E-Article

Within-Host Niche Differences and Fitness Trade-offs Promote Coexistence of Plant Viruses

Erin A. Mordecai,[1,*] Kevin Gross,[2] and Charles E. Mitchell[3]

1. Department of Biology, Stanford University, 371 Serra Mall, Stanford, California 94305; 2. Department of Statistics, North Carolina State University, Raleigh, North Carolina 27695; 3. Department of Biology and Curriculum for the Environment and Ecology, University of North Carolina at Chapel Hill, North Carolina 27599

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abstract: Pathogens live in diverse, competitive communities, yet the processes that maintain pathogen diversity remain elusive. Here, we use a species-rich, well-studied plant virus system, the barley yellow dwarf viruses, to examine the mechanisms that regulate pathogen diversity. We empirically parameterized models of three viruses, their two aphid vectors, and one perennial grass host. We found that high densities of both aphids maximized virus diversity and that competition limited the coexistence of two closely related viruses. Even limited ability to simultaneously infect (coinfect) host individuals strongly promoted virus coexistence; preventing coinfection led to priority effects. Coinfection generated stabilizing niche differences by allowing viruses to share hosts. However, coexistence also required trade-offs between vector generalist and specialist life-history strategies. Our predicted outcomes broadly concur with previous field observations. These results show how competition within individual hosts and vectors may lead to unexpected population-level outcomes between pathogens, including coexistence, competitive exclusion, and priority effects, and how contemporary coexistence theory can help to predict these outcomes.

Keywords: coexistence, competition, pathogen, plant, barley yellow dwarf viruses (BYDVs).

Introduction

The maintenance of diverse communities of species, despite competition that promotes exclusion, is fundamental to the structure and function of ecological systems (Carroll et al. 2011). Theory predicts that species coexistence requires niche differences (e.g., differences in resource use, host-specific natural enemies, or location in time and space) to be large enough to overcome fitness differences (e.g., competitive ability, fecundity, or survival; Chesson 2000). As a result, two types of mechanisms can promote coexistence: stabilizing processes, which increase niche differences, and equalizing processes, which reduce fitness differences (Chesson 2000). Whether processes effect niche or fitness differences depends on whether they provide species advantages only when they are rare or regardless of their relative abundances, respectively (Chesson 2000; see the appendix, available online, for details). Recent work has begun to identify the strength of niche differences and fitness differences and their influence on ecological processes, largely in plant communities (e.g., Levine and HilleRisLambers 2009; Carroll et al. 2011). By contrast, few studies have applied this powerful theoretical approach to the coexistence of pathogens (Colijn et al. 2010; Cobey and Lipsitch 2012). Here, we integrate a novel dynamical model with decades of empirical data to understand the processes that generate niche and fitness differences and thereby mediate coexistence in a globally important group of plant viruses.

Pathogens such as bacteria, fungi, and viruses often live in diverse communities within their hosts, despite potentially intense competition for host resources (Pedersen and Fenton 2007). Competing pathogens can deplete shared host resources (e.g., blood cells, energy reserves), elicit host responses that prevent subsequent infection or replication (e.g., immune responses, quarantine), or reduce host population size (Graham 2008; Cobey and Lipsitch 2013), although facilitation can also occur (Recker et al. 2009). In light of such strong competition, the processes that maintain the diversity of pathogens remain unclear. For example, competing pathogens may exhibit trade-offs between generality and specialization or between transmission and virulence. Such trade-offs could be stabilizing, equalizing, or both, depending on whether they differentially benefit rare species and whether they reduce competitive asymmetry (see the appendix).

Understanding the maintenance of pathogen diversity is a key goal for basic and applied infectious disease research. For example, the transmission and evolutionary dynamics of influenza, malaria, dengue, human immunodeficiency

* Corresponding author; e-mail: erin.mordecai@stanford.edu.

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virus, *Pneumococcus*, *Giardia*, and helminth parasites depend on interactions between multiple pathogen strains or species (Råberg et al. 2006; Pedersen and Fenton 2007; Graham 2008; Pepin et al. 2008; Cobey and Lipsitch 2012). Studying the community ecology of pathogens could not only improve predictions about disease spread but also inform disease control programs (Pedersen and Fenton 2007). However, simply understanding that pathogens compete does not necessarily lead to straightforward predictions because most diseases are embedded in complex ecological systems that contain multiple interacting pathogen, host, and vector species (Pedersen and Fenton 2007; Kedem et al. 2013).

Logistical and ethical limits on experiments place major constraints on pathogen diversity research. Studies are often limited to two species, minimal biological realism, and observational rather than experimental techniques (Fitt et al. 2006; Graham 2008; Cobey and Lipsitch 2012, 2013). Here, we explore the maintenance of pathogen diversity using a group of plant viruses, the barley yellow dwarf viruses (BYDVs), which overcome these limitations. The BYDVs are some of the most widespread, economically and ecologically important, and well-studied plant viruses (Rochow 1969, 1970, 1982; Aapola and Rochow 1971; Gildow and Rochow 1980; Rochow et al. 1983; Hu et al. 1988; D'Arcy and Burnett 1995; Gray and Gildow 2003; Malmstrom et al. 2005*b*; Borer et al. 2007; Seabloom et al. 2009). Sixty years of research on this group of aphid-transmitted pathogens of cereal crops and wild grasses have revealed strong competitive interactions between viruses within their plant hosts and aphid vectors as well as some facilitative interactions. The BYDVs provide a unique opportunity to explore the consequences of ecological interactions between viruses for the outcome of competition (Malmstrom et al. 2005*a*). Within this virus group, competitive exclusion can occur in the field (Rochow 1969; Power 1996), but coexistence is also common in natural and agricultural systems (Comas et al. 1995, 1996; Pons et al. 1995; Seabloom et al. 2009). Moreover, individual plants in the field often harbor multiple BYDVs even when overall prevalence is low (Seabloom et al. 2009). This system, which contains five common viruses, four major vector species, and hundreds of grass host species, falls at an intermediate level of diversity suitable for studying complex, multispecies interactions using a classic vector-borne disease modeling approach.

Here, we focus on three viruses in this group that are common globally in the field: *Barley yellow dwarf virus–PAV*, *Barley yellow dwarf virus–MAV*, and *Barley yellow dwarf virus–RPV* (hereafter, PAV, MAV, and RPV, respectively). The viruses were first discovered in California, where native perennial grasses can carry infections for multiple years. *Rhopalosiphum padi* aphids typically transmit PAV and RPV, while *Sitobion avenae* aphids transmit PAV and MAV (fig. 1*A*, 1*B*). Because PAV and MAV are closely related (in the genus *Luteovirus*), simultaneous infection (i.e., coinfection) is limited in aphids by interference and in plants by cross-protection (Aapola and Rochow 1971; Gildow and Rochow 1980; Rochow et al. 1983; Wen et al. 1991; Gray and Gildow 2003; fig. 1*C*). However, PAV-MAV coinfection does occur, and plants coinfected with PAV and MAV have similar pathology to singly infected plants (K. M. Marchetto and A. G. Power, unpublished data). RPV is more distantly related (in the genus *Polerovirus*). It does not cross-protect in plants or interfere in aphids with PAV or MAV (table A1, available online), but RPV-coinfected plants have greater pathology (K. M. Marchetto and A. G. Power, unpublished data). Although MAV by itself can use only *S. avenae*, it can be transmitted by a second vector, *R. padi*, when it coinfects a plant cell with PAV or RPV and its genome is packaged in the protein coat of the other virus (Rochow 1970, 1982; Hu et al. 1988). This process, referred to as dependent transmission, is a mechanism of facilitation. Both aphid species feed preferentially on virus-infected plants over uninfected plants (Ajayi and Dewar 1983; Medina-Ortega et al. 2009; Ingwell et al. 2012). Once infected, both vectors and plants carry and transmit the viruses for life but do not transmit them to offspring (D'Arcy and Burnett 1995).

In this article, we build a model that tracks virus transmission and plant population dynamics over multiple growing seasons in a California grassland for three viruses, two vector species, and a single perennial grass host. Although many grass species can host BYDVs and differences among host species may further contribute to virus coexistence, we focus here on a single grass species both because it is more tractable and because it allows us to focus on the processes within host populations that promote diversity. The relatively simple semidiscrete model structure captures many realistic aspects of virus and vector biology, including some that were not in previous models, and is fully parameterized from the empirical literature.

We use the model to determine the effects of three important factors on the outcome of competition: (i) the densities of the two aphid vector species, (ii) the ability of viruses to coinfect plants and/or aphids, and (iii) life-history trade-offs between vector specialist and generalist viruses. In addition, we explore several other mechanisms of competition and facilitation indicated in the empirical data. Here, we define three possible outcomes of competition. Stable coexistence occurs when each species can invade when rare in the presence of its competitors. Competitive exclusion occurs when one competitively superior species excludes the others and only it can invade when rare regardless of initial conditions. Priority effects occur when any one species can exclude the other(s) but no species can invade when rare and which species persists depends on initial conditions. We find that either coexistence or competitive exclusion can occur within empirically realistic

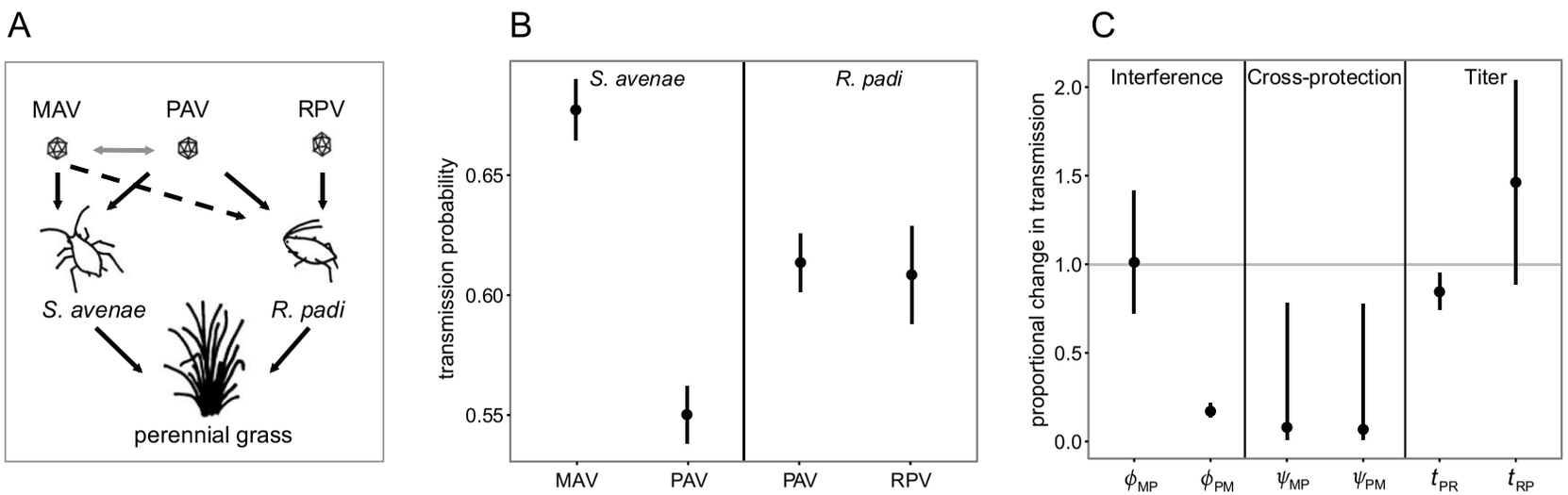

Figure 1: Key interactions among species in the study system. *A*, Conceptual diagram: the solid arrows represent transmission, the dashed arrow represents dependent transmission of MAV by *Rhopalosiphum padi* in the presence of a helper virus, and the gray arrow represents strong competition. *B*, Per-contact transmission probabilities for *R. padi* and *Sitobion avenae* and the two virus species each vector can transmit, corresponding to β values in the model. *C*, Proportional change in transmission in the presence of a second virus, due to interference within aphids (ϕ), cross-protection within plants (ψ), or reduced titer in coinfected plants (t). Values less than 1 represent a reduction in transmission (i.e., competition), and values greater than 1 indicate facilitation. We show only the pairs of competition parameters that differ from 1. Parameter subscripts ij represent the effect of virus j on the transmission of virus i. In *B* and *C*, points are estimated values, and error bars are 95% confidence intervals. All parameters are defined in table A1.

ranges of aphid densities. Surprisingly, increasing the density of an aphid species can promote either the persistence or the exclusion of the viruses it transmits, depending on competitive interactions with other viruses. We also find that coinfection is necessary but may not be sufficient for viruses to coexist in the plant population. Because coinfection can lead to competition among viruses, life-history trade-offs are also critical for virus coexistence.

Methods

Models

The basic model structure is a semidiscrete compartmental model, coupling continuous-time transmission dynamics within growing seasons with discrete-time plant population dynamics across growing seasons. For simplicity, we give one-virus, one-vector, one-host transmission equations here as an example of the equation structure and present the three-virus, two-vector, one-host model in full in the appendix.

Each year, an epidemic begins at the start of the growing season with transmission from perennial plants already infected from the previous year. The change in the density of infected hosts (I) is

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \frac{S}{S + yI} Va\beta, \qquad t \neq \tau_k, \tag{1}$$

where the between-growing-season transitions occur at times τ_k, $k = 1, 2, 3, \ldots$. Plant infection rate is a function of the frequency of susceptible hosts (S), weighted by the relative preference (y) of aphids for feeding on infected hosts (I) as well as the number of infected vectors (V), the vector movement rate (i.e., biting rate, a), and the per-contact transmission probability (β). We assume that this transmission probability is symmetric between plants and aphids because we could not estimate separate plant-to-aphid and aphid-to-plant transmission probabilities from the data available (see the appendix). Frequency-dependent transmission occurs in this and other vector-borne disease systems (Keeling and Rohani 2008; A. G. Power, personal communication). The rate of change in the density of infected aphids (V) is

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \frac{yI}{S + yI} Ua\beta - \delta V, \qquad t \neq \tau_k. \tag{2}$$

Aphid infection rate is a function of the contacts between uninfected aphids (U) and infected plants, weighted by aphid preference. Aphids are born and die at a constant rate, δ, resulting in constant total aphid density throughout the growing season (20 weeks, based on California grasslands) that is set by the density of plants and the per-plant density of *Rhopalosiphum padi* and *Sitobion avenae* aphids (z_r and z_s, respectively). Although virus infection could affect aphid demographic rates, such as fecundity and mortality (Jiménez-Martínez et al. 2004*a*), we assume aphid vital rates are constant here.

Plant population growth depends on the production and germination of new seeds and the survival of established plants. The size of the susceptible plant population at the start of a growing season (S) is equal to

$$S(\tau_k^+) = S(\tau_k)(1 - \mu_S) + \frac{\lambda(S(\tau_k) + \varepsilon I(\tau_k))}{1 + \alpha(S(\tau_k) + \varepsilon I(\tau_k))}, \tag{3}$$

where τ_k denotes the end of growing season k and τ_k^+ denotes the beginning of growing season $k + 1$. This is equal to the survival ($1 - \mu_S$) of susceptible plants from the end of the previous season ($S(\tau_k)$), plus the newly produced seeds that germinate, assuming no dormant seed bank. Seed production is a function of plant density in the previous year ($S(\tau_k)$ and $I(\tau_k)$), per capita fecundity (λ), and per capita competitive effects (α), with the assumption that infected plants have lower biomass (by a factor ε) and therefore also lower fecundity and competitive effects (Malmstrom et al. 2005*b*), as described in the appendix. The number of infected plants (I) at the beginning of year $k + 1$ is

$$I(\tau_k^+) = I(\tau_k)(1 - \mu_I). \tag{4}$$

This is a function of the survival ($1 - \mu_I$) of plants infected at the end of the previous year ($I(\tau_k)$).

To incorporate three virus species and two aphid species, we added equations for all possible plant and aphid infection classes, accounting for effects of cross-protection and interference on coinfection in plants and aphids, respectively (see the appendix). We assumed that coinfected plants and aphids transmit the viruses independently and that coinfection in plants with RPV lowers PAV transmission due to lower titer (K. M. Marchetto and A. G. Power, unpublished data; fig. 1*C*). Coinfected plants also have greater pathology and mortality.

In this system, viruses interact through several mechanisms. Viruses compete directly by preventing subsequent infection with other viruses in plants (cross-protection) and aphids (interference) and through altered transmission from coinfected plants (titer effects, for PAV-RPV coinfections only, which can be positive or negative). Interference within aphids is thought to occur because viruses compete with serologically similar viruses for receptor sites on the membranes of aphid salivary glands (Gildow and Rochow 1980). Viruses also compete indirectly, through demographic effects on hosts (via reduced seed production or survival). PAV and RPV can facilitate the transmission of MAV through dependent transmission (Rochow 1970, 1982; Hu et al. 1988). To model direct competition, we multiplied the per-contact probability of becoming infected (β)

for a previously infected host or vector by a factor representing the reduction due to cross-protection (ψ) or interference (ϕ), respectively. For PAV and RPV in coinfection, we multiplied the per-contact transmission probability of each virus by a factor (t_{PR} or t_{RP}) representing effects of coinfection on transmission. We modeled indirect competition by allowing plant seed production and mortality to depend on infection status. For dependent transmission, we included double transmission from MAV-RPV- or PAV-MAV-coinfected plants to *R. padi* aphids and from coinfected *R. padi* to plants with probability $\beta^{r}_{M,MR}$ and $\beta^{r}_{M,PM}$, respectively.

We parameterized the model using data on transmission (Rochow 1969, 1970, 1982; Gildow and Rochow 1980; Rochow et al. 1983; Hu et al. 1988), plant susceptibility and competence (Cronin et al. 2010), aphid density and demography (Ajayi and Dewar 1983; Power 1991; Schmidt et al. 2003; Jiménez-Martínez et al. 2004*b*; Malmstrom et al. 2005*b*; Borer et al. 2009; Medina-Ortega et al. 2009; Seabloom et al. 2009; Ingwell et al. 2012; M. E. Welsh, J. P. Cronin, and C. E. Mitchell, unpublished data), virus competition (Aapola and Rochow 1971; Gildow and Rochow 1980; Rochow et al. 1983; Wen et al. 1991; Gray and Gildow 2003; K. M. Marchetto and A. G. Power, unpublished data), and plant pathology and demography (Dyer and Rice 1997; Dyer 2003; Corbin and D'Antonio 2004; Malmstrom et al. 2005*a*; K. M. Marchetto and A. G. Power, unpublished data). Most of these studies describe laboratory or greenhouse experiments in which plants and/or aphids were infected with viruses maintained in colonies in the laboratory. For example, studies commonly describe the fraction of individuals successfully infected in a trial. Some plant and aphid demography studies were conducted in the field. All model parameters are listed in table A1. We fit means and 95% confidence intervals for all parameters using the raw data provided in the studies. Narrow confidence intervals reflect large within-study sample sizes as well as data being available from multiple studies (e.g., transmission parameters). For more details on parameter fitting from empirical data, see the appendix.

Analysis

To understand the outcome of competition, we calculated per capita growth rates when rare for each virus in the presence of the other viruses (i.e., invasion growth rates) by simulation. Stable coexistence occurs when each virus can invade when rare (Turelli 1978). The density of available aphid vectors (z_r for *R. padi* and z_s for *S. avenae*) controls the growth rate of each virus and is likely to vary across space and time. We calculated invasion growth rates for the three viruses across a range of aphid densities (z_r and z_s from 0 to 0.5 aphids per plant). *Rhopalosiphum padi* and *S. avenae* ranged, respectively, from 0.001 to 0.21 and from 0.026 to 1.32 aphids per plant in the field (Ajayi and Dewar 1983; Power 1991; Schmidt et al. 2003; M. E. Welsh, J. P. Cronin, and C. E. Mitchell, unpublished data).

We first explored the mechanisms that control the outcome of competition between PAV and MAV because they compete most intensely. We then added RPV to examine the three-virus outcome. We also conducted numerical experiments to examine two key mechanisms: (i) coinfection and (ii) life-history trade-offs between vector generality and specialization. We examined coinfection by eliminating it in the model (i.e., setting $\psi = 0$ and $\phi = 0$), and we examined life-history trade-offs by setting the transmission rate of MAV equal to that of PAV in *S. avenae* ($\beta^{s}_{M} = \beta^{s}_{P}$) and by setting the effect of PAV interference on MAV equal to the effect of MAV interference on PAV ($\phi_{MP} = \phi_{PM}$). We also performed a partial sensitivity analysis on the two-virus model by setting the cross-protection, pathology, and aphid preference parameters to their upper and lower 95% confidence limits (table A1) and comparing the results with the outcome of competition with the default parameter set. Finally, we explored the effect of titer on coinfection, mortality of coinfected hosts, and dependent transmission in the three-virus model. By comparing the resulting phase diagrams, which plot the outcome of competition across densities of the two aphid species, we can infer the strength of stabilization and effects on fitness differences of each biological property of the system (see the appendix for details).

To link our model to field observations, we performed virus population growth simulations for three empirical case studies that provided data on aphid densities in the field. For the first case study, M. E. Welsh, J. P. Cronin, and C. E. Mitchell (unpublished) monitored *R. padi* and *S. avenae* abundance in a California grassland on naturally occurring native and exotic grasses over three years (2011–2013). We simulated deterministic dynamics using mean annual aphid densities, and we simulated stochastic dynamics by drawing annual aphid densities from a bivariate gamma distribution with parameters estimated by maximum likelihood from the mean annual aphid densities in the field. For the second case study, we simulated deterministic population growth for the average aphid density values measured by Schmidt et al. (2003) in winter wheat fields in Germany in 2001. For the final case study, we performed a deterministic simulation using aphid density values measured by Power (1991) in oat fields in New York State from 1986 through 1988. All model analyses were performed in R (ver. 2.15.1), using the package deSolve.

Results

Without interspecific competition, both PAV and MAV would persist whenever the density of aphids they use

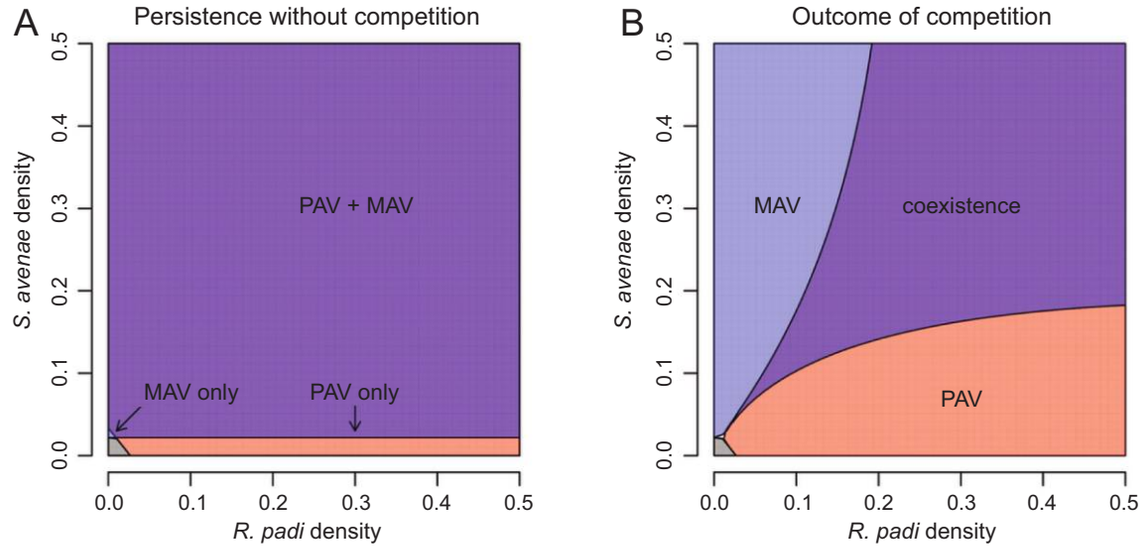

Figure 2: Ranges of aphid densities in which PAV (the vector generalist) and MAV (the vector specialist on *Sitobion avenae*) can persist, with and without competition, for *Rhopalosiphum padi* (*X*-axis) and *S. avenae* (*Y*-axis), in number per plant. *A*, Persistence in the absence of competition, with regions of PAV persistence shaded pink, MAV persistence shaded blue, both species persistence shaded purple, and neither species persistence shaded gray. This outcome is generated by running the model with each species alone and overlaying the two results. *B*, Outcome of competition between PAV and MAV across densities of the two aphids. The species coexist (purple region) at relatively high densities of both aphids, while MAV wins at low *R. padi* densities (blue region), PAV wins at low *S. avenae* densities (pink region), and neither species can persist at very low combined aphid densities (gray region). Priority effects (barely visible white region adjacent to gray region) occur for a very small region at the intersection of the other outcomes.

exceeded a low threshold value (fig. 2*A*). By contrast, competition between PAV and MAV dramatically reduced the region of coexistence, even when PAV and MAV could coinfect both aphids and plants (fig. 2*B*). MAV competitively excluded PAV at low *Rhopalosiphum padi* densities when *Sitobion avenae* density was moderate to high (fig. 2*B*, blue region) because it had more efficient transmission and did not suffer interference within the shared aphid, *S. avenae* (fig. 1*B*, 1*C*). By contrast, PAV excluded MAV at high *R. padi* densities when *S. avenae* density was low to moderate (fig. 2*B*, pink region). Coexistence occurred only at relatively high densities of both vectors (fig. 2*B*, purple region), where PAV's vector generality advantage offset MAV's competitive advantage in the shared vector (fig. 1).

We used the model to investigate how the ability to coinfect plants and aphids as well as life-history trade-offs between vector generality, transmission efficiency, and competition within shared aphids (fig. 1) affect the outcome of competition. We explored their effects on niche differences and fitness differences by determining how the focal processes affected the ranges of aphid densities over which virus species could persist. Specifically, the signature of stabilizing processes, which promote coexistence by causing species to limit themselves more strongly than they limit their competitors, is to increase the range of aphid densities in which multiple species can persist (see the appendix). In the absence of niche differences, multiple species cannot stably persist for any aphid densities, whereas the larger the range of aphid densities in which multiple species persist, the larger the niche differences between those species (fig. A1; figs. A1–A6 are available online). By contrast, processes that affect fitness differences, which determine which species wins in the absence of niche differences, expand the range of aphid densities in which some species can persist while concomitantly contracting the persistence range of other species, without affecting the degree of overlap in the persistence ranges of each species (fig. A1). We identified these signatures of stabilizing and equalizing processes by removing coinfection and life-history trade-offs from the model and comparing the outcome of competition with that of the full model.

Without the ability to coinfect, the viruses would be unable to coexist (fig. 2*B*) and instead would experience priority effects or competitive exclusion (fig. 3*A*). The shift from coexistence to priority effects indicates that coinfection acts as a stabilizing process, reflecting niche differences. More broadly, the outcome of competition in the full model (fig. 2*B*) represents an intermediate outcome between maximal competition resulting in competitive exclusion or priority effects (fig. 3*A*) and no competition resulting in coexistence (fig. 2*A*). Coinfection in plants had a much larger

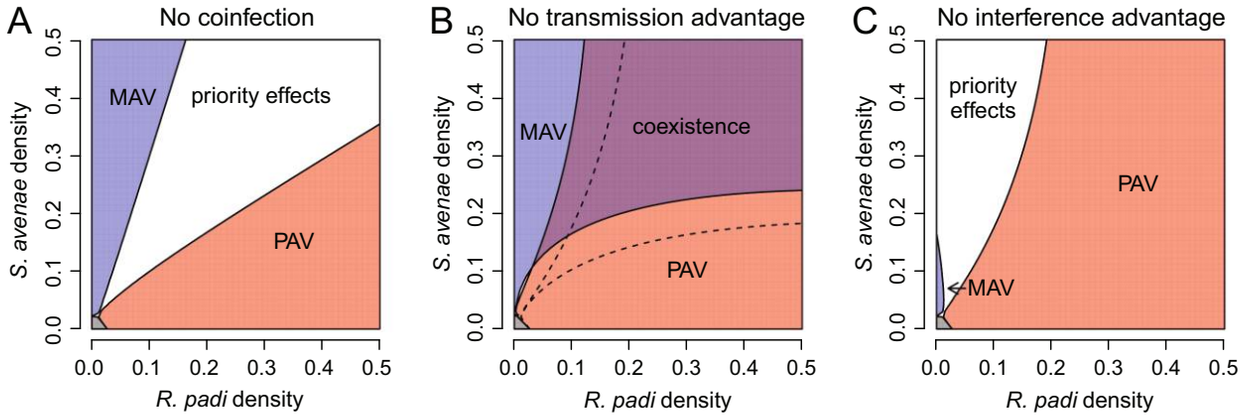

Figure 3: Effect of removing coinfection and life-history trade-offs on the outcome of competition between PAV (the vector generalist) and MAV (the vector specialist on *Sitobion avenae*). Figure descriptions are as in figure 2. In *A*, we remove coinfection in both aphids and plants. In *B*, the MAV transmission rate advantage is removed by setting the transmission rates of PAV and MAV in *S. avenae* aphids equal to the average of the two viruses' empirical values. Dashed lines show the boundaries of the coexistence region in the full model (fig. 2*B*). In *C*, the MAV interference advantage is removed by setting the interference MAV experiences from PAV equal to the interference it exerts on PAV (i.e., setting ϕ_{MP} equal to ϕ_{PM}). Compared with the full model in figure 2*B*, removing coinfection eliminates coexistence and promotes priority effects and competitive exclusion (*A*), and removing life-history trade-offs increases the region of PAV dominance (*B*, *C*) and can prevent coexistence (*C*).

effect on coexistence than coinfection in aphids (fig. A2) because the longer life span of plants relative to aphids gives them a higher probability of becoming coinfected.

Vector generality provides a clear fitness advantage for PAV, but vector specialization on *S. avenae* confers fitness advantages for MAV in transmission ($\beta^s_M > \beta^s_P$) and in its ability to infect aphids already carrying PAV ($\phi_{MP} > \phi_{PM}$; table A1; fig. 1*C*). Removing MAV's transmission advantage would reduce the range of aphid densities over which MAV could persist and allow PAV to dominate through a broader range of aphid densities (fig. 3*B*). Removing MAV's within-aphid competitive advantage would have an even stronger effect, reducing MAV dominance to a very small region of very low *R. padi* densities and promoting priority effects and PAV dominance (fig. 3*C*). The MAV within-aphid competitive advantage is both stabilizing and equalizing because it increases both the range of aphid densities in which MAV can persist and its overlap with the region of PAV persistence.

Together, these results (fig. 3) show that the stabilizing effect of coinfection and the equalizing effect of fitness trade-offs combine to promote virus coexistence; removing any of these processes would reduce the region of coexistence. Although coinfection strongly promotes coexistence, it is not by itself sufficient, as MAV and PAV also require fitness trade-offs to coexist across a broad range of aphid densities. A sensitivity analysis confirmed that the strength of cross-protection had large effects on the outcome of competition but that the magnitude of pathology and aphid preference did not (fig. A3).

An expanded version of the model included RPV. This virus is more distantly related and does not exert or experience any cross-protection in plants or interference in aphids. Moreover, it competes only by reducing PAV titer in coinfection (fig. 1*C*), through pathology of infected hosts, and through increased host mortality in coinfection (table A1). Because of this limited competition, RPV coexisted with the other two viruses whenever *R. padi* exceeded a low threshold density (fig. 4). Moreover, RPV expanded the region in which MAV could coexist with PAV (fig. 4, compared with the two-species coexistence region [dashed lines]). RPV facilitated MAV persistence directly through dependent transmission and indirectly by competing with PAV (fig. A4). RPV effects on PAV transmission in coinfection reduced PAV persistence and increased MAV persistence symmetrically (fig. A4*A*). By contrast, dependent transmission promoted MAV persistence in a large range of high *R. padi* and low *S. avenae* densities but had relatively little effect on PAV persistence, which was most limited at low *R. padi* and high *S. avenae* densities (fig. A4*C*, A4*D*). The higher mortality of plants coinfected with RPV had little effect on the outcome of competition because overall pathogen-induced mortality was low (fig. A4*B*; table A1).

We connected our model predictions to empirical systems by exploring three case studies that measured per-plant densities of *R. padi* and *S. avenae*. For the California grassland study by M. E. Welsh, J. P. Cronin, and C. E. Mitchell (unpublished), mean annual densities of *R. padi* and *S. avenae* were 0.008 and 0.027 aphids per plant, respectively. Densities of two aphid species were strongly

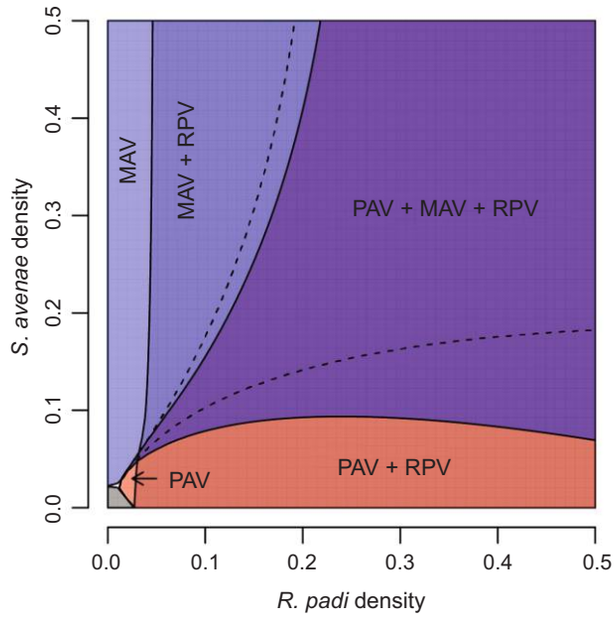

Figure 4: Outcome of competition for three virus species. Figure descriptions are as in figure 2. RPV (the vector specialist on *Rhopalosiphum padi*; darker shading) coexists with the other two viruses whenever *R. padi* exceeds a threshold density and expands the region in which PAV (the vector generalist) and MAV (the vector specialist on *Sitobion avenae*) can also coexist. Dashed lines show the PAV-MAV coexistence region from the two-virus model (fig. 2*B*). RPV expands the PAV-MAV coexistence region by competing with PAV in coinfection (reducing its titer) and by facilitating MAV transmission by *R. padi* through dependent transmission.

negatively correlated across years ($r = -0.99$). The model predicted that at these mean aphid densities MAV would competitively exclude PAV (which could persist if MAV were absent; fig. 5*A*). RPV could not persist at these low aphid densities due to its lower transmission efficiency compared with PAV and MAV (fig. 5*A*). Because growth rates when rare were very close to the replacement rate of 1 for both PAV and MAV (0.98 and 1.01, respectively), competitive exclusion was slow, and PAV initially increased with MAV before declining. (For clarity, within-season dynamics are not shown in this example.) A stochastic simulation drawing from the (correlated) joint distribution of mean annual aphid densities fitted from the data produced similar results, but fluctuations in year-end MAV prevalence were substantial (~0.05–0.15 across years) and strongly autocorrelated (fig. A5). This example highlights how competitive exclusion can occur even when overall prevalence is low (8% of plants infected). Consistent with the model predictions, a BYDV survey by M. E. Welsh, J. P. Cronin, and C. E. Mitchell (unpublished) in 2011–2012 found very low prevalence, with MAV five times more prevalent than PAV and RPV never occurring in more than 10,000 plants surveyed over several years. Because infected plants may survive for years, viruses introduced by immigrating aphids could persist for long periods even when local aphid densities are insufficient for stable virus transmission (virus immigration is not included in the model).

In the winter wheat aphid survey by Schmidt et al. (2003), aphid density averaged 0.009 and 0.492 *R. padi* and *S. avenae* aphids per plant, respectively. In this setting, the model predicted that MAV would rapidly competitively exclude PAV even though *S. avenae* is a competent vector for PAV (fig. 5*B*). As in the previous example, RPV could not persist due to low vector density (fig. 5*B*). Counterintuitively, increasing *S. avenae* densities in this example relative to the previous example (M. E. Welsh, J. P. Cronin, and C. E. Mitchell, unpublished data) actually accelerated competitive exclusion of PAV even though *S. avenae* is a competent vector for PAV. This is because MAV's competitive advantage and high transmission rate in *S. avenae* promotes rapid transmission to the host population, where preemptive competition due to cross-protection is very high, allowing MAV to monopolize available hosts (fig. 2). Notably, many plants become coinfected with PAV and MAV on the route to competitive exclusion, which demonstrates that co-occurrence within plants is not a reliable predictor of stable coexistence at the population scale. Equilibrium prevalence is 10 times higher in this system than in the unmanaged California grassland system (0.81 vs. 0.08), reflecting the influence of aphid abundance on prevalence. The seasonal nature of the system creates a sawtooth pattern in dynamics, in which prevalence rises during the growing season and drops rapidly between growing seasons, when some infected plants die and are replaced by uninfected plants. It is important to note that the model is based on natural populations of perennial grasses, such as the suite of grasses native to California. Competitive exclusion is not likely in agricultural host populations because plants are harvested each year and epidemics begin from viruses immigrating from outside the focal crop population, so the outcome of competition is decoupled from local dynamics. Therefore, these model predictions might more realistically describe virus dynamics in a nearby weed population that experiences similar aphid densities but natural host population dynamics.

In another crop system, Power (1991) measured high aphid densities with *R. padi* exceeding *S. avenae* (0.21 and 0.09 aphids per plant, respectively). Under these conditions, the model predicted that PAV and RPV would coexist with high rates of coinfection (0.68 prevalence of PAV-RPV coinfection, compared with 0.04 and 0.06 prevalence of PAV and RPV alone, respectively), while MAV was competitively excluded (fig. 5*C*). PAV and RPV tend to become entrained under these conditions because their

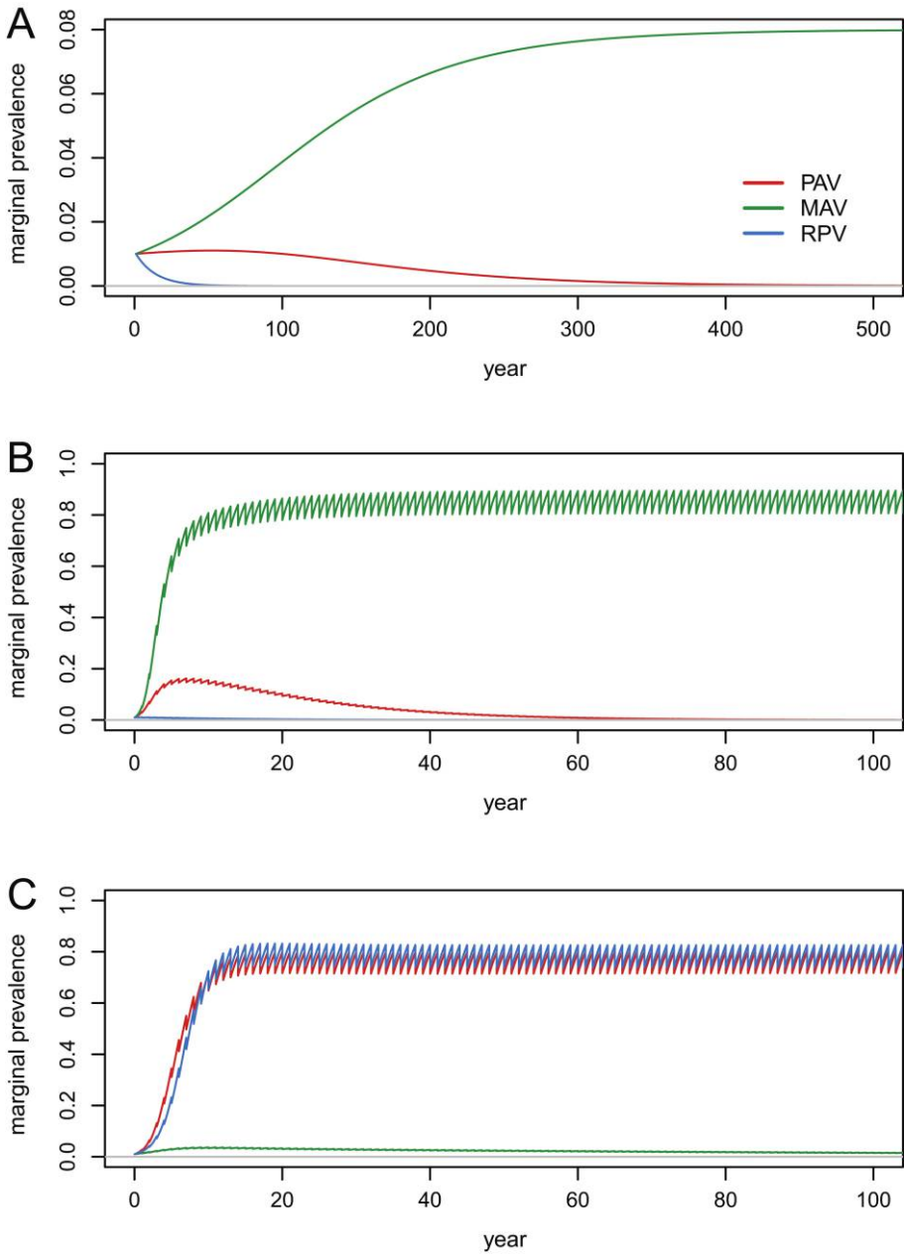

Figure 5: Deterministic virus population growth simulations for three aphid density scenarios from three empirical studies: *A*, M. E. Welsh, J. P. Cronin, and C. E. Mitchell (unpublished); *B*, Schmidt et al. (2003); and *C*, Power (1991). Plots show the marginal prevalence (both in single infection and in coinfection) of MAV, PAV, and RPV over time. Within-season virus dynamics are shown in *B* and *C* but are omitted in *A* for clarity because of the longer timescale.

shared aphid, *R. padi*, readily becomes coinfected and transmits both viruses, leading to efficient coinoculation of plants during a single feeding. Again, within-season dynamics lead to a sawtooth pattern in prevalence over time. As with the Schmidt et al. (2003) example, these predictions do not apply to populations of harvested, agricultural hosts, and model predictions for this scenario might more accurately describe virus dynamics in nearby weed or wild grass populations.

Discussion

Using an unusually tractable and data-rich plant pathogen system, we incorporated a broad suite of plant, aphid, and

virus biology into a data-driven mathematical model. We used the model to identify the processes that control virus coexistence, competitive exclusion, and priority effects by exploring alternative scenarios that would be impossible to manipulate in nature. Previous empirical studies of other pathogens have identified differences between pathogen species that may explain coexistence or exclusion but without a means to test their demographic effects (e.g., Power 1996; Fitt et al. 2006). On the other hand, theoretical models have explored properties of interacting pathogens that influence coexistence but without data linking the models with the natural world (Gatto and De Leo 1998; Ackleh and Allen 2003). Our model system shows how common properties of disease systems—coinfection, generalist-specialist trade-offs, vector transmission, and facilitation—can interact to shape diverse communities of pathogens. Such interactions are critical but difficult to measure and manipulate in most human, animal, and plant pathosystems.

The model revealed several key results that may apply to pathogen systems more broadly. First, vector density has important but sometimes unexpected effects on the outcome of competition. In the absence of competition, the two vector species act as substitutable resources for the generalist virus PAV (Holt et al. 2003; fig. 2*A*). This suggests that increasing the density of either vector species would benefit PAV, parallel to predicted effects of host density on directly transmitted pathogens (Gatto and De Leo 1998). However, competition with MAV when *Sitobion avenae* is present forces PAV to essentially specialize on *Rhopalosiphum padi* and restricts coexistence to high densities of both aphids (fig. 2*B*). Second, generalist-specialist life-history trade-offs can be equalizing, stabilizing, or both (fig. 3*B*, 3*C*). This can often be difficult to discern a priori without a model because the distinction depends on whether a process gives species advantages only when rare or also when common (see the appendix). Third, coinfection can be critical for stabilizing population-level coexistence even in the presence of strong (but not complete) cross-protection within hosts and interference within shared vectors (Castillo-Chavez et al. 1989; Gupta et al. 1994; Lipsitch et al. 2009; Cobey and Lipsitch 2012, 2013). In this system, coinfection within hosts has a much stronger effect on coexistence than coinfection within vectors because pathogens persist within hosts for a substantially longer time. Pathogens that cannot coinfect hosts may be particularly prone to priority effects (Leventhal et al. 2015; fig. 3*A*). Finally, although other niche differences—such as heterogeneity in time, space, or host use—may be present, they may not be necessary for coexistence when coinfection and life-history trade-offs stabilize population growth and reduce population fitness differences (Fitt et al. 2006; Cobey and Lipsitch 2012; fig. 4).

Previous theory has addressed the potential for coexistence of competing pathogens, often in the context of virulence evolution (Anderson and May 1982; Dobson 1985; Bremermann and Thieme 1989; Gupta et al. 1994; Andreasen and Pugliese 1995; Gatto and De Leo 1998). Most of this work has focused on directly transmitted pathogens or helminth parasites. The concept that coexistence cannot occur when pathogens completely cross-protect against each other has been explored previously (Anderson and May 1982; Bremermann and Thieme 1989), and subsequent models have studied conditions that promote pathogen coexistence, such as under density-dependent host mortality combined with a transmission-virulence trade-off (Andreasen and Pugliese 1995) and incomplete cross-protection (Castillo-Chavez et al. 1989; Gupta et al. 1994). For example, Gupta et al. (1994) reported that for competing malaria strains, complete cross-protection precluded coexistence (analogous to our fig. 3*A*), lack of cross-protection permitted strain coexistence across the full range of parameter values for each strain (analogous to our fig. 2*A*), and intermediate cross-protection led to coexistence when strains were relatively equivalent and to competitive exclusion when strains differed more in their vital rates (analogous to our fig. 2*B*). Despite the potentially strong influence of cross-protection and even rare coinfection, recent findings that contact structure influences pathogen evolution depend on the strong assumption that strains have complete cross-protection, providing an advantage to the first strain to invade (i.e., a priority effect; Leventhal et al. 2015). In spite of the theoretical foundation for understanding pathogen coexistence, the strength of these mechanisms is not well known in most disease systems (but see Colijn et al. 2010; Cobey and Lipsitch 2012).

Here, we show that the influences of limited cross-protection and generalist-specialist trade-offs extend to a more complex multivector multipathogen system. We place these mechanisms into a conceptual framework from community ecology (see the appendix), and we assess their relative strength by integrating empirical measurements with mathematical models. We find that transmission-mediated mechanisms (e.g., variation in transmission rates, cross-protection, and interference) have a much stronger effect on the outcome of competition than host mortality. In addition to vector transmission, our model includes realistic attributes, such as host density dependence, seasonality, and vector preference, as well as four mechanistically different modes of competition: cross-protection, interference, titer-dependent transmission reductions, and synergistic mortality. The agreement between previous models and our more biologically detailed model suggests that mechanisms that promote pathogen coexistence and competitive exclusion may be robust to substantial differences between systems.

Our approach provides a basis for further research on the mechanisms by which competing viruses coexist. For example, BYDVs and many other viruses can infect multi-

ple host species. Host diversity could promote virus coexistence if virus species performed differently on different host species (i.e., if viruses are somewhat host specific), including virus-specific differences in host susceptibility, host competence, or vector performance on the host. By contrast, if virus species respond similarly in their performance in different host species, coexistence could become more difficult because competition would be elevated in the most favorable hosts (Seabloom et al. 2013). More broadly, host diversity could qualitatively affect aphid behavior, morphology (i.e., production of alate vs. apterous morphs), physiology, or dynamics in ways that could influence virus coexistence, although there is no evidence for such host effects in our focal aphid species. Annual and perennial grasses may play different roles in sustaining epidemics: annuals are high-quality virus hosts that sustain large aphid populations and can facilitate virus spillover (Malmstrom et al. 2005*b*), but perennial grasses may be critical for sustaining virus carryover between years (Borer et al. 2010; Seabloom et al. 2013), particularly when immigration is low. Therefore, although field and greenhouse studies have revealed no evidence that different BYDVs perform better on different plant species (i.e., host specificity; Seabloom et al. 2013; Mordecai et al. 2015), host diversity may be important for long-term dynamics of these and other viruses.

Coinfection is stabilizing because it allows viruses of different species to partition host and vector individuals. By contrast, once a host or vector is infected with a virus, subsequent acquisition of the same virus does not change the infection status (i.e., titer or pathology) of that individual and thus does not affect virus fitness. In other words, BYDVs, like most other microparasites, replicate within the host and are not intensity dependent (Keeling and Rohani 2008). As a result, a host infected with a given virus is not susceptible to further infection with conspecific viruses but may be susceptible to coinfection with heterospecific viruses. In the presence of competitors, rare species can either coinfect previously infected hosts carrying the common species or infect uninfected hosts, whereas the common species can infect only uninfected hosts (because it is unlikely to encounter a host infected with the rare species). As a result, coinfection implies an ability to partition host or vector resources (e.g., receptor sites), resulting in a niche difference. This echoes a theoretical result that allowing heterospecific but not conspecific pathogens to coinfect hosts promotes coexistence (Lipsitch et al. 2009).

Numerical experiments showed that preventing coinfection leads to priority effects. Recent work suggests that priority effects are most likely to occur among species with high resource use overlap, large effects on the environment, and high sensitivity of growth rates to the environment (Vannette and Fukami 2014). Viruses that compete preemptively (by preventing coinfection) fit all three requirements: each virus requires the same host or vector resources, sequesters those resources through infection (which prevents coinfection), and depends on those resources for population growth. Preemptive competition lowers the effective contact rate between susceptible hosts and infected vectors (and vice versa) for each virus: the aphid biting rate is constant, but contacts between plants or aphids infected with other viruses cannot lead to aphid acquisition or transmission of the focal virus, resulting in wasted bites. More generally, the transmission of many pathogens relies on a fixed contact rate; if pathogens exert preemptive competition, they are likely to be prone to priority effects because of the wasted contact effect (e.g., Leventhal et al. 2015). Distinguishing between pathogen competitive exclusion and priority effects is critical for predicting responses of the pathogen community to perturbations, such as vaccination, treatment, or eradication (Lloyd-Smith 2013).

Field surveys of BYDVs broadly support our findings, although a full test of our model predictions would require data on field aphid densities paired with virus prevalence, which are not currently available. In California and Oregon grasslands, BYDV species richness varied across plant individuals, populations, and reserves, and the viruses transmitted by *R. padi*, PAV and RPV, were positively correlated (Seabloom et al. 2009). These results are consistent with our model predictions of varying virus community composition across aphid densities (fig. 4) and PAV-RPV entrainment (fig. 5*C*). Similarly, in cereal crop fields in Spain, plant and aphid populations carried all three viruses, individual plants and aphids were coinfected in all possible combinations, and aphids of both species were present year-round on different crops (Comas et al. 1995, 1996; Pons et al. 1995). These observations suggest that density may be high year-round for both aphid species (indeed, the authors state that aphid densities were often high), promoting stable three-virus coexistence with high rates of coinfection (fig. 4). By contrast, Rochow recorded a shift from MAV to PAV dominance in oat fields in New York, while RPV persisted at relatively low levels throughout the period (Rochow 1979; Power 1996). We speculate that a shift from moderate *S. avenae* densities and low *R. padi* densities to slightly higher *R. padi* densities could explain this virus community transition (lower left corner of fig. 4). Together, these empirical studies suggest that both coexistence and competitive exclusion occur in the field, potentially depending on aphid densities.

Previous research has examined effects of pathogen interactions in other systems, suggesting parallels to the BYDV system. In wild-plant populations, different strains and species in the genus of anther smut pathogens *Microbotryum* can either coinfect or compete preemptively for *Silene* hosts, depending on pathogen relatedness (Hood 2003; Gold et al. 2009). This could lead to a gradient from coexistence to priority effects as anther smut relatedness declines. By contrast,

for tomato leaf curl viruses, coexistence depends on fitness trade-offs that benefit a subordinate strain in coinfection (Péréfarres et al. 2014). Facilitation in coinfection can be strongly stabilizing (fig. A4*C*, A4*D*). In desert gerbil communities, a trade-off between host generality and specialization has been proposed to promote coexistence of *Mycoplasma* species and *Bartonella* species that share a flea vector and compete through host immune responses (Kedem et al. 2013). Such generalist-specialist trade-offs can be stabilizing, equalizing, or both (fig. 3*B*, 3*C*). Parasite competition also drives disease dynamics in rodent malaria (a model system for human malaria; Råberg et al. 2006), dengue (Pepin et al. 2008), and the childhood diseases measles and pertussis (Keeling and Rohani 2008). Using models to predict the outcome of competition in these systems could lead to different strategies for disease control. Moreover, empirically based modeling studies could help to resolve the debate surrounding when eradicated pathogens leave behind vacated "pathogen niches" to be colonized by other pathogens (reviewed in Lloyd-Smith 2013).

Interactions between pathogens can affect not only competitive coexistence but also the evolution of virulence, strain dynamics, and responses to vaccines and drugs (Råberg et al. 2006; Keeling and Rohani 2008; Cobey and Lipsitch 2012; Lloyd-Smith 2013). Given the nonlinearity inherent in competition and disease transmission, data-driven multispecies models are particularly useful for understanding how species interactions affect pathogen diversity and transmission (Keeling and Rohani 2008; Cobey and Lipsitch 2012, 2013; Péréfarres et al. 2014). A deeper understanding of controls over pathogen community composition will require identifying not just species differences but also the key stabilizing and equalizing processes that govern coexistence.

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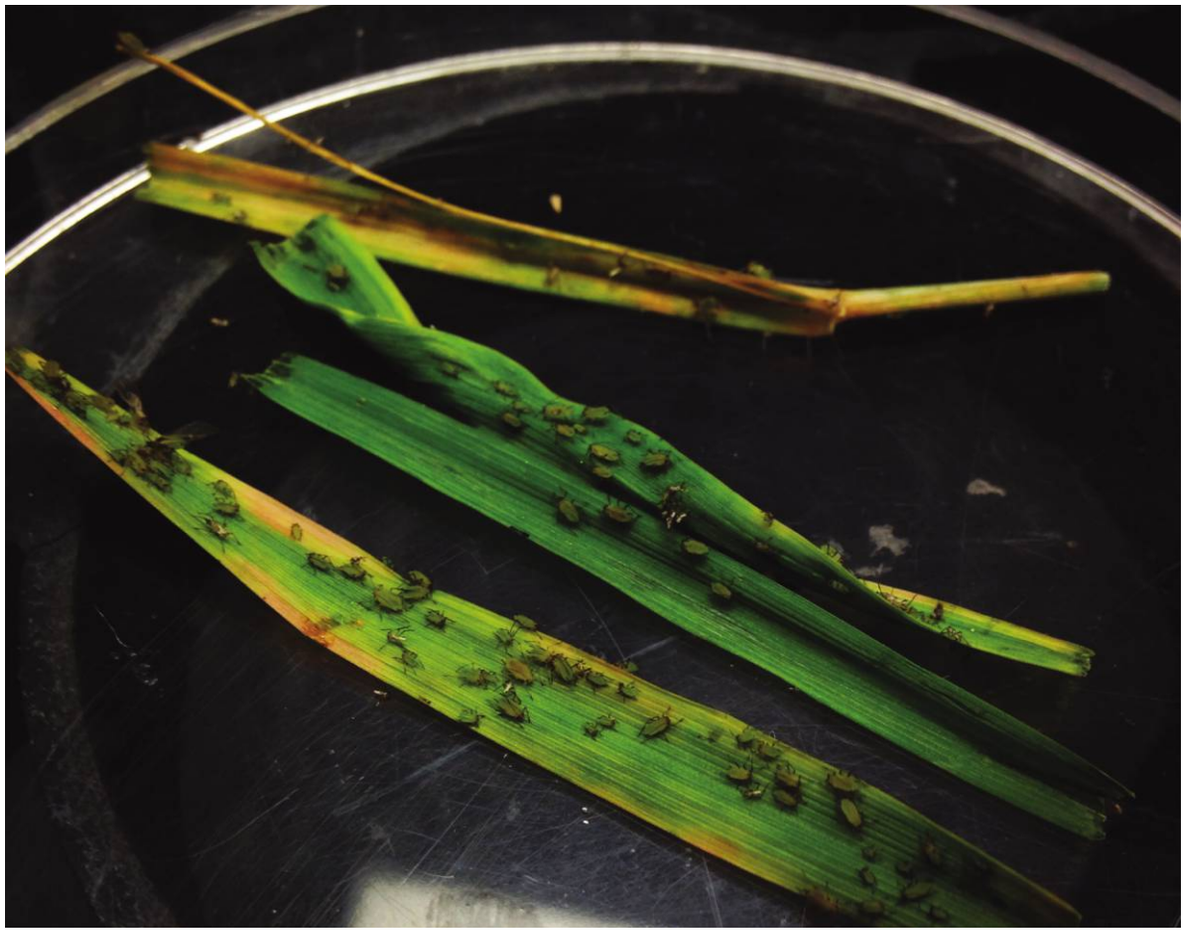

Sitobion avenae aphids feeding on oat tissue infected with barley yellow dwarf virus. Photograph by Erin A. Mordecai.