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Pathogen dynamics during invasion and establishment of white-nose syndrome explain mechanisms of host persistence

Winifred F. Frick,[1,2,7] Tina L. Cheng,[1] Kate E. Langwig,[1,3] Joseph R. Hoyt,[1] Amanda F. Janicki,[4] Katy L. Parise,[5,6] Jeffrey T. Foster,[5,6] and A. Marm Kilpatrick[1]

[1]*Department of Ecology and Evolutionary Biology, University of California, 1156 High St, Santa Cruz, California 95064 USA*
[2]*Bat Conservation International, PO Box 162603, Austin, Texas 78716 USA*
[3]*Center for Communicable Disease Dynamics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts 02115 USA*
[4]*Department of Ecology and Evolutionary Biology, University of Tennessee, 569 Dabney Hall, Knoxville, Tennessee 37996 USA*
[5]*Center for Microbial Genetics and Genomics, Northern Arizona University, Flagstaff, Arizona 86011 USA*
[6]*Department of Molecular, Cellular & Biomedical Science, University of New Hampshire, 46 College Road, Durham, New Hampshire 03824 USA*

Abstract. Disease dynamics during pathogen invasion and establishment determine the impacts of disease on host populations and determine the mechanisms of host persistence. Temporal progression of prevalence and infection intensity illustrate whether tolerance, resistance, reduced transmission, or demographic compensation allow initially declining populations to persist. We measured infection dynamics of the fungal pathogen *Pseudogymnoascus destructans* that causes white-nose syndrome in bats by estimating pathogen prevalence and load in seven bat species at 167 hibernacula over a decade as the pathogen invaded, became established, and some host populations stabilized. Fungal loads increased rapidly and prevalence rose to nearly 100% at most sites within 2 yr of invasion in six of seven species. Prevalence and loads did not decline over time despite huge reductions in colony sizes, likely due to an extensive environmental reservoir. However, there was substantial variation in fungal load among sites with persisting colonies, suggesting that both tolerance and resistance developed at different sites in the same species. In contrast, one species disappeared from hibernacula within 3 yr of pathogen invasion. Variable host responses to pathogen invasion require different management strategies to prevent disease-induced extinction and to facilitate evolution of tolerance or resistance in persisting populations.

Key words: *extinction;* Geomyces; *invasive species;* Pseudogymnoascus destructans; *white-nose syndrome; wildlife disease.*

Introduction

The introduction of novel pathogens has led to catastrophic population declines, species extinctions, and shifts in community composition, with important impacts on ecosystem processes and services (Skerratt et al. 2007, van Riper et al. 2008, Holdo et al. 2009, Langwig et al. 2012). Tracking the disease dynamics of pathogens as they spread across new regions provides a rare opportunity to characterize responses of hosts to virulent invading pathogens. Determining host response as a pathogen invades is necessary for predicting the long-term state of host-parasite interactions and for managing the impacts of disease to prevent extinctions (Anderson and May 1979, De Castro and Bolker 2004, McCallum 2012).

The long-term trajectory of host-parasite interactions—whether hosts are driven extinct or persist with a pathogen—depends on the extent of initial declines, the dependence of transmission on host density, the presence of an environmental reservoir, and evolution by the host or pathogen (De Castro and Bolker 2004). If initial mortality from disease exceeds a population's maximum growth rate and transmission does not decrease sufficiently at low host densities, then extinction can occur (Smith et al. 2006, McCallum 2012), unless the host evolves resistance (the ability to reduce or limit pathogen load leading to lower prevalence or infection intensity) or tolerance (the ability to reduce pathology and tolerate infection without influencing pathogen load; Dwyer et al. 1990, De Castro and Bolker 2004, Råberg et al. 2007,

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[7]E-mail: wfrick@batcon.org

Boots et al. 2009, Atkinson et al. 2013, Duggal et al. 2014). An abiotic pathogen reservoir (i.e., survival of the pathogen outside the host), alternate host species, and social aggregation can all maintain transmission at high levels as host species decline, and increase the likelihood of extinction (De Castro and Bolker 2004). In contrast, if transmission becomes inefficient as host density decreases, or if increased host survival or reproduction at low densities can compensate for disease mortality, then a population is likely to stabilize at a lower density (Hudson et al. 1998, Hochachka and Dhondt 2000, Kilpatrick 2006). Thus, studying how hosts respond to a pathogen as it invades can provide critical insights into the long-term consequences of pathogen invasion (Lambrinos 2008, Hawley et al. 2013, Duggal et al. 2014). This question can be addressed by determining the patterns of pathogen prevalence and loads during pathogen invasion as host populations initially decline. Our study is the first we are aware of to examine the temporal progression of prevalence and infection intensity during a continental-scale invasion and establishment of a pathogen. These data provide critical insight into how remnant populations persist with a pathogen.

White-nose syndrome (WNS) is a recently emerged infectious disease of hibernating bats caused by the fungal pathogen *Pseudogymnoascus destructans* (Lorch et al. 2011, Warnecke et al. 2012) that was first detected in North America in 2006 (Blehert et al. 2009; Appendix S1: Fig. S1). The fungus infects bats when they return to caves and mines to hibernate (Langwig et al. 2015*c*), and invades their skin over the winter which disrupts natural torpor cycles and causes mortality during hibernation (Meteyer et al. 2009, Langwig et al. 2012, Reeder et al. 2012, Warnecke et al. 2012). Initial impacts of WNS on six species of hibernating bats in the northeastern and midwestern USA have varied from nearly complete extirpation to arrested population growth (Langwig et al. 2012, 2015*a*). Subsequently, some populations of several species (including *Myotis lucifugus* that were predicted to be regionally extirpated by the disease; Frick et al. 2010) subsequently stabilized at 2–30% of pre-WNS colony size in the 5 yr after WNS detection (Langwig et al. 2012, Frick et al. 2015).

The differential outcomes among species exposed to a pathogen present a rare opportunity to examine the ecological and evolutionary drivers influencing the long-term outcome of novel host-pathogen interactions. Previous studies have described seasonal infection dynamics (Langwig et al. 2015*c*), quantified variation among species in infection prevalence during initial invasion (Langwig et al. 2015*a*), and compared invasion infection patterns in North America with patterns of infection prevalence and intensity in an endemic region (Hoyt et al. 2016), but the temporal progression of infection dynamics as the pathogen becomes established and host populations stabilize or go extinct have yet to be described.

We examine infection dynamics of *P. destructans* in seven species of bats in 258 colonies over the past decade as the pathogen spread and established across half of North America (Appendix S1: Fig. S1). We assess evidence for four non-exclusive mechanisms that influence the long-term outcomes for the host-pathogen interaction in WNS: (1) inherent (preexisting) resistance or tolerance: low prevalence and/or fungal load during invasion with limited population impacts; (2) density-dependent transmission: reductions in incidence as colonies declined, which lowers infection prevalence over time, since bats clear infection each summer (Langwig et al. 2015*c*); (3) evolution of tolerance or demographic compensation: sustained high prevalence and fungal load in persisting colonies that stabilize following declines; and (4) evolution of resistance: a decrease in fungal load and infection prevalence following initial declines. Without one of these mechanisms, colonies and entire species may be driven extinct. We compared patterns of infection dynamics and pathogen load during invasion and establishment to those expected under each of these mechanisms.

Materials and Methods

Data collection

We sampled between 1 and 50 hibernating bats of each species at 137 sites using epidermal swabbing during internal hibernacula surveys by state agency biologists conducted during the hibernation from November–March during five consecutive winters from 2009/2010 through 2014/2015. Participating biologists were provided a detailed sampling protocol and video instructions to standardize sampling across sites and years. We restricted analysis to seven species in which lesions diagnostic for WNS have been observed (Meteyer et al. 2009) and used a minimum of three sampled individuals per species per site (mean = 10, SD = 6) for a total of 4677 bats at 137 sites for prevalence analyses, and at least three infected bats (mean = 9, SD = 5) for a total of 3,229 infected bats at 128 sites for analysis of fungal loads (Appendix S2: Table S1). Epidermal swab samples were collected by dipping a sterile polyester swab in sterile water and rubbing the swab five times over the bat's forearm and muzzle (Langwig et al. 2015*c*).

We also collected 2–60 swab samples (mean = 14, SD = 9) from the ceiling or walls of hibernacula at least 10 cm from a roosting bat to measure environmental contamination with a total of 1234 samples from 79 sites sampled after the initial year of pathogen invasion. Swabs were stored in RNAlater until extraction and tested for presence and quantity of DNA of *Pseudogymnoascus destructans* using quantitative PCR (Muller et al. 2013). All samples were run in duplicate and considered positive if at least one run was positive below a cycle threshold (C_t) of 40 and quantified using a quantification curve from serial dilutions (nanograms of *P. destructans* $= 10^{-3.348 \times C_t + 22.049}$, $r^2 = 0.986$; Janicki et al. 2015). Load values were averaged across multiple runs and then converted to attograms by multiplying loads in nanograms by 10^9.

Statistical analyses

We conducted analyses using either prevalence or fungal loads as response variables, and each bat as a data point. We used generalized linear mixed effects models with site as a random effect and either a binomial (prevalence) or Gaussian (fungal loads) distribution. Fungal loads were $\log_{10}$ transformed. We tested the same fixed effects in both sets of analyses: species, years since *P. destructans* was detected at a site, number of days since the start of hibernation and two-way interactions among these variables. We used Akaike's Information Criterion to compare models with linear and nonlinear (square-root, reciprocal, and quadratic) transformations of years since *P. destructans* detection and days in hibernation to examine different forms of nonlinearity in temporal progression in infection. We then fit a global model using the best-fit transformations of years since *P. destructans* detection and days in hibernation. We tested for significant interactions among species, years since detection, and days in hibernation using likelihood ratio tests. We fit mixed effects models in Program R v. 3.1.2 with package lme4.

For each site, the years since *P. destructans* detection is the difference between the year of sampling and the year when WNS was reported in that county by histopathology or visual signs of fungus on bats as reported by the WNS National Plan (https://www.whitenosesyndrome.org/resources/map). We added one to the year of detection for each site so that sites where *P. destructans* is detected on bats by qPCR in the year before visual signs of disease are observed would have a value of 0 (rather than −1). Detection of *P. destructans* by qPCR often precedes WNS disease surveillance by visual methods if few individuals at a site are infected or sites contain primarily species that rarely display visual signs of WNS (Janicki et al. 2015). We calculated the number of days in hibernation as the difference between sample date and an estimated date when a species entered hibernation based on latitude to account for species and spatial differences in onset of hibernation (Appendix S3).

Results

The fraction of bats infected with *Pseudogymnoascus destructans* was relatively low at sites in the first year of detection, but prevalence increased rapidly over the following winter (Fig. 1A). Increases in prevalence varied among species both within the hibernation season (Fig. 1; Appendix S1: Fig. S2; likelihood ratio test: $\chi^2 = 37.02$, df = 6, $P < 0.001$) and across years since initial invasion (Fig. 2A; Appendices S1: Fig. S2 and S2: Table S2; likelihood ratio test: $\chi^2 = 103.54$, df = 6, $P < 0.001$). Infection prevalence in the majority of colonies of three species, *Myotis septentrionalis*, *Myotis lucifugus*, and *Perimyotis subflavus*, reached 100% by late winter within 2 yr of pathogen invasion (Figs. 1A, 2A). Prevalence increased more gradually for the other four species, but was still >75% in most colonies by year three for all species except *Myotis grisescens* (Fig. 2A). In addition, 25% (311 of 1234 samples from 79 sites) of environmental samples tested positive for the fungus after the initial invasion year, indicating that the fungus rapidly becomes prevalent within the hibernaculum environment. Prevalence reached very high levels in early hibernation starting in the third year after initial detection and remained at peak levels through late winter in all species and throughout subsequent years (Fig. 2A; Appendix S2: Table S3).

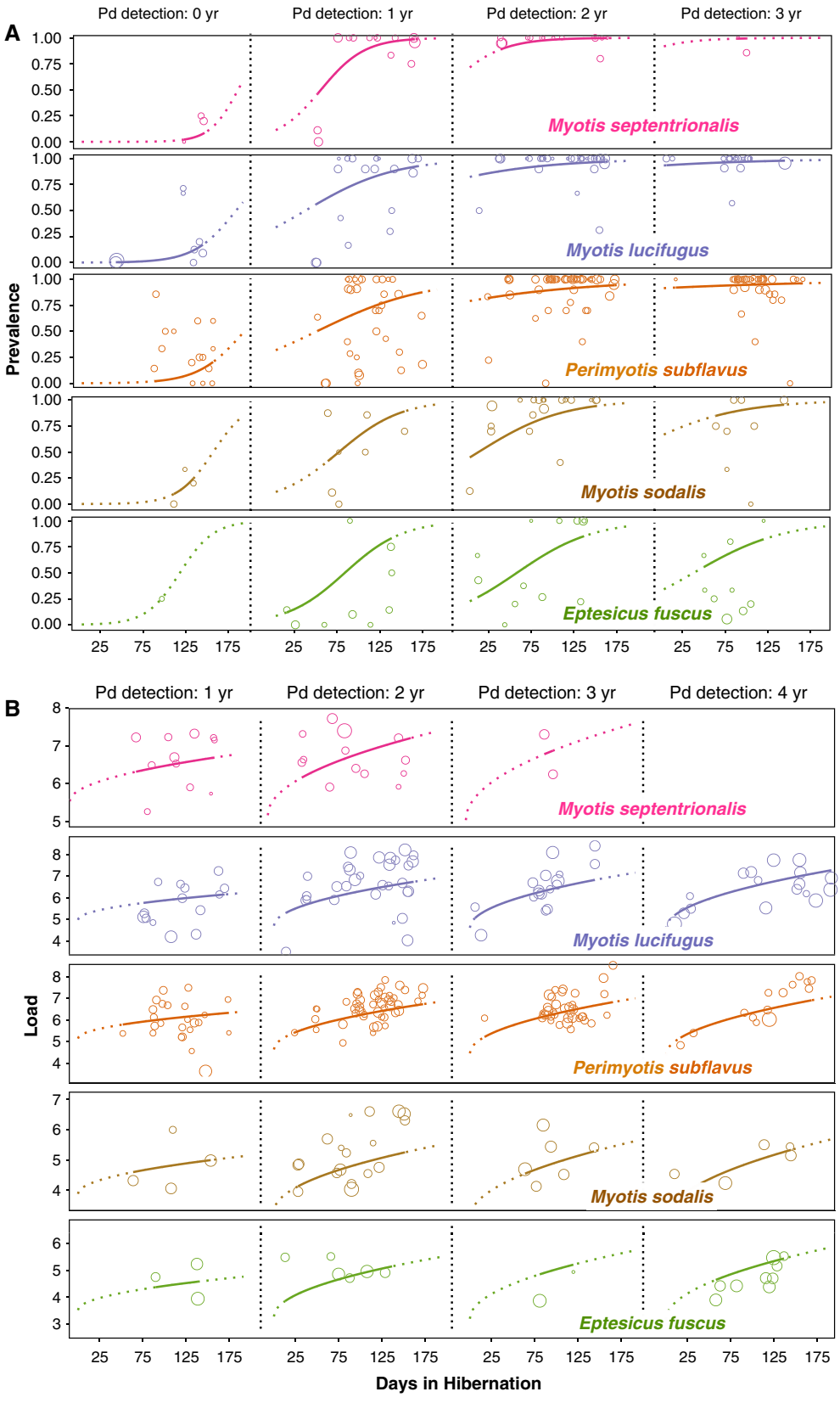
Fungal loads also increased asymptotically over years, but approached different maximum values for different species (Figs. 1B, 2B; Appendix S2: Tables S1 and S4), partly because the increase in loads varied among species with years since initial detection (Figs. 1B, 2B; Appendices S1: Figs. S3 and S2, Table S4; likelihood ratio test: $\chi^2 = 30.70$, df = 6, $P < 0.001$). The same three species (*M. septentrionalis*, *M. lucifugus*, and *P. subflavus*) that had the fastest increase in prevalence (Fig. 2A) also had higher loads after the pathogen established compared to other species (Fig. 2B; Appendices S1: Fig. S3 and S2: Table S4). The increase in fungal load within hibernation seasons became steeper with increasing years since invasion, such that they ended at higher levels by late winter as the pathogen established (Fig. 1B; Appendices S1: Fig. S4 and S2: Table S4).

There was no significant difference in the increase in fungal load among species within hibernation seasons (Fig. 1B; Appendix S1: Fig. S3; likelihood ratio test: $\chi^2 = 6.13$, df = 6, $P = 0.41$). However, because fungal loads differed in early winter, there was substantial variation within and between species in fungal loads by late winter, even at sites where colonies persisted for 6–8 yr after *P. destructans* was detected (Figs. 2B, 3). Late winter fungal loads varied across more than two orders of magnitude after pathogen establishment (Figs. 1B, 2B, 3).

Discussion

We found evidence for three mechanisms driving long-term outcomes of host-pathogen interactions in WNS, including evidence for inherent resistance or tolerance in at least three species (*Myotis leibii*, *Eptesicus fuscus, Myotis grisescens*) and development of tolerance and resistance in two species (*Myotis lucifugus* and

Fig. 1. Prevalence of infection (A) and fungal loads (B) of *Pseudogymnoascus destructans* (Pd) on bats during hibernation during the initial years of invasion. Solid lines show fitted model and dashed lines extend model fit from the start until the end of hibernation which are beyond the range of data. The fitted models are generalized linear mixed effects models that use each bat as a data point. Circles are site prevalence estimates (A) or mean loads at each site (B). Circle size is scaled to 1/SE. For loads, the initial year of Pd detection is not shown because prevalence was very low for most species. Loads are in $\log_{10}$ attograms. Note the differences in scale on the *y*-axis for fungal loads for different species (B).


A
Pd detection: 0 yr
Pd detection: 1 yr
Pd detection: 2 yr
Pd detection: 3 yr
Prevalence
Myotis septentrionalis
Myotis lucifugus
Perimyotis subflavus
Myotis sodalis
Eptesicus fuscus
B
Pd detection: 1 yr
Pd detection: 2 yr
Pd detection: 3 yr
Pd detection: 4 yr
Load
Days in Hibernation

Perimyotis subflavus). We also show the infection patterns leading to extensive extirpation of *Myotis septentrionalis*. In the 10 yr since WNS was first detected in North America, it has killed millions of bats, caused severe regional declines, and resulted in site-level extirpations in multiple species (Frick et al. 2015). Although WNS threatens some species with extinction, some colonies of heavily impacted species now appear to be persisting with the pathogen (Langwig et al. 2012, Frick et al. 2015, Maslo et al. 2015). Our results illustrate the changes in infection dynamics during pathogen invasion and establishment that have led to these differential outcomes.

Infection prevalence rapidly saturated near 100% after fungal invasion in six of the seven species examined, demonstrating that in all but one species, few individual bats escape *Pseudogymnoascus destructans* infection. This was surprising because both total colony sizes of all species and many single species' colony sizes declined by more than 90% in many hibernacula (Langwig et al. 2012, Frick et al. 2015). These declines would be expected to lead to substantially reduced transmission, given that this pathogen can be transmitted by direct contact between bats (Lorch et al. 2011, Warnecke et al. 2012). Our results show that few individuals escape infection, and instead, for most species, prevalence reached and remained near 100% near the beginning of winter within just 2–3 yr after the pathogen was detected.

The early infection of entire winter colonies of several species, despite enormous colony size declines, can be explained by the extensive environmental reservoir on hibernacula surfaces that we observed, as suggested in previous studies (Lorch et al. 2013, Langwig et al. 2015*a*). Bats appear to become infected as soon as they begin hibernating at hibernacula where the fungus has established (Langwig et al. 2015*c*). Long-term pathogen persistence in the environment could result from the long-term viability of *P. destructans* even in the absence of bats (Hoyt et al. 2015*a*). The environmental reservoir may also be maintained by shedding of fungal conidia by less impacted species such as *E. fuscus* and *M. leibii* and from scattered remnant colonies of *M. lucifugus, P. subflavus*, and *Myotis sodalis*.

The long-term persistence of an environmental reservoir bodes very poorly for species incapable of persisting at sites with the fungus, and strongly selects for individuals that can survive infection. One species, *M. septentrionalis*, has been extirpated from most sites within 3 yr of the fungus being detected (Langwig et al. 2012, Frick et al. 2015). Our results show that prevalence and fungal loads increase rapidly on this species until it disappears from sites, indicating that it cannot control the growth of the fungus or tolerate high loads. In contrast, some colonies of the two other most highly impacted species, *M. lucifugus* and *P. subflavus*, appear to have stabilized following steep initial declines (Langwig et al. 2012, Frick et al. 2015), although in some sites fewer than five individuals or even just solitary bats remain (Fig. 3). At sites with persisting colonies,

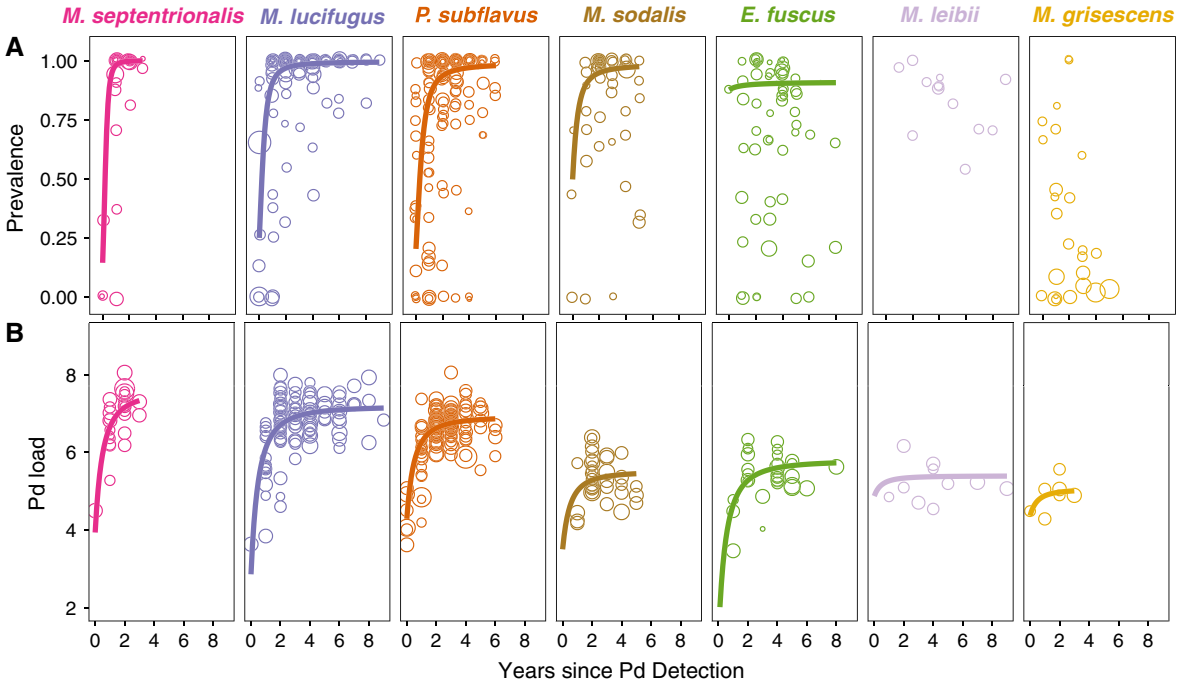


FIG. 2. Progression of prevalence (A) and loads (B) of *Pseudogymnoascus destructans* (Pd) on seven species of bats over the 10 yr since pathogen detection. Lines show fitted models for late hibernation (day 157). The fitted models are generalized linear mixed effects models that use each bat as a data point. Circles show prevalence and mean load estimates at sites, adjusted for sampling date. Circle size is scaled to 1/SE. Loads are in $\log_{10}$ attograms.

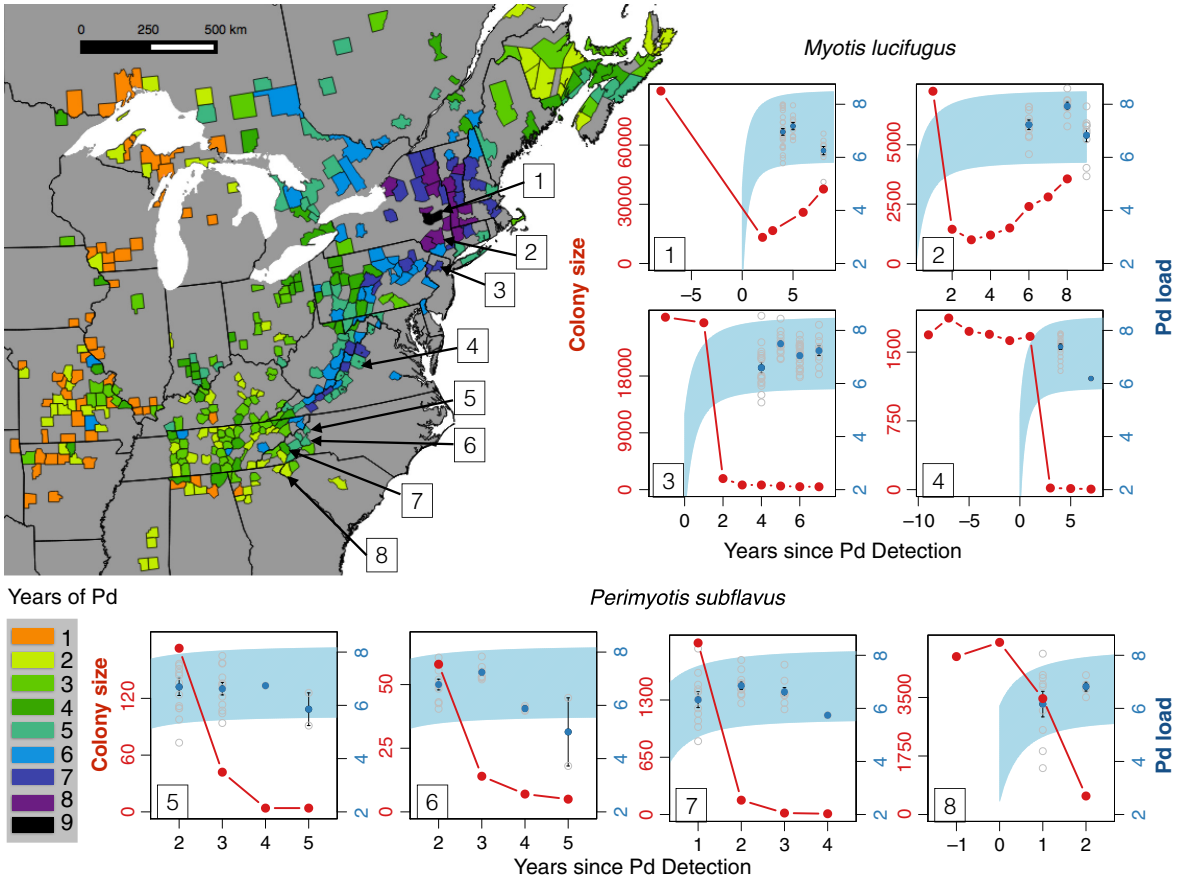


FIG. 3. Pathogen loads during and after initial population declines from disease for *Myotis lucifugus* and *Perimyotis subflavus*. Shaded blue areas on graphs show the 95% confidence interval of predicted late hibernation fungal loads over time from the fitted model for all sites combined for that species. Blue circles show mean loads (±1SE) at that site and gray circles show observed loads for each sampled bat. Both site means and fungal loads on individual bats are adjusted for sampling date. Loads are in $\log_{10}$ attograms.

prevalence remains very high (~100%), but bats experience a wide range of fungal loads, which correspond to disease-induced impacts (Langwig et al. 2016). At some sites, fungal loads are just as high as during epidemic decline years, whereas at other sites loads have decreased to levels observed in far less impacted species (such as *E. fuscus* or *M. leibii*). Intriguingly, this suggests that some colonies of *M. lucifugus* and *P. subflavus* may have become tolerant to the fungus, whereas others may have become resistant (Langwig et al. 2017). Another species, *M. sodalis*, had high prevalence but loads consistent with less-impacted species (Fig. 2; Langwig et al. 2012), yet this species may be more sensitive to infection intensity and experience mortality at lower load thresholds contributing to variable host response (Langwig et al. 2016). More detailed data are needed to identify the mechanisms of tolerance or resistance, and to determine the fitness costs associated with resistance and tolerance. Furthermore, monitoring of population dynamics and trends at these persisting sites will be necessary to assess the regional impacts of WNS and viability of these species over time (Maslo et al. 2015).

Several mechanisms could allow bats to have reduced infection intensity or higher tolerance to *P. destructans* infections. Increased fat stores or muscle mass in early hibernation or reduced disruption of torpor behavior from infection would enable bats to tolerate infection (Lilley et al. 2016). Lower fungal growth associated with resistance could be due to antifungal bacteria present in the skin microbiomes (Hoyt et al. 2015*b*), higher immune function, or poorer environmental conditions for fungal growth where they roost (Langwig et al. 2012, Johnson et al. 2014). Lower loads could also result from delayed exposure to the pathogen by delaying hibernation or slightly reduced transmission rate.

The variation in host responses following pathogen invasion suggest that different management actions will be necessary for different species suffering from the same disease (Langwig et al. 2015*b*). Management intensive strategies such as vaccination, treatment, or habitat disinfection may be the only way to prevent global extinction of species such as *M. septentrionalis* that show no ability to persist with the pathogen in hibernacula. In contrast, actions that increase survival and reproduction of

persisting populations will facilitate the evolution of resistance and tolerance (Kilpatrick 2006, Maslo et al. 2015) and these actions may be the best long-term strategy to increase small remnant populations and allow them to persist. In addition, if traits conferring resistance or tolerance are heritable, then translocation of individuals from persisting populations to areas where a species has been extirpated could facilitate recovery.

Many pathogens have been introduced into new regions in the past century with devastating impacts on wild populations (Skerratt et al. 2007, van Riper et al. 2008). Our results demonstrate how multiple mechanisms can enable species to persist with invading pathogens. For WNS, persistence appeared to require the evolution of resistance or tolerance because environmental and biological reservoirs maintained high infection prevalence, even as populations of some species crashed to very low abundance. The ecological and evolutionary responses of species will determine their fate in a world where pathogen introductions show no signs of abating.

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Supporting Information

Additional supporting information may be found in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/ecy.1706/suppinfo