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Multi-scale model of epidemic fade-out: Will local extirpation events inhibit the spread of white-nose syndrome?

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Abstract. White-nose syndrome (WNS) is an emerging infectious disease that has resulted in severe declines of its hibernating bat hosts in North America. The ongoing epidemic of white-nose syndrome is a multi-scale phenomenon because it causes hibernaculum-level extirpations, while simultaneously spreading over larger spatial scales. We investigate a neglected topic in ecological epidemiology: how local pathogen-driven extirpations impact large-scale pathogen spread. Previous studies have identified risk factors for propagation of WNS over hibernaculum and landscape scales but none of these have tested the hypothesis that separation of spatial scales and disease-induced mortality at the hibernaculum level might slow or halt its spread. To test this hypothesis, we developed a mechanistic multi-scale model parameterized using white-nose syndrome county and site incidence data that connects hibernaculum-level susceptible-infectious-removed (SIR) epidemiology to the county-scale contagion process. Our key result is that hibernaculum-level extirpations will not inhibit county-scale spread of WNS. We show that over 80% of counties of the contiguous USA are likely to become infected before the current epidemic is over and that geometry of habitat connectivity is such that host refuges are exceedingly rare. The macroscale spatiotemporal infection pattern that emerges from local SIR epidemiological processes falls within a narrow spectrum of possible outcomes, suggesting that recolonization, rescue effects, and multi-host complexities at local scales are not important to forward propagation of WNS at large spatial scales. If effective control measures are not implemented, precipitous declines in bat populations are likely, particularly in cave-dense regions that constitute the main geographic corridors of the USA, a serious concern for bat conservation.

Key words: bats; emerging infectious disease; epidemic fade-out; hibernacula; multi-scale model; parasite-mediated extinction; Pseudogymnoascus destructans; *white-nose syndrome.*

Introduction

Emerging infectious diseases that spread over large spatial scales and cause severe population declines are increasingly recognized as an important threat to the persistence of vulnerable populations (Daszak et al. 2000, De Castro and Bolker 2005, Pedersen et al. 2007, Fisher et al. 2012). White-nose syndrome (WNS) in North America is an example of an emerging infection that has spread rapidly over a wide geographic range and has resulted in local extirpations of its hibernating bat hosts (Frick et al. 2010). In total, 5.5–6.7 million bats are estimated to have died from white-nose syndrome in the eastern United States (U.S. Fish and Wildlife Service 2012) and population declines are estimated to be greater than 80% in the Northeast alone (Turner et al. 2011). WNS was discovered in a cave in Schoharie County, New York in 2006. By the summer of 2014, WNS was confirmed in 25 states in the United States and in five provinces in Canada. Rapid expansion of the *Pseudogymnoascus destructans* (formerly known as *Geomyces destructans*) fungus, the causative agent of WNS (Lorch et al. 2011, Warnecke et al. 2012), together with reports of mass mortality in infected hibernation sites (hibernacula; Turner et al. 2011, U.S. Fish and Wildlife Service 2012), generated widespread concern that endangerment of already vulnerable bat species will be exacerbated (Blehert et al. 2009, Foley et al. 2011).

Spread of white-nose syndrome occurs on at least three spatial scales: (1) within groups of individuals that roost in hibernation sites (individual level), (2) between hibernacula (hibernaculum level), and (3) at large landscape scales, e.g., county-level transmission between counties, a scale for which incidence data are available as the U.S. Fish and Wildlife Service records occurrences of white-nose syndrome in the contiguous United

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States by county (*available online*).[6] From a multi-scale perspective, any contagion pattern at the county scale arises from interactions of smaller scale units or groups of bat populations within counties. The key question is, how to model this hierarchical dependence? What amount of individual-level and hibernaculum-level information is necessary to correctly capture the dynamics of spread? Two models have been proposed to understand drivers of WNS spread at different spatial scales. To determine the factors driving WNS spread at large spatial scales, Maher et al. (2012) modeled the spread of white-nose syndrome between U.S. counties as a stochastic contagion process. They fit alternative infection-dispersal kernels to county incidence data and concluded that the probability of spread between counties decreased with distance between counties and increased with the number of caves in a county and the duration of winter. To identify risk factors influencing spread of WNS in the northeast, Wilder et al. (2011) used a proportional hazards model to show that colony size and distance from the epicenter were the most important determinants of white-nose syndrome arrival rate to a colony. A dynamical model of WNS spread uniting disparate spatial scales is so far lacking.

In our model, a contagion process within a county is represented as occurring among groups of animals, each associated with a hibernaculum (not individual animals), and thus a county is composed of a population of hibernacula. The transmission process between hibernacula is poorly understood. Hypothesized mechanisms for spread at the hibernaculum scale include susceptible-infectious (SI) transmission, where hibernacula are categorized as either susceptible or infectious. Hibernacula could remain infectious indefinitely as a result of environmental contamination with WNS spores (Lindner et al. 2011, Lorch et al. 2013) or through resistant bats transmitting the infection to other hibernacula. Another possibility is susceptible-infectious-susceptible (SIS) transmission, whereby following elimination of the infection from hibernacula, sites are repopulated by susceptible bats (a rescue effect). An alternative plausible transmission mechanism is susceptible-infectious-removed (SIR) epidemiology, where local extirpations lead to permanent elimination of the infection from hibernacula and thus these sites no longer contribute to transmission. A variation of the SIR transmission pathway that lies between SIR and SI processes is hibernacula becoming environmental reservoirs of the infection following their depopulation due to disease-induced mortality in bat hosts and continuing to contribute to forward transmission for a period of time, which is terminated when residual fungal spores lose viability. In contrast to the SI contagion process explored by Maher et al. (2012), SIR transmission could represent a best-case scenario for propagation of WNS at larger spatial scales, in that it may eventually mitigate large-scale spread. All of these alternatives are plausible pathways for transmission of the disease between hibernacula. However, due to the widespread occurrence of local extirpation events of bat populations, hibernaculum-level SIR epidemiology represents an important potential transmission pathway operating on a local spatial scale whose impact on the emergent spatiotemporal county spread pattern has not yet been explored. Further, the connection between macro- (county) and SIR micro- (hibernaculum) scales could lead to either of two general patterns. On the one hand, if habitat networks are dense and dispersal occurs over sufficiently large distances, then large-scale spatial spread is expected to result, ensuing in extirpation of the host over broad regions (Grenfell and Harwood 1997, Earn et al. 1998). On the other hand, if habitat networks are sufficiently sparse and pathogen dispersal occurs only locally, then local extirpation events may result in habitat fragmentation so that extirpations in a county exceed secondary infections, eventually leading to eradication of the parasite.

We initially hypothesized that the separation of spatial scales and disease-induced mortality within hibernacula might slow or halt the macroscale spread of WNS in the United States. To test this hypothesis, we developed a multi-scale model of white-nose syndrome that connects two spatial scales, the county-scale (macroscale) and hibernaculum (microscale) transmission processes. The integration of two spatial scales enables the exploration of how disease-induced mortality (modeled as an SIR transmission process at the hibernaculum level) may drive the emergent phenomenon of extinction of the pathogen on large spatial scales. In general, spatially explicit multi-scale models account for local infection processes within patches with the aim of explaining emergent spatial dynamics (e.g., Hufnagel et al. 2004, Viboud et al. 2006, Tuite et al. 2011). Such models have been used to perform retrospective analyses of the factors that govern patterns and rates of spread of infectious diseases, such as measles and influenza in humans (Grenfell et al. 2001, Viboud et al. 2006), phocine distemper virus in seals (Swinton et al. 1998), plague in great gerbils (Davis et al. 2008), and to evaluate the impacts of different control strategies for foot-and-mouth disease (Keeling et al. 2001) and bovine tuberculosis (Brooks-Pollock et al. 2014), but to our knowledge, such models have not been used to predict how local parasite-mediated extirpation events affect emergent macroscale spatiotemporal infection patterns.

Following Maher et al. (2012), we supposed that the macroscale spread of WNS might be determined by the interaction of climate and the spatial configuration of counties with caves on a landscape graph. Counties were assumed to be heterogeneous on the graph because the number of potential hibernacula within counties in the contiguous United States varies by three orders of magnitude (Culver et al. 1999; see Appendix A: Fig. A3).

[6] http://www.whitenosesyndrome.org/resources/map

We used the number of caves as a surrogate for the total bat population size across all species in a single county. Within counties, we assumed WNS epidemiology to follow susceptible-infected-removed (SIR) dynamics. Local extirpations at the hibernaculum level in the model were used as a surrogate for WNS-induced mortality and the time to extirpation was assumed to be exponentially distributed. To account for the potential presence of hibernaculum infection reservoirs, we compared the spread patterns predicted by the SIR multi-scale model with the macroscale SI model developed by Maher et al. (2012) and a multi-scale SIR model with gamma-distributed hibernaculum extirpation time. These alternatives to SIR transmission assume that environmental reservoirs can contribute to transmission indefinitely and for a period of time respectively. Using multi-scale SIR and SI models, we additionally investigated how local extirpations and the presence of environmental reservoirs affect the prediction of Frick et al. (2010) that the regional population of little brown bats (*Myotis lucifugus*) in the northeastern United States will be reduced to 0.01% of its original size by 2026. Our multi-scale SIR model with exponentially distributed extirpation time predicts that local extirpation events will not mitigate macroscale spread due to the strong coupling between counties. The macroscale spatiotemporal infection pattern that emerges from local SIR epidemiological processes falls within a narrow spectrum of outcomes, suggesting that recolonization, rescue effects, and multi-host complexities at local scales are not important to forward propagation of WNS at large spatial scales. These findings have important implications for management of the infection.

Material and Methods

Microscale model

We used data at two spatial scales to derive a model that included both hibernaculum-level spread within counties and macroscale propagation between counties. The microscale data comprised hibernaculum infection histories from the winters of 2005–2006 through 2009–2010 in New York and Pennsylvania (C. Herzog and C. Butchkoski, *unpublished data*). Specifically, we used hibernaculum infection histories to parameterize a compartmental SIR system of ordinary differential equations for each county. The SIR system for each county described the evolution of the numbers of susceptible hibernacula $S(t)$, infectious hibernacula $I(t)$, and hibernacula removed from the system as a result of disease-induced mortality of all bat hosts within hibernacula $R(t)$. The number of susceptible, infectious, and removed hibernacula in each county sum to the total number of hibernacula in each county (Appendix A: Fig. A3). Transmission between hibernacula was assumed to be density dependent because larger colonies and regions with high bat population density are more likely to become infected (Wilder et al. 2011). Moreover, bats are highly social and are known to migrate between hibernacula (Fenton 1969). Hibernacula were assumed to have an exponentially distributed extirpation time with mean $1/\gamma$ years. These assumptions lead to the classical SIR model in epidemiology (Anderson and May 1992)

$$\begin{aligned} dS/dt &= -\beta SI \\ dI/dt &= \beta SI - \gamma I \\ dR/dt &= \gamma I \end{aligned} \tag{1}$$

where t is time, γ is per hibernaculum removal rate, β is per hibernaculum transmission rate. If the infection propagates through a county according to this model, a disease-free equilibrium state will eventually be reached, i.e., epidemic burnout within a county is guaranteed to occur. The model also predicts that a minimum proportion of susceptible hibernacula, $\exp(-R_0)$, will escape infection (Keeling and Rohani 2008).

The SIR framework leads naturally to a threshold for hibernaculum-level pathogen establishment, the basic reproduction number R_0. Here, R_0 is the average number of secondary infections of hibernacula to arise from a single infectious hibernaculum, assuming the entire population of hibernacula within a single county is susceptible. When WNS enters a cluster (county) consisting of only susceptible hibernacula, the SIR model predicts that the intrinsic growth of the infection among groups of bats, each associated with a hibernaculum, will initially be exponential with rate λ. To calculate the basic reproduction number R_0, we used the equation $R_0 = 1 + \lambda/\gamma$ (Wearing et al. 2005). To estimate the intrinsic growth rate λ of WNS within a single county, we fitted a generalized linear model with Poisson-distributed errors and identity link function to the New York–Pennsylvania hibernaculum infection-history data set from 2005–2010 (see Appendix A for details on the procedure).

Macroscale model

Macroscale incidence data was aggregated to the county level. Maher et al. (2012) describe how the macroscale data, consisting of counties in the United States containing potential hibernacula, numbers of potential hibernacula within those counties, and county-scale infection histories, were compiled. Macroscale propagation of WNS over discrete yearly time steps was modeled using a county-level stochastic contagion process on a network. Network models provide a framework for accounting for the impact of underlying landscape structure on disease propagation. Counties of the United States containing potential hibernacula (Appendix A: Fig. A3) were represented as nodes on a landscape graph. Counties on the landscape network were connected by links representing the probability of dispersal of WNS between counties. Depending on the underlying landscape graph, propagation of WNS

between counties may lead to different spatial patterns. For example, county infections could exhibit little or no spatial structuring, i.e., county infections may not be aggregated in space and long-range transmission events are common. On the other hand, infected counties could be highly clustered, e.g., the WNS parasite spreads only to a county's nearest neighbors. A small-world network represents an intermediate case whereby propagation of the disease between counties is mainly local but with some long-distance dispersal events. Links between counties i and j were weighted according to a generalized gravity dispersal kernel that accounted for landscape spatial heterogeneities and climate (see Appendix A for full details). Maher et al. (2012) compared various dispersal functions, and they determined that a generalized gravity-dispersal model was the best fit to the county-scale infection history data up to 1 June 2011 (see footnote 6). This model accounts for the occurrence of short-range and long-distance WNS transmission events. We simultaneously fitted the coefficients of the dispersal function to county-scale infection history data acquired from U.S. Fish and Wildlife Service (see footnote 6) using maximum likelihood, following the procedure of Maher et al. (2012).

A county and its hibernacula were removed from the landscape network following epidemic burnout (the county elimination time was determined by the micro-scale SIR model with exponentially distributed extirpation time). Unification of the macro- and micro-spatial scales is described in Appendix A. The multi-scale SIR model has the same structure as the model described by Maher et al. (2012) prior to propagation of WNS between counties. The only difference in network properties between the two models is that caused by extirpation (see Appendix A for details). The links are weighted differently, but the same procedure is used to determine the weights in each case, so any difference is a result of the additional removed class. As time progresses, the SIR network structure changes as nodes are removed, but again, this is caused exclusively by extirpation. A side-by-side comparison of the code for the SI and SIR models clearly shows that they are identical except for the possibility of removal. R code for simulating the models is available in the Supplement.

Simulations of the multi-scale model

We performed 10 000 simulations of the multi-scale model in yearly time steps until the macroscale epidemic terminated (usually $<$100 years). Details of how the multi-scale simulations over the landscape network were performed are described in Appendix A. To summarize the extent of projected spatial spread and to ascertain which counties are at the greatest risk of infection, we generated heat maps indicating the fraction of simulations for which each county was infected. To compare spatial characteristics of county-level spread of the SIR multi-scale model to the model developed by Maher et al. (2012), we calculated macroscale incidence, prevalence, and maximum and median distances from the origin spread statistics. To clarify how important the unique initial (spatial) conditions were to these results, we assessed their sensitivity to different initial conditions (see Appendix C for details).

We used the multi-scale model to forecast the macroscale final size of the white-nose syndrome epidemic. Here, the macroscale final size of the epidemic is the total proportion of counties that are predicted to become infected over the course of the epidemic, whereas the epidemic final size within a single county, which can be calculated from the final-size relation (Keeling and Rohani 2008), is the total proportion of hibernacula that get infected. Theoretical predictions for the final size of an epidemic on large spatial scales are not well known, but see Ma and Earn (2006) for the general theory. To investigate the macroscale final epidemic size over a range of basic reproduction numbers, 1000 simulations of the multi-scale model were generated using $1/\gamma$ values ranging from 1/10 to 10 years. To calculate R_0 for each infectious period, we fixed the intrinsic growth rate λ at the value obtained from fitting the rate of change of infected hibernacula to the hibernaculum incidence data. We obtained the macroscale final-size epidemic predictions through counting the number of uninfected counties at the end of each simulation. To calculate the final epidemic size for a county, we solved the SIR final-size relation numerically (Keeling and Rohani 2008).

Decline of little brown bat populations

We used the multi-scale SIR model to test the hypothesis that multi-scale spatial structure will diminish the speed and extent of the reduction of the little brown bat population in the northeast (see Plate 1). To calculate the number of northeastern little brown bats at year t, we used the number of susceptible hibernacula per county as a surrogate for the population size of uninfected bats in each county, which was determined by the multi-scale SIR model. Further details on the calculation are given in Appendix A. We calculated the mean number of susceptible little brown bats and mean annual decline rate over the first five years using the simulations initialized with one infected county (Schoharie County). We then projected the population decline up to the winter of 2046/2047 using the simulations initialized with the cumulative number of infected counties on 1 June 2011. The mean population size and annual decline rate were calculated over all 119 counties in the northeast for each year t. To examine the implications of hibernacula remaining infectious indefinitely as a result of environmental contamination, we compared the mean population size and annual decline rate calculated from a multi-scale SI model (see Appendix A for details) to the SIR predictions.

Environmental contamination

Assuming that the hibernaculum extirpation time follows an exponential distribution implies that there is a high probability that the duration of the infection may be much shorter than the mean of three years (the infection duration is overdispersed around the mean if it follows an exponential distribution). However, it has been suggested that *P. destructans* can persist in hibernacula for long periods of time (i.e., over the summer or longer) even when bats are absent (Lorch et al. 2013). Thus, environmentally contaminated sites may continue to contribute to transmission of WNS. To account for this, we modified the hibernaculum-level SIR model to allow for a gamma-distributed infectious period. This model ensures that the probability of extirpation is more likely to increase over time, peaking about the mean of three years (Appendix A: Fig. A4), compared to the probability of extirpation predicted by an SIR model with exponentially distributed infectious period (Lloyd 2001). The infectious hibernaculum class is divided into different infectious compartments that each contribute to transmission (see Appendix A for model equations). The gamma-distributed hibernaculum-level model was then coupled to the county-level model. The spatiotemporal pattern predicted by this multi-scale model was compared to the spread pattern predicted by the exponentially distributed multi-scale model through performing 10 000 simulations and subsequently generating heat maps and calculating incidence, prevalence, and maximum and median distance statistics.

PLATE 1. Little brown bat (*Myotis lucifugus*) infected with white-nose syndrome. Photo credit: Alan Hicks (New York State Department of Environmental Conservation).

RESULTS

Local extinction events do not prevent large-scale spread of white-nose syndrome

Simulations of the multi-scale SIR model with exponentially distributed infectious periods predicted initial rapid expansion of the pathogen followed by local extirpations inhibiting macroscale spread, eventually leading to global fade-out of the disease (point estimates for the multi-scale model parameters used for the simulations are given in Appendix B: Table B1). However, fade-out almost never occurred before the pathogen reached the large majority of susceptible counties. Fig. 1 shows county-level probabilities of infection by 2021. The model predicts that WNS has a near-certain probability of reaching all the dominant cave-bearing formations, including the Rocky Mountains, by 2021. A similar spatiotemporal pattern of spread is predicted under the gamma-distributed extirpation time SIR multi-scale model for environmental contamination by WNS (Appendix B: Fig. B1). Continuing to simulate our model forward predicts that WNS will reach the Pacific seaboard with probability >0.8 in the absence of control measures. Our results show that widespread disease-induced mortality does not seem to eliminate spread on county-level scales, but microscale burnout may mitigate the risk of localized host extirpation in parts of the Southeast and Southwest, since counties in these regions are predicted to escape infection (Appendix B: Fig. B2). In Appendix C, Figs. C1–C3 and C5 indicate that regions that contain the dominant cave-bearing formations of the United States, potentially holding a large number of hibernacula (the northeast, and the Appalachian, Ozark, and Rocky Mountains) have a near-certain risk of extensive WNS infection, regardless of the introduction location of the pathogen. These regions are associated with favorable climatic attributes for the spread of WNS (Maher et al. 2012). Sensitivity analysis of the impact of the location of the epidemic epicenter on disease dynamics also suggests that regions isolated from the main cave-bearing formations exhibit a higher probability of stochastic fade-out and epidemics emanating from these regions take off more slowly (Appendix C: Figs. C4, C6, C7B, C7C, C8B, C8C, and C9). For example, infections initialized in Gadsden County, Florida, fail to take off due to the climate in this region, and the majority of counties close to Clackamas County, Oregon, and Pima County, Arizona, do not have a near-certain probability of infection (Figs. C2 and C3),

suggesting that underlying landscape features contribute to WNS infection risk. Therefore, our study lends support to the view that cave-dense regions form geographic corridors that appear to be facilitating rapid and extensive expansion of WNS.

Comparison of SIR macroscale epidemic dynamics with SI macroscale dynamics

The spatial configuration of the landscape along which the SIR epidemic propagates is dynamic in our model as a result of hibernaculum extirpations inducing county-level burnouts on the landscape graph, in contrast to the static network along which a SI epidemic spreads (Maher et al. 2012). To compare how macroscale SI and SIR epidemics evolve over long timescales, we compared long-term macroscale spread dynamics of the SI model of Maher et al. (2012) and the SIR multi-scale model with exponentially distributed infectious period developed in this study (Fig. 2). Both models predict rapid growth in incidence of infected counties with incidence peaking in 2013/2014 (Fig. 2a). Where they differ is in predictions of the epidemic tail. Under the SIR model, the prevalence of infected counties (the proportion of infected counties in the contiguous United States) will reach a maximum in the winter 2018/2019 and then will gradually decrease as a result of the number of county burnouts per year becoming greater than the yearly rate of new infections (Fig. 2b). In contrast, the SI model predicts that prevalence will grow at about the same rate initially before gradually slowing down until all counties are infected. Furthermore, the maximum distance from the epicenter is similar for both SI and SIR models until after 2035/2036, indicating that county-level burnout caused by hibernaculum extirpation events will not lead to significant deceleration of the spread of WNS. However, the SIR model predicts that maximum distance from the origin will plateau, reaching a peak in the winter of 2035/2036 before gradually declining (Fig. 2c). The median distance of infected counties from the origin is similar for SI and SIR models until the latter stages of the SIR epidemic, when the median distance from the origin starts to increase rapidly from 2035/2036 onward (Fig. 2d). The increase in the median distance is caused by large-scale burnout of infected counties that are closer to the epicenter from the landscape. Both the maximum and median distance statistics suggest that WNS will eventually spread to the Pacific seaboard, even with removal of counties from the landscape network through local extirpations (Fig. 2c, d and Appendix B: Fig. B2). Moreover, the spatiotemporal pattern of infection indicated by the spatial statistics in Fig. 2 is similar to the pattern predicted by those calculated from the multi-scale SIR model with gamma-distributed infectious period, which allows for environmentally contaminated sites to contribute to transmission (Appendix B: Fig. B3). Thus, the range of outcomes for the pattern of infection predicted by the three models is narrow. Taken together, the statistics in Fig. 2 and Appendix B: Fig. B3 suggest that the short-term macroscale propagation of WNS, assuming SIR dynamics, will be similar to an SI epidemic.

Final epidemic size

Simulations of the SIR multi-scale model with exponentially distributed extirpation time predict a mean macroscale final epidemic size of ~84%, assuming a hibernaculum extirpation time of three years (see Appendix A for detailed justification for this choice). To investigate the sensitivity of the macroscale mean epidemic size to hibernaculum extirpation time, we calculated macroscale and within-county mean final epidemic sizes over a realistic range of hibernaculum extirpation times. Not surprisingly, we found that the macroscale final size predicted by the model increases as the time to extirpation increases (Fig. 3a). For cave-level infectious periods greater than or equal to one year, disease-induced mortality will not lead to a significantly reduced macroscale final epidemic size, with ~72–93% of counties predicted to become infected, assuming hibernaculum extirpation times between 1 and 10 years (Fig. 3b). Finally, we note that in the northeast, the proportion of infected counties is predicted to be greater than ~90% for all infectious periods greater than one year (Fig. 3a), indicating that local extirpations will likely do little to mitigate spatial spread in this region.

Population declines of little brown bats in the northeastern United States

We also used the multi-scale SIR model with exponentially distributed extirpation time to estimate bat population declines and to determine the final size of the epidemic in little brown bats in the northeastern United States. Frick et al. (2010) predicted that by 2026 the regional little brown bat population in the northeastern United States (New York, Pennsylvania, Vermont, Massachusetts, and Connecticut) will be reduced to 0.01% of its pre-WNS level. However, the model they used to make this prediction did not incorporate spatial spread. We tested the hypothesis that the multi-scale spatial structure will diminish the speed and extent of the reduction of the little brown bat population as a result of mortality from WNS, relative to this prediction. Our analysis suggests that microscale epidemic burnouts are predicted to prevent the utter extinction of the regional population of little brown bats, but they will not inhibit that population from declining precipitously. Fig. 4a shows that the northeastern population will persist in the long term, declining asymptotically to ~8% of the original population size by the winter of 2032/2033. The mean annual decline rate will peak at a maximum of 17% in the winter of 2018/2019 before declining as a result of local extirpations (Fig. 4b).

Spores of *P. destructans* may have the potential to persist in the environment over long timescales (Lindner et al. 2011, Puechmaille et al. 2011, Lorch et al. 2013, Reynolds and Barton 2014) suggesting that

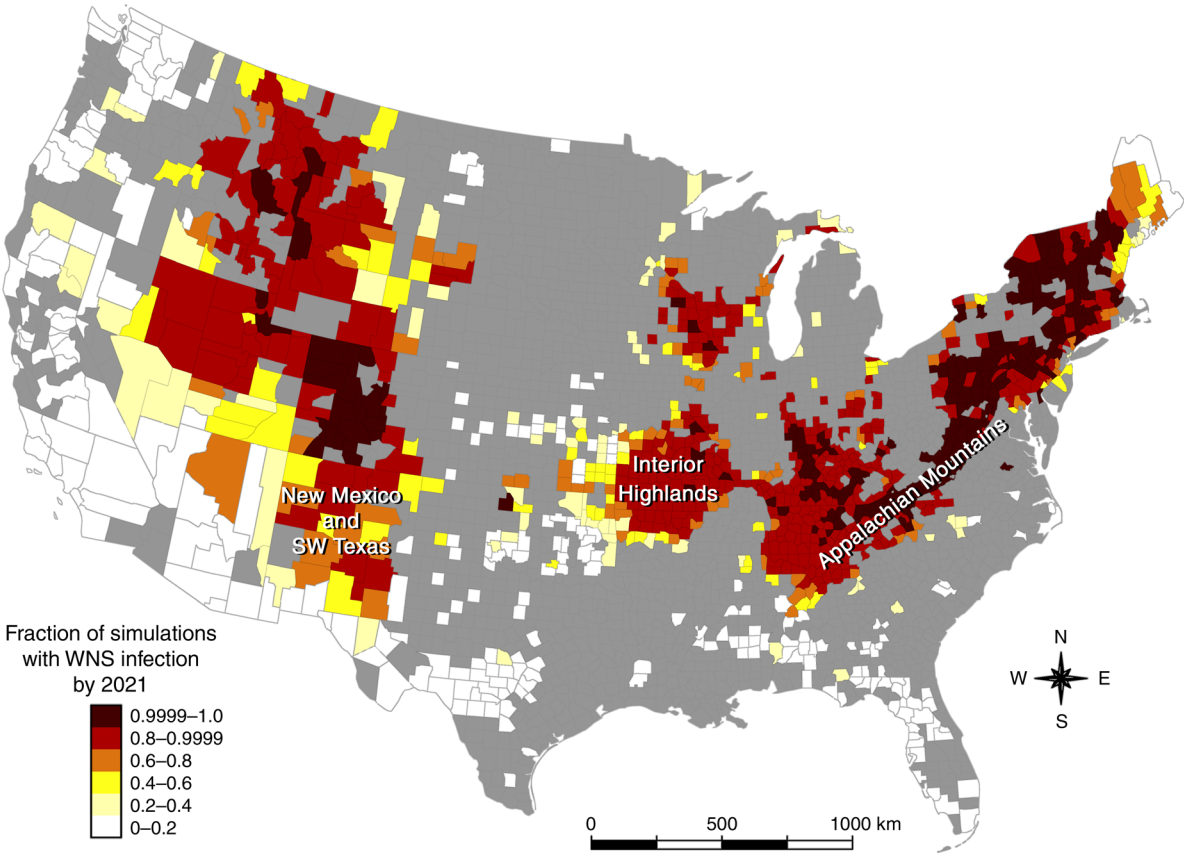

FIG. 1. The predicted spread of white-nose syndrome in the contiguous United States by year 2021, assuming an exponentially distributed hibernaculum extirpation time of three years. Counties are colored according to the fraction of simulations in which they were infected with white-nose syndrome (WNS) out of 10 000 simulations. Assuming a hibernaculum extirpation time of three years (see Appendix A), the dominant cave-bearing formations of the United States have a near-certain risk of WNS infection by 2021. Counties colored gray have no potential hibernacula and were excluded from the model. All simulations were initialized using the observed infected counties up to 1 June 2011 (see footnote 6).

hibernacula could possibly remain infectious even after all bats have died. This phenomenon would yield SI dynamics over long timescales, if, in the extreme case, hibernacula remain infectious indefinitely. In contrast, the SIR model with exponentially distributed extirpation time assumes that hibernacula remain infectious for an average of three years, during which they depopulate. To examine the implications of hibernacula remaining infectious indefinitely as a result of environmental contamination, we compared the projections of a multi-scale SI model to our SIR projections. Even assuming that hibernacula can remain infectious following extinction of bat populations, the SI model predicted that 0.01% of the original mean population size (650 bats), the threshold for population extinction set by Frick et al. (2010), will be reached in 2045/2046 (Fig. 4c). Although this prediction is more than double the time to extinction of 16 years predicted by Frick et al. (2010), it nonetheless presents a significant problem for bat conservation in North America.

DISCUSSION

The spread of infectious diseases at large spatial scales is ultimately constituted by local-scale processes, such as transmission and disease-induced mortality of hosts. A neglected problem in disease ecology is how local parasite-driven extirpation events mitigate host extinction risk on a patchy, heterogeneous landscape. We proposed that the connection between macro- and microscales can lead to qualitatively different macroscale patterns on heterogeneous landscapes: (1) if habitat networks are dense and pathogen dispersal occurs over sufficiently large distances, then large-scale spatial spread is expected to result, ensuing in host extirpation over broad regions, or (2) if habitat networks are sufficiently sparse and pathogen dispersal occurs only locally, then local extirpation events may result in habitat fragmentation so that extirpations exceed secondary infections, leading to eradication of the parasite. White-nose syndrome can drive bat populations within hibernacula to extinction, and the disease propagates over disparate spatial scales (Frick et al.

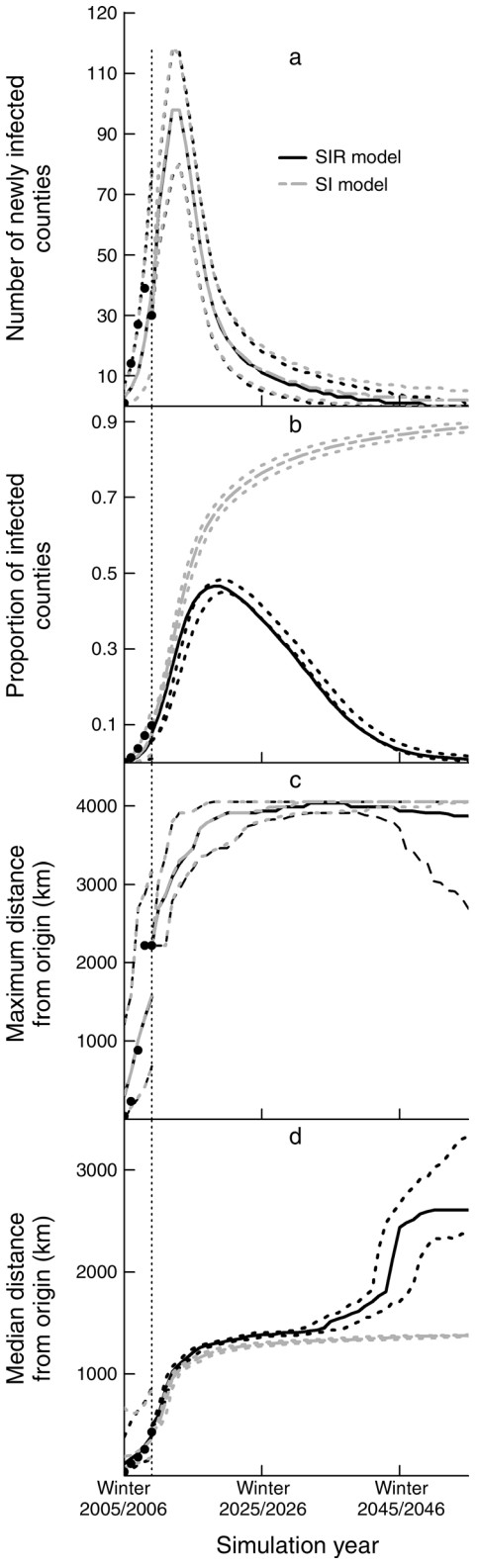

FIG. 2. Comparison of propagation of susceptible-infectious-removed (SIR) and susceptible-infectious (SI) epidemics through summary statistics. SIR multi-scale projections assume an exponentially distributed hibernaculum extirpation time of three years. The dotted vertical line divides simulated spread from Schoharie County, New York, from the winter of 2005/2006 to the 2010/2011 state and forecasts obtained by forward simulation from the 2010/2011 state. Solid lines are median values and dashed lines represent 95% prediction intervals. Predictions from the SIR (this paper) and SI (Maher et al. 2012) models are marked in black and gray respectively. Panel (a) shows the number of newly infected counties per year, with incidence peaks in the winter of 2013/2014; (b) the proportion of infected counties, with prevalence peaks in the winter of 2018/2019 before gradually subsiding; (c) the maximum distance from the origin (Schoharie County); maximum distance will not be attained until the winter of 2035/2036; (d) the median distance from Schoharie County; median distance increases from the winter of 2035/2036 onward, indicating that the infection prevalence will be concentrated farther from the origin.

2010, Langwig et al. 2012, Maher et al. 2012), making it a suitable study system to address these issues. How hibernaculum-level extirpations might contribute to WNS epidemic dynamics on large spatial scales has not previously been studied. More generally, we are the first to have tested the hypothesis that separation of spatial scales and disease-induced mortality within white-nose syndrome might slow or halt its macroscale spread. Methodologically, we showed how local population models (disease transmission models) may be summarized and upscaled to explain macroecological phenomena, such as final epidemic size. Our model predicts that eventual large-scale burnout of WNS will occur before the pathogen will reach all counties of the contiguous United States, but hibernaculum-level extirpations are unlikely to mitigate large-scale spread of WNS and subsequent decimation of little brown bat populations (Figs. 1 and 2a; Appendix B: Figs. B1 and B2). Epidemic burnouts at the hibernaculum level do not lead to habitat fragmentation at larger spatial scales and are unlikely to lead to sudden collapse of the epidemic.

Our model indicates that spread of white-nose syndrome will continue to be rapid and spatially synchronous. Spatially synchronous spread is associated with infections that have high transmission potential such as measles, influenza, and rabies (Grenfell and Harwood 1997, Grenfell et al. 2001, Viboud et al. 2006, Hampson et al. 2007). Individual bat species may have specific home ranges that connect hibernacula, but WNS connectivity is unknown. We therefore assume a fully connected network with weights determined by data such that many links have a negligibly small probability of transmission. The strong transmission links between counties and the small-world nature of the landscape network, where coupling between counties is mainly short-range with some strong long-range flows, facilitates a large and spatially synchronous epidemic. The dominant cave-bearing formations of the Appalachian and Ozark Mountains form a strongly linked component of the landscape graph, through which the infection

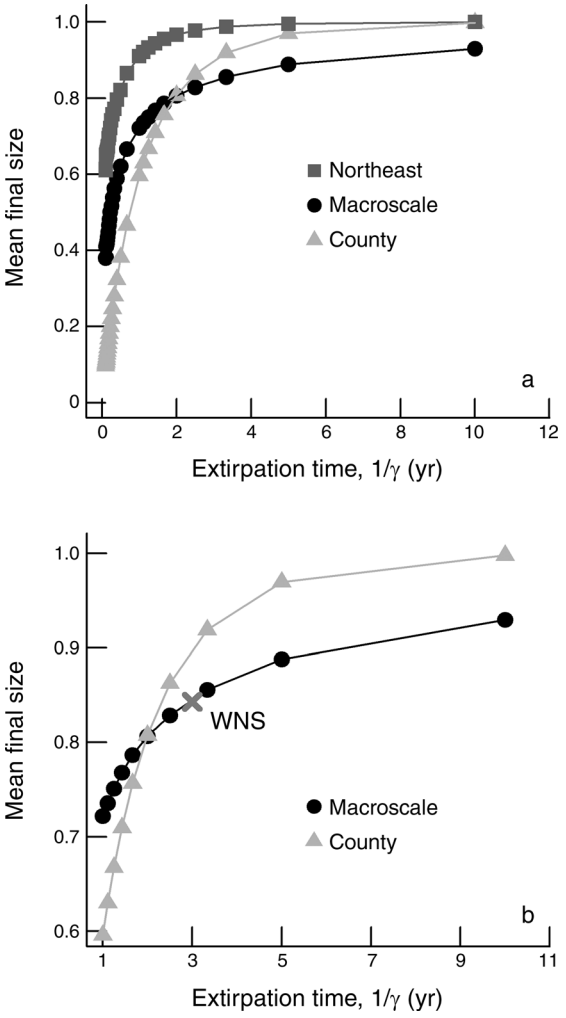

FIG. 3. Mean epidemic final size predictions for different spatial scales. Panel (a) shows mean final sizes calculated for exponentially distributed hibernaculum extirpation times between 1/10 years and 10 years. Mean final size is the number of counties removed due to hibernaculum extirpation events expressed as a fraction of the number of counties with caves in the contiguous United States (macroscale, black circles) and the northeastern United States (northeast, dark gray squares) respectively. These calculations are compared with SIR final size predictions assuming a closed hibernaculum population within a single county (gray triangles). Note that the predictions for the northeast do not upscale. The northeast mean final size is >60% for all extirpation times, due to the features of the landscape surrounding Schoharie county. Panel (b) shows macroscale mean final size predictions range between ~72–93% for exponentially distributed extirpation times between 1 and 10 years. A cross indicates the macroscale final epidemic size for WNS with a 3-year infectious period.

is predicted to disseminate rapidly. Our prediction of rapid and spatially synchronous spread appears to be confirmed in the winter of 2012/2013, where 67 counties were newly infected compared with the median predicted 82 counties (95% prediction interval: 64–101), and as of 25 July 2014, 54 counties have been newly infected in the winter of 2013/2014, compared with a median prediction of 98 counties (95% prediction interval: 76–118). Our integrated modeling framework suggests that extirpation events cannot overcome this strong coupling, even allowing for a range of hibernaculum extirpation periods (Fig. 3), because sequential elimination of nodes from the landscape graph according to the timing of infection does not lead to collapse of WNS transmission along the strongly linked component. Additionally, our

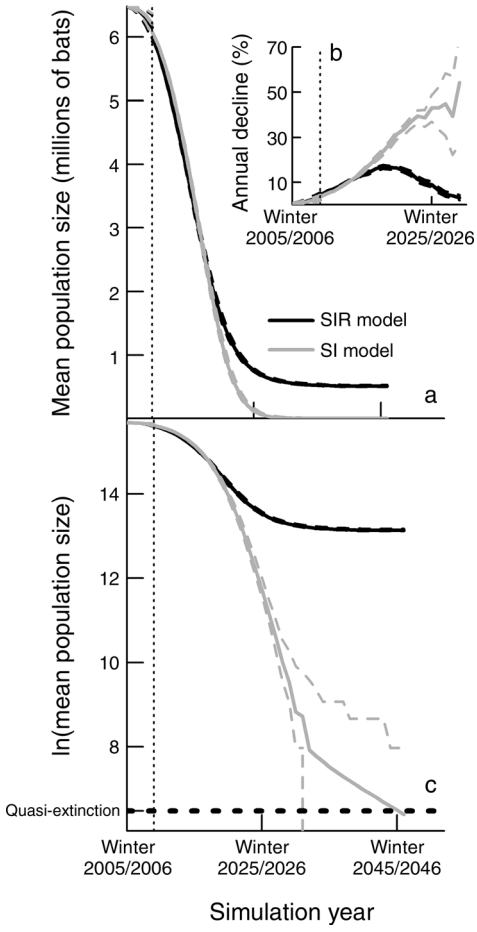

FIG. 4. Predictions for the little brown bat (*Myotis lucifugus*) population in the northeastern United States. The dotted vertical line divides the simulated spread from Schoharie County, New York, from the winter of 2005/2006 to the 2010/2011 state and forecasts obtained by forward simulation from the 2010/2011 state. Predictions from the SIR (this paper) and Maher et al. (2012) models are marked in black and gray respectively, with solid lines indicating mean values and dashed lines representing 95% prediction intervals. Panel (a) shows mean population size under SIR dynamics with exponentially distributed hibernaculum extirpation time will persist at ~8% of the pre-WNS population. Panel (b) shows annual mean decline peaks in the winter of 2018/2019. Panel (c) shows the log-transform of the decline in little brown bat numbers. Assuming SI dynamics at both the hibernaculum and county scale, extinction is predicted by 2045/2046. The thick dashed line marks the quasi-extinction threshold of 0.01% of the estimated pre-WNS population (6.5 million bats).

work suggests how the structure of the habitat network contributes to the spatial synchronization, because the structure is small-world-like and infections can spread faster on small-world networks (Watts and Strogatz 1998).

County heterogeneities and the temperature gradient are key to persistence of WNS over long timescales. Comparing SIR dynamics to SI dynamics showed that disease-induced mortality will neither lower, nor delay, the peak in median incidence of infected counties. This is not surprising because SIR epidemics initially resemble SI epidemics. What is more surprising, however, is the prediction that the median macroscale prevalence of the infection remains elevated over a long timescale (Fig. 2b; Appendix B: B3b). The results of our sensitivity analysis revealed that the prediction of enduring prevalence results from county-level heterogeneities in expected epidemic duration. Cave numbers within counties, a surrogate for the size of the total bat population (which is unknown), ranged from a single potential hibernaculum to ~1500 sites. Therefore, county-level epidemic durations are predicted to vary considerably, with counties containing large numbers of potential hibernacula, thereby possessing potentially large bat populations, having the longest epidemics. Moreover, the distribution of the number of potential hibernacula per county had a long tail, with ~22% of counties having the potential to remain infectious on the landscape graph for greater than 20 years (the estimated median epidemic duration for a county is 10 years). Once infected, the multi-scale models predict that these counties will remain infected over a long timescale, thereby contributing to the slow decline in infection prevalence. If the distribution of bats among counties was homogeneous, infection prevalence would drop much more rapidly (Appendix C: Fig. C7D). Therefore, our findings suggest that regions with high cave density contribute most to macroscale prevalence, potentially explaining why hibernaculum-level extirpation events may not greatly inhibit macroscale spread. Additionally, the temperature gradient is predicted to constrain disease spread (Maher et al. 2012), but counties with long winters are predicted to continue to contribute to macroscale incidence and prevalence over long timescales, resulting in a large spatially synchronized epidemic.

When a highly infectious disease emerges, decision makers may be interested in obtaining a prediction of the expected magnitude of the epidemic (Bailey 1953, Ludwig 1975, Anderson and May 1992, House et al. 2013). Our model predicts a mean final epidemic size of 84%, assuming an exponentially distributed hibernaculum extirpation time of three years. For hibernaculum extirpation times between 1 and 10 years, simulations of the multi-scale SIR model predict that between 72–93% of counties will become infected during the WNS epidemic. Such high predicted final epidemic sizes suggest that policy makers cannot rely on disease-induced mortality (or any other mechanism that could substantially reduce the presence of WNS, such as culling or the application of a biocontrol agent) to substantially alleviate the macroscale final size.

Elucidating useful predictors of the eventual epidemic size on heterogeneous spatial networks remains a key problem in spatial epidemiology (Tildesley and Keeling 2009). The final-size relation defines a clear relationship between hibernaculum extirpation time and the final epidemic size within a county with a large number of hibernacula. We found that the final-size prediction for a single county calculated using the SIR model with an exponentially distributed infectious period is not a useful predictor of the final size of the macroscale epidemic (Fig. 3). This is not surprising, as the final-size prediction appears to only apply to a select few special cases (Ma and Earn 2006). Sensitivity analysis showed that landscape features, such as climate and regional cave density, contribute to epidemic impact at the macroscale (Appendix C: Figs. C1–C6), suggesting that the disparity in final-size predictions is due to landscape features that impact macroscale spatial spread. Indeed, many factors will contribute to the final size of an epidemic on a heterogeneous spatial network (May and Lloyd 2001).

Our results suggest that microscale epidemic burnout may mitigate the risk of regional population extinction of little brown bats in the northeastern United States, but they will not inhibit that population from declining precipitously. Only very slightly different than the prediction made by Frick et al. (2010), our model suggests that the northeastern population will persist in the long term, only at a greatly reduced size. Frick et al. (2010) used a projection matrix model parameterized using hibernaculum infection history to estimate the yearly number of infected hibernacula, a proxy for prevalence of WNS. They estimated the little brown bat population to be ~6.5 million before the introduction of WNS. However, their model did not account for geographic complexity and spatial spread because they did not distribute these animals into different landscape patches before simulating the bat decline. Instead, bats were assumed to occupy the northeastern region as a single population that could be divided into susceptible and infectious subclasses. In other words, Frick et al. (2010) implicitly assumed all 119 counties in the region were infected with WNS, which was not the case by 2010 (see footnote 6). In contrast, our modeling approach incorporates macroscale stochastic spread, as well as landscape heterogeneities, into the northeastern population projection. Our approach yields a lower bound of 8% of the pre-WNS population that are expected to persist in the region. The northeastern population may avoid extinction, but the serious decline of a once common species is a grave cause for concern and will likely contribute to the loss of ecosystem services in the northeastern United States (Boyles et al. 2011).

The spatial scale of WNS dispersal is poorly understood. Little is known about how much and how far hibernating bats may move during the winter, but they are known to move several hundred kilometers from summer ranges to hibernacula (Kurta and Murray 2002, Norquay et al. 2013) and may also move considerable distances between fall swarming caves (where some infection may occur) and their eventual hibernation sites (Schowalter 1980). Individual bat species may have a maximum range, but given that there are multiple bat hosts and that WNS can potentially be spread by other mechanisms, for example, translocation by humans (Lindner et al. 2011), we do not assume a particular dispersal scale a priori, but rather seek to fit the spatial scale to the observed data. The interactions among different spatial scales in population expansion is a key problem in many areas of ecology (Vellend et al. 2006) and epidemiology (Grenfell et al. 2001) and warrants further consideration in the management of white-nose syndrome.

Our model does not explicitly consider the effects of bat community composition within hibernacula on macroscale dynamics. For example, following introduction of WNS to a hibernaculum, the majority of the bat population may consist of host species that are more resistant to WNS (Turner et al. 2011, Langwig et al. 2012). Assemblages within hibernacula consisting of mostly resistant species may slow down spread of the infection at larger spatial scales. On the other hand, resistant hosts are mobile and may contribute to transmission of WNS, but it is unknown if, or how much, resistant species contribute to forward transmission. Additionally, on large spatial scales, there are differences in bat species composition across North America and particularly between the East and the West; however, of the species most often reported with WNS symptoms, two of them (*Myotis lucifugus* and *Eptesicus fuscus*) are found throughout the USA, and two more species (*Myotis septentrionalis* and *Perimyotis subflavus*) are found throughout the eastern half. These are not only spatially widespread species, but they are also among the most abundant cave-roosting bats within their ranges (Barbour and Davis 1979). Moreover, Maher et al. (2012) showed that the incorporation of bat-species richness to the WNS dispersal kernel did not improve the fit of their macroscale SI model to the county incidence data. The multi-scale SIR model is an extension of the SI model with an additional removed class, and thus refitting the model with species richness included will not yield further improvement. Our framework accounts for the multi-host nature of *P. destructans* by fitting parameters of the models to infection histories over two spatial scales, thereby implicitly integrating over species.

Our model does not allow for metapopulation rescue effects. In metapopulations, rescue effects occur when the movement of colonizers from abundant source populations reestablishes depopulated sites, leading to persistence of the metapopulation as a whole (Brown and Kodric-Brown 1977, Grenfell and Harwood 1997). There is evidence that bat populations can locally stabilize at reduced numbers even after WNS has been detected (Langwig et al. 2012), which could potentially allow for a slow regional build-up of susceptibles (bat reproductive output is low at $\sim$1 pup per year for the majority of species). Colonization of extirpated sites by susceptible hosts might eventually lead to new infections, either through contact with a local environmental reservoir or through contact with infectious colonizers. Recurring epidemics would promote persistence of the pathogen over larger spatial and temporal scales. While the multi-scale SIR model is a coarse spatial description of the system, by assuming that local extirpation events occur, we can ask if these have the potential to slow down, or halt, spread, whereas using a model that allows for rescue effects does not enable us to answer this question. Even assuming SIR epidemiology without any rescue effects, *P. destructans* is predicted to persist over long timescales (cf. Fig. 2b and Appendix B: Fig. B3b). Using the SIR framework allows us to test the hypothesis that separation of spatial scales and disease-induced mortality may slow or halt spread and to test the hypothesis that local extirpations can break down the spatial coupling and persistence of the pathogen.

Our multi-scale SIR modeling framework, while an idealization of WNS spread, appears to be representative of spread at the county scale in the contiguous United States. Some aspects neglected by our model include regional stochasticity and the potential for bat recovery and resistance (see Appendix D for full discussion of these points). We realize that SIR epidemiology is only one of a spectrum of possibilities for macroscale spread of WNS; immunity, resistance, environmental reservoirs, and rescue effects may all promote long-term persistence of the disease. Recently, Lorch et al. (2013) showed that *P. destructans* has the potential to persist over the summer in hibernacula and potentially for one to two years. Thus, a hibernaculum could continue to contribute to transmission for a long time period following depopulation by hibernating bats. The multi-scale SIR model with gamma-distributed extirpation time, which is an intermediate case between the extremes of SIR and SI epidemiology, implicitly takes into account the existence of potential environmental reservoirs for WNS that contain viable spores for a finite period of time. Alternatively, WNS spread may follow SI dynamics if sites remain contaminated indefinitely, which Maher et al. (2012) have already considered. The short-term propagation dynamics of the two SIR models resemble those predicted by the SI model (Fig. 2 and Appendix B: Fig. B3), which represents an extreme scenario of indefinite environmental transmission. Additionally, the long-term predictions for the emergent spatiotemporal infection pattern on large spatial scales that arise

from the models fall within a narrow range (Fig. 1 and Appendix B: Figs. B1–B3). Moreover, through considering hibernaculum infectious periods that vary between 1 and 10 years, we show that the range of predictions for the final size of the WNS epidemic is narrow and our prediction of ~84% of counties becoming infected may be viewed as a lower bound for the epidemic final size. All of the models predict a large final size for the epidemic, due to the habitat network structure, which is an important finding for management.

In conclusion, our analysis indicates that disease-associated mortality within counties will not inhibit large-scale spread of white-nose syndrome at the county level and that, at a minimum, over 80% of counties of the contiguous United States are likely to become infected before the current epidemic is over. It follows that serious declines in bat populations are likely, particularly in cave-dense regions that constitute the main geographic corridors of the United States. Moreover, we have shown that the geometry of habitat connectivity is such that host refuges are exceedingly rare, which is a serious concern for bat conservation. Such predictions are alarming and underscore the need for adequate control strategies for this emerging infectious disease. Our analysis suggests that mitigation measures will need to be urgently applied ahead of the invasion front to combat the threat of WNS to bat populations.

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Supplemental Material

Ecological Archives

Appendices A–D and the Supplement are available online: http://dx.doi.org/10.1890/14-0417.1.sm