fraction of infected hosts in Patch P. However, the effect is more pronounced for high vertical transmission probabilities, which require much lower horizontal transmission probabilities in order to contain the symbiont to Patch M. (This can be seen in the increasing length of the top of the blue region in Fig. 2 D–F compared to its right side.) Finally, when the dispersal rate is maximum ($d = 0.5$ for the two patch case, meaning newborns have an equal chance of ending up in either patch), all host evolutionary trajectories lead to complete horizontal and no vertical transmission (Fig. 2 C, F). This is because high vertical transmission leads to a high fraction of parasitized hosts for all horizontal transmission probabilities, including $h = 0$.

While the basin of attraction of high horizontal versus high vertical transmission depends on the dispersal rate, evolutionary trajectories always lead to a beneficial (to hosts) distribution of the symbiont, in the sense that they maintain a high fraction of infected hosts in the patch where the symbiont is mutualistic and a low fraction of infected hosts in the patch where the symbiont is parasitic.

Symbiont effects on expected lifespan produce very similar results whether the symbiont affects adult mortality or newborn

survival (Fig. S3). In our model, they produce the same ecological equilibria (this is due to the fact that establishment and mortality terms always appear multiplied together in the ecological equilibrium terms; see eq. 4). This in turn produces similar selection pressures on transmission and leads to the same evolutionary stable strategies (ESSs). The main difference between the two effects is that the chance of dying as an adult is affected by the infection status of the other adults in the patch, while the chance of newborn establishment is not. This affects the magnitude but not the direction of the derivative of the mutant growth rate (see Fig. S17). In particular, adult mortality causes the magnitude of the derivative to be larger, although the exact difference in the magnitude depends on the transmission probabilities, symbiont effect, and which partner controls transmission evolution.

Symbiont affects fecundity

When the symbiont affects fecundity, high horizontal transmission probabilities always lead to a high ecological equilibrium fraction of infected hosts in Patch P. In contrast, high vertical transmission probabilities, combined with low horizontal transmission probabilities, produce the largest difference in the fraction of infected hosts between Patches M and P (Fig. 2 G-L). As a result, most trajectories lead to complete vertical and no horizontal transmission, ($h = 0$, $v = 1$).

However, unlike the case where the symbiont affects lifespan, not all trajectories lead to transmission probabilities that contain the symbiont to the patch where it is beneficial. When dispersal is not maximum ($d < 0.5$), populations that start with too high horizontal transmission probabilities evolve toward complete infection, due the fact that symbionts become abundant everywhere, and therefore, the host has little chance of escaping them in Patch P by a small decrease in transmission rates. Therefore, there is little additional cost to hosts from increasing transmission in Patch P, and a slight benefit in Patch M. Trajectories that lead to complete infection end up in one of two regions. In the first region, the population has complete horizontal transmission and at least some vertical transmission, ($h = 1$, $v > 0$).

In the second region, the population has complete vertical transmission and high horizontal transmission, ($h > h^*$, $v = 1$). The precise value of h^* depends on the dispersal rate and the costs/benefits provided by the symbiont. Interestingly, if the symbiont is more costly in Patch P than it is beneficial in Patch M, all trajectories lead to the point ($h = 0$, $v = 1$). On the other hand, if the symbiont is more beneficial in Patch M than harmful in Patch P, populations are more likely to evolve toward complete infection (Fig. S5).

As the dispersal rate increases, lower horizontal transmission probabilities are able to sustain a high frequency of parasitized hosts (as shown by the increasing size of the blue regions at the top of Fig. 2 from panels J to K; see also Fig. S4). More evolutionary trajectories start in regions where the symbiont is not well contained. For some of these trajectories, a small decrease in transmission probabilities is not as beneficial to hosts in Patch P as an increase is to hosts in Patch M. More trajectories therefore lead to complete infection in both patches.

Finally, when newborns have an equal chance of ending up in either patch (dispersal rate = 0.5, Fig. 2 I, L), the two patches have the same frequency of infected hosts at all transmission probabilities. When the symbiont's costs in Patch P exactly equal its benefits in Patch M (as in Fig. 2), transmission is selectively neutral. The benefits of a small increase or decrease in one patch are exactly balanced with the cost of that change in the other. If the costs and benefits are not equal (Fig. S5), hosts will either evolve toward low transmission and loss of the symbiont (when the costs are higher than the benefits) or high transmission and complete infection (when the benefits are higher than the costs).

SYMBIONT AFFECTS LIFESPAN AND FECUNDITY

In the Supporting Information, we investigate the case where the symbiont affects both host lifespan and fecundity. In general, if the symbiont's effect on one fitness component is significantly stronger than the other, transmission evolution largely resembles the case where only the stronger effect is present (Figs. S6 and S7). One exception is if the symbiont largely affects fecundity and the dispersal rate is maximum. When the symbiont affects fecundity equally in both patches and does not affect lifespan, transmission mode is selectively neutral when dispersal is maximum. However, a small symbiont effect on lifespan can break the symmetry and allow hosts to evolve toward either complete infection, loss of the symbiont, or even the point ($h = 1$, $v = 0$). (The last of these provides a small degree of symbiont containment.)

When the symbiont has a strong effect on both components of host fitness, the results are more complicated. The outcome depends on the conditions that trigger the effects on each component as well as the relative strengths of the effects on each component. However, two general trends emerge. The first is that using high horizontal combined with low vertical transmission to contain the symbiont to M-patches is only an option when the symbiont can decrease lifespan. For example, when the symbiont affects fecundity, adding a conditional (in Patch P) or unconditional (in Patches M and P) lifespan cost to infection allows horizontal transmission to evolve as a method of containment (Figs. S6 and S8).

Related to this, symbiont containment can often be improved by increasing the costs of infection. If trajectories do not lead to containment, increasing the cost of infection through fecundity or lifespan effects, can increase the number of trajectories leading to symbiont containment (Figs. S6, S8, and S9). This is true even if hosts in M-patches bear the additional cost of infection (Figs. S8 and S9). (On the other hand, increasing the cost of infection can also cause the symbiont to be lost in some cases, generally when

the dispersal rate is maximum and the symbiont largely affects fecundity, e.g., Fig. S8.)

Simulations

At high dispersal rates, the simulations of finite host populations behave much like the infinite population case (Fig. 3 C, F, I, L). However, as the dispersal rate decreases, the simulations diverge from the analytical results, in that the patches behave more like separate populations. At low dispersal rates, hosts residing in the patch where the symbiont is beneficial have higher average transmission probabilities than predicted for the infinite population case (Fig. 3 A, G has a large proportion of simulations with high average horizontal and vertical transmission probabilities, while the infinite population case predicts only one high transmission probability). Patches where the symbiont is parasitic tend to lose the infection (or have the symbiont at very low frequencies due to spontaneous infection) and then have transmission probabilities that evolve neutrally (Fig. 3 D, J Fig. S10). As the population size increases, lower dispersal rates are needed for the population to behave like separate patches, and the population resembles the infinite population at increasingly lower dispersal rates (Fig. S11). Simulations of unequal numbers of M- and P-patches behave similarly at high dispersal rates to the infinite-population case in which symbiont effects are unequal between M- and P-patches (Figs. S14 and S15). At low dispersal rates, between-patch polymorphism also helps contain symbionts to M-patches.

SYMBIONT CONTROL

In both the analytical model and simulations, symbionts evolve high horizontal and vertical transmission probabilities (Figs. S12 and S13; R_0 for infinite population case shown in Fig. S16). In particular, symbionts always evolve complete vertical transmission in the infinite population case. The horizontal transmission probability evolves neutrally once 100% vertical transmission is reached, because all hosts are born already infected. The difference between selection pressure on hosts and symbionts is shown in Figure 4. In general, the most conflict is found at high vertical transmission probabilities. When the symbiont affects lifespan, conflict occurs at high vertical and horizontal transmission. As the dispersal rate increases and vertical transmission becomes less beneficial to hosts, the region of conflict expands to include low vertical transmission and intermediate horizontal transmission. This creates a triangular region where too much transmission, and particularly too much vertical transmission, leads to host–symbiont conflict. When the symbiont affects host fecundity, most conflict still occurs at high vertical transmission probabilities, but now intermediate horizontal transmission provokes the most conflict. This is because hosts at high horizontal transmission probabilities evolve toward complete infection, reducing the conflict between hosts and symbionts.

Discussion

We investigate conditional mutualisms with spatial variation in symbiont quality and find that hosts evolve different transmission modes depending on the ecological distribution of infected hosts, which in turn depends on the aspect of fitness symbionts affect. When symbionts affect host lifespan, hosts are able to evolve high horizontal and low vertical transmission, which contains the symbiont to the patch where it is a mutualist. They are able to do this because hosts with the "wrong" infection status die more quickly and do not remain in the population to affect incoming newborns' chance of infection. This sets up a difference in the distribution of infected hosts so that newborns benefit from higher horizontal transmission rates, because their probability of acquiring the symbiont is higher where it is beneficial.

When the symbiont affects fecundity, hosts with the "wrong" infection status reproduce less, but remain in the population just as long as ones with the "right" infection status. This allows them to affect the infection status of incoming newborns. Unless the distribution of infected hosts is already skewed toward more infected hosts in the patch where the symbiont is beneficial, hosts gain no benefit from evolving horizontal transmission. Even worse, an increase in horizontal transmission produces some hosts with the "wrong" infection status, who then persist in the population to alter the infection probabilities of incoming newborns. This means that past a threshold transmission probability, horizontal transmission is no longer effective at maintaining different distributions of infected hosts. Hosts are left with using vertical transmission to contain the symbiont when dispersal is low and host lineages are mostly confined to the same patch. When dispersal is at its maximum, the patches have equal fractions of infected hosts, and the costs and benefits of infection determine if the infection is lost (when the symbiont is more harmful in P-patches than beneficial in M-patches), spreads to everyone (when the symbiont is less harmful in P-patches than beneficial in M-patches), or drifts because transmission rate is neutral (when symbiont costs and benefits are exactly equal).

When the symbiont affects lifespan and fecundity, the nature and magnitude of the costs of infection have a large influence on transmission evolution. Hosts are only able to use horizontal transmission to contain the symbiont when the symbiont decreases lifespan. This decrease in lifespan does not have to be conditional on hosts' environment in order to allow symbiont containment. Furthermore, adding conditional or unconditional lifespan or fecundity costs of infection can increase the fraction of host evolutionary trajectories that lead to symbiont containment, rather than complete infection. These results suggest that the costs of a conditional mutualism are key to determining its evolutionary outcome. They also suggest that a conditional mutualism that has more costs than benefits may actually increase hosts'

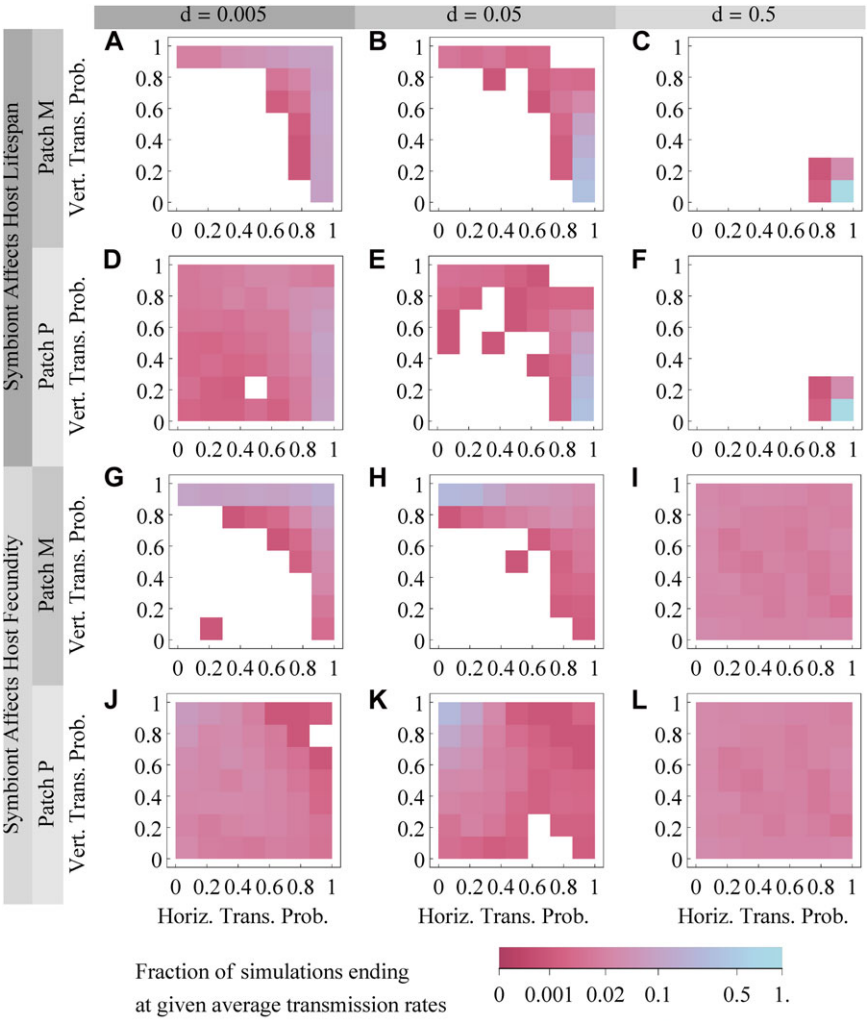

Figure 3. **Simulations of transmission evolution under host control. Colors indicate fraction of populations ending with each combination of average horizontal and vertical transmission probabilities. White indicates that no populations ended in the given range of transmission probabilities. Simulations were started from a grid of start points spaced 0.1 apart in transmission probability. Ten simulations at each start point were run for 10^7 time steps for every parameter combination. Parameters: 2 patches, $N = 200$, mutation rate = 0.02, mutation SD = 0.05, spontaneous infection probability = 0.005, panels (A–F): $m_{M,I} = m_{P,U} = 0.5$, $f_{M,U} = f_{M,I} = f_{P,U} = f_{P,I} = m_{M,U} = m_{P,I} = 1$; panels (G–L): $f_{M,U} = f_{P,I} = 0.5$, $f_{M,I} = f_{P,U} = m_{M,U} = m_{M,I} = m_{P,U} = m_{P,I} = 1$.**

fitness more in the long-term than more "mutualistic" conditional mutualisms, by increasing hosts' chances of evolving transmission modes that contain the symbiont to locations where it is beneficial.

The simulations largely confirm that our results hold for finite populations. However, they suggest an alternative way that hosts in small populations may respond to a conditional mutualism when dispersal rate is low. If dispersal rate is small enough relative to the population size, the subpopulations of hosts in each patch behave more like separate populations, and exhibit local adaptation. Hosts in M-patches evolve high horizontal and vertical transmission rates, while hosts in P-patches lose the symbiont (or have it at low frequency due to spontaneous infection) and have transmission evolve neutrally. This suggests that at low dispersal rates, it is possible that hosts in small populations have more options for transmission mode evolution. Hosts whose symbiont affects their fecundity may not be constrained to use purely vertical transmission when the dispersal rate is low. However, the main problem for hosts still occurs at high dispersal rates, when the patches do not behave like separate populations, and hosts whose symbiont affects fecundity are forced to have the same fraction of infected hosts in both patches. As it is unlikely in nature that symbiont costs and benefits will be exactly balanced, in practice this may lead to the symbiont being lost if it is slightly more harmful or maintained in all hosts if it is slightly more beneficial.

Our model of symbiont control shows that, as predicted, when there are no direct costs to transmission and population size

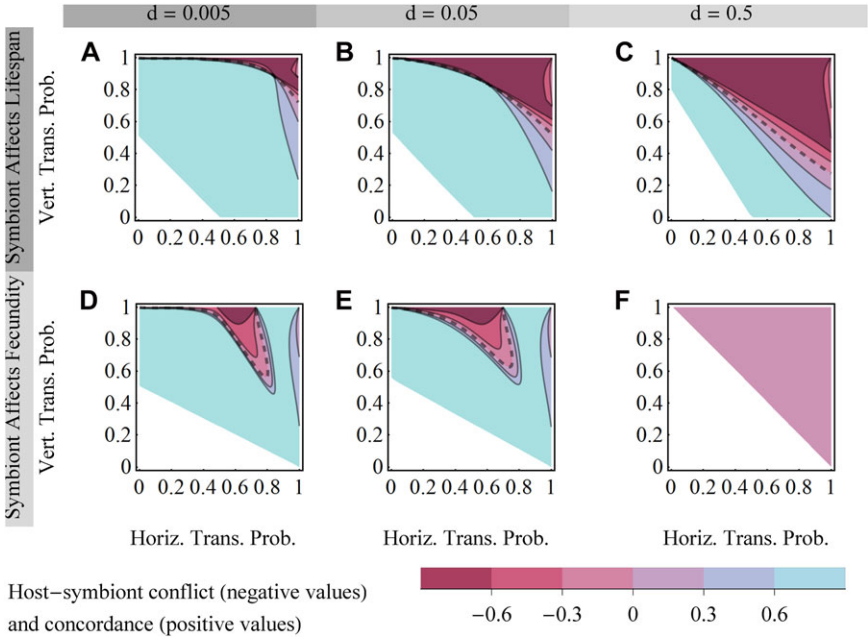

Figure 4. Host–symbiont conflict: Host–symbiont conflict when symbiont affects lifespan (top row) or fecundity (bottom row). Colors indicate the degree to which host and symbiont evolutionary trajectories point in the same direction, defined as the cosine of the selection vectors under host and symbiont control, or 0, if at least one of the selection vectors has magnitude 0. If trajectories are perpendicular or a partner does not experience selection, conflict is 0. Negative values indicate trajectories point in opposite directions (conflict), and positive values indicate that trajectories point in the same direction (concordance). Dashed lines separates regions of conflict and concordance. White regions indicate transmission rates where the infection cannot be maintained. Parameters, top row: $m_{M,I} = m_{P,U} = 0.5$, $f_{M,U} = f_{M,I} = f_{P,U} = f_{P,I} = m_{M,U} = m_{P,I} = 1$; parameters, bottom row: $f_{M,U} = f_{P,I} = 0.5$, $f_{M,I} = f_{P,U} = m_{M,U} = m_{M,I} = m_{P,U} = m_{P,I} = 1$.

is fixed, symbionts evolve high transmission rates and end up infecting all hosts in the population. In both the analytical and simulation models, symbionts evolve complete vertical transmission and evolve a nonzero probability of horizontal transmission that guarantees complete infection of all hosts (this may be less than a 100% chance of horizontal transmission, because vertical transmission also contributes to the chance of infection). Further, vertical, rather than horizontal, transmission is maximized because at high frequencies of infected hosts, vertical transmission is the best way to guarantee that newborns are infected (Lipsitch et al. 1995).

Our results provide predictions for the distribution and traits of conditional mutualisms. For example, the dispersal rate and symbiont effects predict the distribution and transmission of a conditional mutualism under host or symbiont control (Table 2). Furthermore, in some cases knowing some of the parameters of dispersal, symbiont effects, control, transmission, and distribution maybe be enough to predict the other parameters. For example, if a symbiont conditionally affects fecundity and is horizontally transmitted, we can predict that symbiont will not be contained to areas where it is a mutualist. Nonetheless, if there is not also complete vertical transmission, we may predict that transmission is still a host trait.

As an example, in the symbiosis between aphids and their obligate symbiont *Buchnera aphidicola*, a mutation in the promoter of *ibpA*, which encodes one *B. aphidicola*'s heat shock proteins, causes mutant *B. aphidicola* to increase host fecundity (relative to wild-type *B. aphidicola*) in cool conditions and nearly eliminate reproduction in warm conditions (Dunbar et al. 2007). The mutant has been found at frequencies up to 20% in natural populations, despite its large potential cost and the fact that *B. aphidicola* is strictly vertically transmitted. Our results suggest that the lack of horizontal transmission is not necessarily a barrier to the persistence of the symbiont in natural populations, and may in fact benefit its hosts, provided that aphid dispersal between regions with different temperatures is relatively rare.

One other example to which we can apply our model is the symbiosis between the grass *Agrostis hyemalis* and the fungus *Eplichloë amarillans*. *Eplichloë amarillans* increases host fecundity under drought conditions and decreased host biomass in the presence of certain soil microbes (Davitt et al. 2011). It is difficult to know exactly how biomass affects lifespan and fecundity, but as long as biomass has a smaller effect on lifespan than fecundity, we would predict that vertical transmission, particularly if seeds disperse to new environments only rarely, would be more likely to arise. Indeed, vertical transmission is observed in this symbiosis,

Table 2. Model predictions.

		Dispersal rate	
		Low	High
Symbiont affects	Lifespan	Pure horizontal or pure vertical transmission; symbiont contained	Pure horizontal transmission; symbiont contained
	Fecundity	Pure vertical transmission (symbiont contained) or horizontal or mixed-mode transmission (symbiont not contained)	Any transmission possible; symbiont not contained

Predicted transmission mode and distribution of infection when transmission is a host trait. Symbiont containment refers to whether the fraction of infected hosts is higher in M-Patches than P-Patches ("symbiont contained") or not ("symbiont not contained"). The case where transmission is a symbiont trait is trivial.

although without knowing the relative effect of biomass on lifespan and fecundity, it is difficult to be certain whether the system matches our predictions.

While many other conditional mutualisms are known, in most of these the symbiont's effect on different components of host fitness is currently unknown. Our results suggest that quantifying context-dependent variation in fitness components could allow predictions of transmission mode evolution and symbiont spread.

The widespread symbiosis between legume plants and rhizobium bacteria is an interesting case to consider: the outcome of this symbiosis is often context-dependent (Heath and Tiffin 2007). Lack of suitable rhizobium partners can dramatically reduce growth and survival of legume plants. The lack of vertical transmission in this system suggests that rhizobia are contained to where they are more beneficial, but to our knowledge, this hypothesis has not been tested explicitly. Regardless, the mechanism of containment is likely to be different than our model, as rhizobia can live freely in the soil, which is where plants take them up from. This suggests that containment is likely driven by the feedbacks between legume abundance (and competition with non-legumes) and soil rhizobium density. The effects of such plant–environment feedback when the symbiont can be free-living is an interesting future direction to consider.

Our results further suggest different transmission outcomes depending on whether transmission is a host or symbiont trait. However, it is also possible that host and symbiont traits may interact to determine transmission. Which transmission mode will evolve under host–symbiont coevolution is an area for future research. The specific outcome may depend on the manner in which host and symbiont traits interact, as well as the level of control each party has. Our results suggests that for a large range of transmission probabilities hosts and symbionts actually experience selection in a similar direction, potentially narrowing the range of transmission probabilities where host–symbiont co-evolution may proceed differently than if a single party controlled transmission.

Another area for future investigation is the potential costs and benefits of transmission. We assumed transmission does not come with come with any additional costs or benefits beyond altering the probability of infection. We did this to get baseline predictions of how transmission would evolve without any biological constraints. However, many symbioses show costs or benefits of one mode of transmission, or a trade-off between transmission modes. For example, in the symbiosis between *Epichloë* fungal endophytes and grasses, horizontal transmission is the mechanism for endophyte sexual reproduction. This could potentially alter evolutionary trajectories by incentivizing endophytes to evolve horizontal transmission more rapidly, even when vertical transmission might produce more infections. On the other hand, many infectious diseases require costly host investment in immunity to prevent horizontal transmission, making the effects of the conditional mutualism dependent on the level of horizontal transmission. Even if there are no direct costs or benefits of transmission, transmission modes might be constrained by biological relationships between horizontal and vertical transmission. For example, temperate bacteriophage can transmit vertically or horizontally, but horizontal transmission requires killing their hosts, eliminating the possibility of future vertical transmission, and forcing a trade-off between the two modes. These trade-offs are likely to have strong effects on the possible trajectories and endpoints of transmission evolution. We hope to investigate the effects of transmission costs, benefits, and trade-offs in a future model.

Finally, our model considers environmental variation that occurs purely in space. However, environments may vary in time as well. Temporal variation in the environment separates dispersal into two components that are intertwined in our spatial model: the correlation between parent and offspring environments and the pool of neighbors available for horizontal infection. A model with temporal variation could, thus, provide insight into these

two aspect of "dispersal," as well as adding an important aspect of environmental change. We are currently investigating this case (Brown and Akçay in prep).

In conclusion, our model illustrates that in conditional mutualisms, it is not just the costs and benefits of infection that matter, but also the component of fitness that the symbiont affects. The component of fitness influences the distribution of the infection on ecological timescales, meaning it may be useful for predicting the spread of conditional mutualisms of interest. The ecological distribution of infected hosts also strongly influences transmission mode evolution. As transmission mode is predicted to itself create selective pressure on virulence, the ecological distribution of infected hosts over evolutionary time may feed back not only on transmission but also on the nature of the symbiosis itself. Thus, the feedback we found between symbiont effects on host fitness and transmission evolution may be important for predicting both the short- and long-term future of conditional mutualisms. As more symbioses are being found to have conditional effects, understanding the precise nature of symbiont effects on their hosts will be essential for predicting the short- and long-term dynamics of these symbioses.

AUTHOR CONTRIBUTIONS

E.A. and A.B. designed the analytical model and simulations and wrote the manuscript. A.B. wrote the code for the analytical model and simulations.

ACKNOWLEDGMENTS

We thank M. Levine for comments on the manuscript and J. Plotkin for advice on the model.

A.B. was funded by the University of Pennsylvania and a DOD NDSEG fellowship. Computational work was supported in part by a NAS Keck Futures Initiative grant to J. Van Cleve, E.A., and T. Linksvayer.

DATA ARCHIVING

The code for the simulations and analysis of the analytical model is on Data Dryad, https://doi.org/10.5061/dryad.3q0mk00.

CONFLICT OF INTEREST

The authors have no conflict of interest.

Appendix : Calculations for Infinite Population Model

EQUILIBRIUM DISTRIBUTION OF INFECTED HOSTS

From equations 1 and 2, we can see that the fraction of infected hosts in a patch affects hosts' birth, establishment, and death probabilities, as well as symbionts' transmission opportunities. So, before we can find the invasion fitness of a mutant host or symbiont, we need to find the equilibrium fraction of infected hosts. We find the equilibrium fraction of infected hosts analytically for an infinite host population with two patches. We call these patches M and P and assume they are each of size $\frac{N}{2} \to \infty$. In patch M, the symbiont is a mutualist that increases either infected host fecundity or lifespan (depending on the nature of the conditional mutualism) above that of uninfected hosts. In patch P, the reverse is true. We will usually assume either $f_{M,I} = f_{P,U} > f_{M,U} = f_{P,I}$ or $m_{M,I} = m_{P,U} < m_{M,U} = m_{P,I}$. In the Supporting Information, we relax this assumption and also consider the case where the symbiont affects lifespan through newborn establishment probability ($s_{M,I} = s_{P,U} > s_{M,U} = s_{P,I}$).

To find the equilibrium fraction of infected hosts in patches M and P, we must solve

$$\begin{cases} \Delta i_M = & 0 \\ \Delta i_P = & 0 \end{cases}$$

for the fraction of infected hosts in each patch, i_M and i_P.

To do this, we must write down formulas for the change in infected hosts in a patch. The fraction of infected hosts in a patch should increase if an infected newborn establishes and an uninfected adult dies. It should decrease if an uninfected newborn establishes and an infected adult dies. All other events (newborn failing to establish, uninfected newborn establishing in place of an uninfected adult, infected newborn establishing in place of an infected adult) should not lead to a change in the frequency of infected hosts in the patch.

Because each patch is of size $\frac{N}{2}$, the addition or subtraction of a single infected host should change the frequency of infected hosts in the patch by $\frac{1}{N/2} = \frac{2}{N}$. The rate of change in frequency in infected hosts in a patch should then be

$$\frac{\Delta i_q}{\Delta t} = \frac{2}{N}\,[\Pr(\text{Infected host establishes}) \times \Pr(\text{Uninfected host dies}) - \Pr(\text{Uninfected host establishes}) \times \Pr(\text{Infected host dies})]$$

where t is time in units of host births, such that one host is born every time t increases by 1 and Δi_q and Δt refer to the change over one time step.

Equations 1 and 3 give the probability that a single host in patch q will reproduce or die. By multiplying these probabilities by the total number number of infected ($i_q N/2$) or uninfected ($(1-i_q)N/2$) hosts in patch q, we can get the probability that the patch as a whole will produce a newborn or lose an adult of each infection status. Then, using Equation 2 for the newborn establishment probabilities and taking into account the fact that newborn hosts may enter a patch via dispersal, the rate of change in the fraction of infected hosts is

$$\frac{\Delta i_q}{\Delta t} = \frac{1}{N\overline{f}\overline{m_q}} \cdot \Big\{\Big[\big((1-d)(f_{q,U}(1-i_q) + f_{q,I}(1-v)i_q) + d(f_{q',U}(1-i_{q'}) + f_{q',I}(1-v)i_{q'})\big)\, h i_q$$

$$+ ((1-d) f_{q,I} v i_q + d f_{q',I} v i_{q'})\big] \cdot s_{I,q} m_{q,U} (1 - i_q)$$
$$- \big[(1-d)(f_{q,U}(1-i_q) + f_{q,I}(1-v) i_q)$$
$$+ \; d(f_{q',U}(1-i_{q'}) + f_{q',I}(1-v) i_{q'})\big]$$
$$\times \; (1 - h i_q) \cdot s_{U,q} m_{q,I} i_q \Big\}$$

where q represents patch M or P, and q' is the other patch. Note that the rate of change is now scaled by $\frac{1}{N}$, because there are $\frac{N}{2}$ hosts in the patch which each have their chance to reproduce scaled by $\frac{1}{N}$. Dividing both sides by $\frac{1}{N}$ and taking the limit as $N \to \infty$ allows us to study the system in continuous time, τ, where $\tau = tN$.

Finally, by constraining all fecundities and mortalities ($f_{M,U}$, $m_{M,U}$ etc.) to be greater than 0, we can ensure that the average fecundity, $\overline{f}$, and both average mortalities, $\overline{m_M}$ and $\overline{m_P}$, are always greater than 0. Then, we can solve the slightly simpler set of equations

$$\begin{cases} \overline{f}\,\overline{m_M} \dfrac{di_M}{d\tau} = 0 \\ \overline{f}\,\overline{m_P} \dfrac{di_P}{d\tau} = 0 \end{cases} \tag{A1}$$

We solve this system numerically in the Supporting Information using Mathematica version 11.1 (Wolfram Research Inc. 2017).

It is possible that some of the equilibrium fractions of infected hosts may not be stable. To find stable equilibria, we select those solutions of equation A1 for which the eigenvalues of the Jacobian are negative. The Jacobian is defined as

$$J = \begin{bmatrix} \dfrac{\partial\left(\dfrac{di_M}{d\tau}\right)}{\partial i_M} & \dfrac{\partial\left(\dfrac{di_M}{d\tau}\right)}{\partial i_P} \\ \dfrac{\partial\left(\dfrac{di_P}{d\tau}\right)}{\partial i_M} & \dfrac{\partial\left(\dfrac{di_P}{d\tau}\right)}{\partial i_P} \end{bmatrix}$$

We find the eigenvalues of the Jacobian at each equilibrium numerically using Mathematica (Supporting Information) and select those equilibria that are stable for invasion analysis.

TRANSMISSION MODE EVOLUTION: HOST CONTROL

We can now investigate transmission mode evolution when transmission is a host trait. We want to find the invasion fitness of a mutant host with slightly different horizontal and vertical transmission rates than the resident. To do this, we can think of the growth of the mutant when rare as a multitype branching process (Lehmann et al. 2016). We write a matrix (X_t) that gives the expected number of mutants produced by an uninfected or infected mutant in each patch every time step (measuring time in units of host births, t). Rows of X_t correspond to the location and infection status of mutants produced. The first two rows correspond to uninfected and infected mutants produced in patch M, and the third and fourth rows are the same for patch P. Columns of X_t correspond to the type of mutant producing a new mutant (or "producing" itself by surviving to the next time step). Columns are in the same order as rows. Then, we have

$$\begin{bmatrix} \#\text{Uninfected mutants in M at } t+1 \\ \#\text{Infected mutants in M at } t+1 \\ \#\text{Uninfected mutants in P at } t+1 \\ \#\text{Infected mutants in P at } t+1 \end{bmatrix}$$
$$= X_t \begin{bmatrix} \#\text{Uninfected mutants in M at } t \\ \#\text{Infected mutants in M at } t \\ \#\text{Uninfected mutants in P at } t \\ \#\text{Infected mutants in P at } t \end{bmatrix}$$

To find X_t, let A be a matrix that gives the probability a mutant gives birth to an uninfected or infected offspring that successfully establishes in each patch (rows and columns in same order as in X_t). Let B be a matrix that gives the probability that an uninfected or infected mutant in each patch dies. Then

$$X_t = I + A - B$$

where I is the identity matrix and indicates that besides giving birth and dying, mutants may simply persist in the population from one time step to the next.

We can get the probabilities in A from the product of equations 1 and 2. The probabilities we need for A are the following:

Pr(Uninfected mutant produces uninfected offspring)

$$= \begin{cases} \Pr(U, q \to U, q) & \text{if offspring} \\ \quad = (1-d)\dfrac{f_{q,U}}{N\overline{f}}(1 - h^* i_q) s_{q,U}, & \text{stays in } q \\ \Pr(U, q \to U, q') & \text{if offspring} \\ \quad = d\dfrac{f_{q,U}}{N\overline{f}}(1 - h^* i_{q'}) s_{q',U}, & \text{disperses to } q' \end{cases} \tag{A2}$$

Pr(Uninfected mutant produces infected offspring)

$$= \begin{cases} \Pr(U, q \to I, q) & \text{if offspring} \\ \quad = (1-d)\dfrac{f_{q,U}}{N\overline{f}} h^* i_q s_{q,I}, & \text{stays in } q \\ \Pr(U, q \to I, q') & \text{if offspring} \\ \quad = d\dfrac{f_{q,U}}{N\overline{f}} h^* i_{q'} s_{q',I}, & \text{disperses to } q' \end{cases} \tag{A3}$$

Pr(Infected mutant produces uninfected offspring)

$$= \begin{cases} \Pr(I, q \to U, q) & \text{if offspring} \\ \quad = (1-d)\dfrac{f_{q,I}(1-v^*)}{N\overline{f}}(1 - h^* i_q) s_{q,U}, & \text{stays in } q \\ \Pr(I, q \to U, q') & \text{if offspring} \\ \quad = d\dfrac{f_{q,I}(1-v^*)}{N\overline{f}}(1 - h^* i_{q'}) s_{q',U}, & \text{disperses to } q' \end{cases} \tag{A4}$$

Pr(Infected mutant produces infected offspring)

$$= \begin{cases} \Pr(I, q \to I, q) & \text{if offspring} \\ \quad = (1-d)(\frac{f_{q,I}(1-v^*)}{N\overline{f}} h^* i_q s_{q,I} & \text{stays in } q \\ \quad + \frac{f_{q,I} v^*}{N\overline{f}} s_{q,I}), & \\ \Pr(I, q \to I, q') & \text{if offspring} \\ \quad = d(\frac{f_{q,I}(1-v^*)}{N\overline{f}} h^* i_{q'} s_{q',I} & \text{disperses to } q' \\ \quad + \frac{f_{q,I} v^*}{N\overline{f}} s_{q',I}), & \end{cases} \tag{A5}$$

Using the above probabilities of mutant reproduction, we can write A as

$$A = \begin{bmatrix} \Pr(U, M \to U, M) & \Pr(I, M \to U, M) & \Pr(U, P \to U, M) & \Pr(I, P \to U, M) \\ \Pr(U, M \to I, M) & \Pr(I, M \to I, M) & \Pr(U, P \to I, M) & \Pr(I, P \to I, M) \\ \Pr(U, M \to U, P) & \Pr(I, M \to U, P) & \Pr(U, P \to U, P) & \Pr(I, P \to U, P) \\ \Pr(U, M \to I, P) & \Pr(I, M \to I, P) & \Pr(U, P \to I, P) & \Pr(I, P \to I, P) \end{bmatrix}$$

Because all cases in equations A2–A5 have a $\frac{1}{N}$ term, we can re-write A as

$$A = \frac{1}{N} A'$$

Unlike A, A' does not depend on N.

To find B, we start from the fact that, if a newborn establishes in patch q, an adult host in the patch has a $\frac{2}{N} \cdot \frac{m}{\overline{m}_q}$ chance of dying (because there are $\frac{N}{2}$ hosts in each of patch M and P). Because the population is comprised almost entirely of residents, the probability that a newborn establishes can be approximated using the probability that a newborn resident establishes. For patch q, where the other patch is q', a host (mutant or resident) with mortality m has a probability of dying of

$$\Pr(\text{A given host in patch } q \text{ dies}) = \frac{2m}{N\overline{m}_q} \Pr(\text{A newborn resident establishes in } q)$$

where

$$\begin{aligned} &\Pr(\text{A newborn resident establishes in } q) \\ &= \frac{1}{2\overline{f}} \{[(1-d)(f_{q,U}(1-i_q) + f_{q,I}(1-v) i_q) \\ &+ d(f_{q',U}(1-i_{q'}) + f_{q',I}(1-v) i_{q'})] \cdot \\ &((1-hi_q) s_{q,U} + hi_q s_{q,I}) + ((1-d) f_{q,I} v i_q + d f_{q',I} v i_{q'}) s_{q,I}\} \\ &\equiv \frac{1}{2} b_q \end{aligned} \tag{A6}$$

The $\frac{1}{2}$ in the probability a resident establishes is due to the fact that each patch represents only half of the population and thus has its probability of reproducing normalized by $\frac{1}{2\overline{f}}$. We separate it out from the rest of the expression (b_q) to make it easier to deal with A - B later. This gives

$$\Pr(\text{A given host in patch } q \text{ dies}) = \frac{m}{N\overline{m}_q} b_q \tag{A7}$$

We can then write B as

$$B = \frac{1}{N} \cdot \begin{bmatrix} b_M \frac{m_{M,U}}{\overline{m}_M} & 0 & 0 & 0 \\ 0 & b_M \frac{m_{M,I}}{\overline{m}_M} & 0 & 0 \\ 0 & 0 & b_P \frac{m_{P,U}}{\overline{m}_P} & 0 \\ 0 & 0 & 0 & b_P \frac{m_{P,I}}{\overline{m}_P} \end{bmatrix}$$

All the nonzero entries of B have a $\frac{1}{N}$ term. We can re-write B in terms of $\frac{1}{N}$ and B', a matrix that does not depend on N.

$$B = \frac{1}{N} B'$$

Then we can write X_t as

$$X_t = I + \frac{1}{N}(A' - B')$$

One problem with X_t is that as $N \to \infty$, $X_t \to I$. To fix this, we rescale time in units of $\tau = tN$. Then the expected number of mutants produced per mutant of each patch and infection status can be written as

$$X_\tau = X_t^N = \left(I + \frac{1}{N}(A' - B') \right)^N$$

As the population size goes to infinity, we get the following formula for X_τ

$$\lim_{N \to \infty} X_\tau = \lim_{N \to \infty} \left(I + \frac{1}{N}(A' - B') \right)^N = e^{A' - B'} \tag{A8}$$

The mutant should invade if the leading eigenvalue of $X_\tau > 1$ when the resident is at equilibrium. Assuming mutations in transmission mode are small, we can trace the evolutionary trajectory of a population by seeing which mutant with similar transmission rates can invade, and then looking to see what transmission rates allow invasion of that mutant when it is the resident. Practically, this means finding the derivative of the leading eigenvalue of X_τ at a range of resident transmission rates (a positive derivative means a mutant with a slightly higher transmission rate can invade, and a negative derivative means one with a lower transmission rate

can invade). We then use these derivatives to trace the path of transmission mode evolution.

TRANSMISSION MODE EVOLUTION - SYMBIONT CONTROL

When transmission is a symbiont trait, we again investigate the invasion fitness of a mutant with slightly different transmission rates than the resident. We will follow the same general procedure as for host control. However, because a mutant symbiont should spread in the population if it can infect more hosts than the resident symbiont, we will track the number of mutants in units of hosts infected.

Let X_t be the expected number of hosts infected with mutant symbionts in patches M and P by a mutant symbiont in each patch. The first and second rows of X_t will give the infections produced in patches M and P, respectively. The columns of X_t will likewise correspond to the location of the symbiont that produces the new infection.

$$\begin{bmatrix} \#\text{Hosts infected with mutant in M at } t+1 \\ \#\text{Hosts infected with mutant in P at } t+1 \end{bmatrix} = X_t \begin{bmatrix} \#\text{Hosts infected with mutant in M at } t \\ \#\text{Hosts infected with mutant in P at } t \end{bmatrix}$$

We can again define $X_t = I + A - B$, where A is a matrix that gives the probability that a mutant symbiont produces a new in infection in each patch, and B gives the probability that a host infected with the mutant dies. Because a symbiont can produce an infection via horizontal or vertical transmission, we will write A as the sum of A_v and A_h, the probability a mutant produces a new infection via vertical or horizontal transmission. We can get A_v from the probability a newborn host is born infected (Equation 1) and the probability a host born infected establishes (Equation 2).

$$A_v = \frac{1}{N\overline{f}} \begin{bmatrix} (1-d)v^* f_{M,I} s_{M,I} & dv^* f_{P,I} s_{M,I} \\ dv^* f_{M,I} s_{P,I} & (1-d)v^* f_{P,I} s_{P,I} \end{bmatrix}$$

Because horizontal transmission is local, infections produced by horizontal transmission can only appear in the same patch as the original mutant symbiont, meaning A_h's off-diagonal entries will be 0. Infections produced by horizontal transmission depend both on the mutant's horizontal transmission rate, its chance of being chosen as the newborn's infectious contact ($\frac{2}{N}$), and on the number of incoming hosts that are uninfected. The probability that a host is born uninfected in turn depends on the resident's vertical transmission rate (v). The diagonal entries of A_h will then be

$$\Pr(\text{Horizontal transmission in } q) = \frac{1}{N\overline{f}}((1-d)(f_{q,U}(1-i_q) + (1-v)f_{q,I}i_q) + d(f_{q',U}(1-i_{q'}) + (1-v)f_{q',I}i_{q'}))h^* s_{M,I}$$

where q is the patch the host is arriving in and q' is the other patch. Then,

$$A_h = \begin{bmatrix} \Pr(\text{Horizontal transmission in } M) & 0 \\ 0 & \Pr(\text{Horizontal transmission in } P) \end{bmatrix}$$

The probability that a mutant symbiont dies depends on the rate of newborn hosts establishing in its patch. This is given by Equation A7, which will be the diagonal entries of B. (As in the host case, the off-diagonal entries of B will be 0.)

$$B = \begin{bmatrix} \Pr(\text{Infected host in } M \text{ dies}) & 0 \\ 0 & \Pr(\text{Infected host in } P \text{ dies}) \end{bmatrix}$$

We can now see that $A = A_v + A_h$ and B have $\frac{1}{N}$ terms in them. We can re-write A and B as $A = \frac{1}{N}A'$ and $B = \frac{1}{N}B'$, where A' and B' do not depend on N. Then the growth rate of a mutant symbiont in time units of $\tau = tN$ is $X_\tau = e^{A'-B'}$ as $N \to \infty$.

Again the mutant should invade if the leading eigenvalue of $X_\tau > 1$ when the resident is at ecological equilibrium.

LITERATURE CITED

Akçay, E. 2015. Evolutionary models of mutualism. *in* J. L. Bronstein (ed.), Mutualism, Oxford Univ. Press, Oxford, England, pp. 57–76.

Alizon, S., A. Hurford, N. Mideo, and M. Van Baalen. 2009. Virulence evolution and the trade-off hypothesis: history, current state of affairs and the future. J. Evol. Biol. 22:245–259.

Baker, D. M., J. P. Andras, A. G. Jordán-Garza, and M. L. Fogel. 2013. Nitrate competition in a coral symbiosis varies with temperature among Symbiodinium clades. ISME J. 7:1248–1251.

Best, A., S. Webb, A. White, and M. Boots. 2011. Host resistance and coevolution in spatially structured populations. Proc. R. Soc. B. Biol. Sci. 278:2216–2222.

Bezanson, J., A. Edelman, S. Karpinski, and V. B. Shah. 2017. Julia: a fresh approach to numerical computing. SIAM Rev. 59:65–98.

Bibian, A. J., J. A. Rudgers, and T. E. X. Miller. 2016. The role of host demographic storage in the ecological dynamics of heritable symbionts. Am. Nat. 188:446–459. https://www.journals.uchicago.edu/doi/10.1086/687965

Bonaldo, R. M., J. P. Krajewski, and I. Sazima. 2004. Does the association of young fishes with jellyfishes protect from predation? A report on a failure case due to damage to the jellyfish. Neotrop. Ichthyol. 2:103–105.

Bright, M., and S. Bulgheresi 2010. A complex journey: transmission of microbial symbionts. Nat. Rev. Microbiol. 8:218–230.

Carlsson-Granér, U., and P. H. Thrall. 2015. Host resistance and pathogen infectivity in host populations with varying connectivity. Evolution 69:926–938.

Carroll, A. C., and A. Wong. 2018. Plasmid persistence: costs, benefits, and the plasmid paradox. Can. J. Microbiol. 64:293–304.

Chamberlain, S. A., J. L. Bronstein, and J. A. Rudgers. 2014. How context dependent are species interactions?. Ecol. Lett. 17:881–890.

Cheplick, G. P., K. Clay, and S. Marks. 1989. Interactions between infection by endophytic fungi and nutrient limitation in the grasses Lolium perenne and Festuca arundinacea. New Phytol. 111:89–97.

Chung, Y. A., T. E. X. Miller, and J. A. Rudgers. 2015. Fungal symbionts maintain a rare plant population but demographic advantage drives the dominance of a common host. Journal of Ecology 103:967–977. http://doi.wiley.com/10.1111/1365-2745.12406

Daskin, J. H., and R. A. Alford. 2012. Context-dependent symbioses and their potential roles in wildlife diseases. Proc. R. Soc. B Biol. Sci. 279:1457–1465. Context-dependent symbioses and wildlife disease.

Davitt, A. J., C. Chen, and J. A. Rudgers. 2011. Understanding context-dependency in plant-microbe symbiosis: The influence of abiotic and biotic contexts on host fitness and the rate of symbiont transmission. Environ. Exp. Botany 71:137–145.

Débarre, F., S. Lion, M. van Baalen, and S. Gandon. 2012. Evolution of host life-history traits in a spatially structured host-parasite system. Am. Nat. 179:52–63.

Dunbar, H. E., A. C. C. Wilson, N. R. Ferguson, and N. A. Moran. 2007. Aphid thermal tolerance is governed by a point mutation in bacterial symbionts. PLoS Biol. 5:e96. Buchnera and thermal tolerance. http://plos.org/10.1371/Journal.pbio.0050096

Ebert, D. 2013. The epidemiology and evolution of symbionts with mixed-mode transmission. Annu. Rev. Ecol. Evol. System. 44:623–643.

Ewald, P. W. 1987. Transmission modes and evolution of the parasitism-mutualism continuum. Ann. N.Y. Acad. Sci. 503:295–306.

Gibson, A. K., J. Jokela, and C. M. Lively. 2016. Fine-scale spatial covariation between infection prevalence and susceptibility in a natural population. Am. Nat. 188:1–14.

Heath, K. D., and P. Tiffin. 2007. Context dependence in the coevolution of plant and rhizobial mutualists. Proc. R. Soc. B Biol. Sci. 274:1905–1912.

Hochberg, M. E., R. Gomulkiewicz, R. Holt, and J. N. Thompson. 2000. Weak sinks could cradle mutualistic symbioses—strong sources should harbour parasitic symbioses. J. Evol. Biology 13:213–222.

Jousimo, J., A. J. M. Tack, O. Ovaskainen, T. Mononen, H. Susi, C. Tollenaere, and A.-L. Laine. 2014. Ecological and evolutionary effects of fragmentation on infectious disease dynamics. Science 344:1289–1293.

Krist, A. C., J. Jokela, J. Wiehn, and C. M. Lively. 2004. Effects of host condition on susceptibility to infection, parasite developmental rate, and parasite transmission in a snail-trematode interaction. J. Evol. Biol. 17:33–40.

Lehmann, L., C. Mullon, E. Akçay, and J. Van Cleve. 2016. Invasion fitness, inclusive fitness, and reproductive numbers in heterogeneous populations. Evolution 70:1689–1702.

Lipsitch, M., M. A. Nowak, D. Ebert, and R. M. May. 1995. The population dynamics of vertically and horizontally transmitted parasites. Proc. R. Soc. B Biol. Sci. 260:321–327.

Lively, C. M. 2006. The ecology of virulence. Ecol. Lett. 9:1089–1095.

McKinney, W. 2010. Data structures for statistical computing in Python. *in* Stéfan van der Walt and Jarrod Millman (eds). pp. 51–56 *in* Proceedings of the 9th Python in Science Conference. http://conference.scipy.org/proceedings/scipy2010/mckinney.html

Penczykowski, R. M., S. R. Hall, D. J. Civitello, and M. A. Duffy. 2014. Habitat structure and ecological drivers of disease. Limnol. Oceanogr. 59:340–348.

Real, L. A., and R. Biek. 2007. Spatial dynamics and genetics of infectious diseases on heterogeneous landscapes. J. R. Soc. Interface 4:935–948.

Rossum, G. v. 1995. Python tutorial. *Technical Report CS-R9526*, Centrum voor Wiskunde en Informatica (CWI), Amsterdam.

Rudgers, J. A., T. E. X. Miller, S. M. Ziegler, and K. D. Craven. 2012. There are many ways to be a mutualist: endophytic fungus reduces plant survival but increases population growth. Ecology 93:565–574.

Saeki, K., and A. Sasaki. 2018. The role of spatial heterogeneity in the evolution of local and global infections of viruses. PLoS Comput. Biol. 14:e1005952.

Shapiro, J. W., and P. E. Turner. 2014. The impact of transmission mode on the evolution of benefits provided by microbial symbionts. Ecol. Evol. 4:3350–3361.

Smith, N. G. 1968. The advantage of being parasitized. Nature 219:690–694.

Tellier, A., and J. K. Brown. 2011. Spatial heterogeneity, frequency-dependent selection and polymorphism in host–parasite interactions. BMC Evol. Biol. 11:319.

Thomas, F., R. Poulin, J.-F. Guégan, Y. Michalakis, and F. Renaud. 2000. Are there pros as well as cons to being parasitized?. Parasitol. Today 16:533–536.

Thrall, P. H., and J. J. Burdon. 2000. Effect of resistance variation in a natural plant host-pathogen metapopulation on disease dynamics. Plant Pathol. 49:767–773.

Werren, J. H., L. Baldo, and M. E. Clark. 2008. Wolbachia: master manipulators of invertebrate biology. Nat. Rev. Microbiol. 6:741–751.

Wolfram Research Inc. 2017. Mathematica, Ver. 11. Wolfram Research Inc., Champaign, IL.

Yamamura, N. 1993. Vertical transmission and evolution of mutualism from parasitism. Theor. Population Biol. 44:95–109.

Yule, K. M., T. E. X. Miller, and J. A. Rudgers. 2013. Costs, benefits, and loss of vertically transmitted symbionts affect host population dynamics. Oikos 122:1512–1520.

Associate Editor: S. M. Flaxman
Handling Editor: Mohamed. A. F. Noor

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1: The events of a single time step.
Figure S2: Alternate ecological equilibria and host transmission mode evolution when the symbiont affects lifespan.
Figure S3: Host transmission mode evolution when the symbiont affects newborn host establishment probability.
Figure S4: Host evolution when the symbiont affects fecundity at more dispersal rates.
Figure S5: Host evolution when the symbiont affects fecundity, and the cost of infection in Patch P is not equal to the benefit of infection in Patch M.
Figure S6: Host evolution when infected hosts have increased lifespan and fecundity in M-patches and decreased lifespan and fecundity in P-patches.
Figure S7: Host evolution when infected hosts have one component of fitness increased in M-patches and the other decreased, with the reverse happening in the P-patches.
Figure S8: Host evolution when symbiont conditionally affects fecundity (increasing it in Patch M and decreasing it in Patch P) and slightly decreases lifespan in both patches.

Figure S9: Host transmission mode evolution: the addition of an unconditional cost to infection increases the fraction of evolutionary trajectories leading to symbiont containment.
Figure S10: Fraction of infected hosts in each patch when host evolution is simulated in a population of 200 hosts.
Figure S11: Simulations of host transmission evolution in larger populations ($N = 1000$).
Figure S12: Ecological equilibria and symbiont evolutionary trajectories for an infinite population.
Figure S13: Finite population simulations of symbiont transmission evolution.
Figure S14: Host evolution where there are unequal numbers of M- and P-patches and the symbiont affects host lifespan (through establishment probability).
Figure S15: Host evolution where there are unequal numbers of M- and P-patches and the symbiont affects host lifespan.
Figure S16: The average basic reproductive number (R_0) as a function of transmission probability in an infinite, monomorphic population.
Figure S17: Comparison of the magnitudes of the derivatives of mutant growth rates when the symbiont affects establishment or mortality.