

Spatial scale modulates the strength of ecological processes driving disease distributions

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Humans are altering the distribution of species by changing the climate and disrupting biotic interactions and dispersal. A fundamental hypothesis in spatial ecology suggests that these effects are scale dependent; biotic interactions should shape distributions at local scales, whereas climate should dominate at regional scales. If so, common single-scale analyses might misestimate the impacts of anthropogenic modifications on biodiversity and the environment. However, large-scale datasets necessary to test these hypotheses have not been available until recently. Here we conduct a cross-continental, cross-scale (almost five orders of magnitude) analysis of the influence of biotic and abiotic processes and human population density on the distribution of three emerging pathogens: the amphibian chytrid fungus implicated in worldwide amphibian declines and West Nile virus and the bacterium that causes Lyme disease (*Borrelia burgdorferi*), which are responsible for ongoing human health crises. In all three systems, we show that biotic factors were significant predictors of pathogen distributions in multiple regression models only at local scales ($\sim 10^2$ – 10^3 km²), whereas climate and human population density always were significant only at relatively larger, regional scales (usually $> 10^4$ km²). Spatial autocorrelation analyses revealed that biotic factors were more variable at smaller scales, whereas climatic factors were more variable at larger scales, as is consistent with the prediction that factors should be important at the scales at which they vary the most. Finally, no single scale could detect the importance of all three categories of processes. These results highlight that common single-scale analyses can misrepresent the true impact of anthropogenic modifications on biodiversity and the environment.

ecology | dilution effect | chytridiomycosis | West Nile virus | Lyme disease

Humans presently are contributing to unprecedented rates of infectious disease emergence (1, 2), climate change (3, 4), and biodiversity loss and homogenization (5, 6). The ramifications and interdependences of these environmental changes represent some of the most important and challenging scientific problems of today. However, a fundamental but undertested hypothesis in ecology—that the influence of biotic and abiotic drivers on species distributions is scale dependent (7–10)—poses a serious challenge to addressing these daunting problems.

It has long been understood that three processes generally dictate the distribution of all organisms: environmental filtering (abiotic conditions), species interactions (biotic conditions), and dispersal limitations (11). Because climate mostly varies regionally ($< 10^4$ km² according to the Intergovernmental Panel on Climate Change) with relatively minor variation at smaller, local scales (12), it has been widely hypothesized that environmental filters operate mostly at larger, regional scales ($> 10^4$ km²) (Fig. 1) (7–10, 12). In contrast, because there can be considerable variation in species composition locally, biotic processes, such as competition, predation, mutualism, and parasitism, are thought to influence distributional patterns primarily at smaller scales (Fig. 1) (7–10). A result of these hypotheses is that the outcomes of single-scale analyses might misrepresent the true consequences of natural and human-

induced changes to the environment. For example, analyses across geographic areas of different sizes can produce differently shaped elevation–richness curves (10), give contrasting richness–productivity relationships (13), alter the perceived importance of competition and predation on biodiversity (11), and change the factors found to influence community assembly (14).

Although there have been many calls to test these scale-based hypotheses (1, 7–10, 15, 16), there are several reasons why they have not been tested at a broad spectrum of scales (but see ref. 17). First, it can be logistically difficult to repeat experiments at multiple scales, and it often is challenging to determine which scales are most important for a given system (7, 10, 18). Most importantly, however, only recently have the necessary computing power and large-scale, spatially explicit datasets of species occurrence and abiotic factors become available. Therefore, although we have contemporary tests of theory for how deterministic and stochastic processes associated with environmental filtering, biotic processes, and dispersal affect species distributions on relatively small spatial scales (e.g., ~ 100 km²) (10, 13, 17), the lack of tests showing how these factors influence distributions when scaled up to larger (regional to global) areas can be an impediment for identifying generalities in ecology. For example, it has been suggested that controversy surrounding the hypotheses that infectious diseases are being increased by anthropogenic climate change and biodiversity loss (i.e., the dilution effect) is at least partly a product of the scale dependence of these abiotic and biotic factors on disease risk (1, 15, 16).

Here, we use species distribution models and multimodel inference approaches to examine the influences of biotic and abiotic processes and human population density (which can have impacts

Significance

For four decades, ecologists have hypothesized that biotic interactions predominantly control species' distributions at local scales, whereas abiotic factors operate more at regional scales. Here, we demonstrate that the drivers of three emerging diseases (amphibian chytridiomycosis, West Nile virus, and Lyme disease) in the United States support the predictions of this fundamental hypothesis. Humans are contributing to biodiversity loss, changes in dispersal patterns, and global climate change at an unprecedented rate. Our results highlight that common single-scale analyses can misestimate the impact that humans are having on biodiversity, disease, and the environment.

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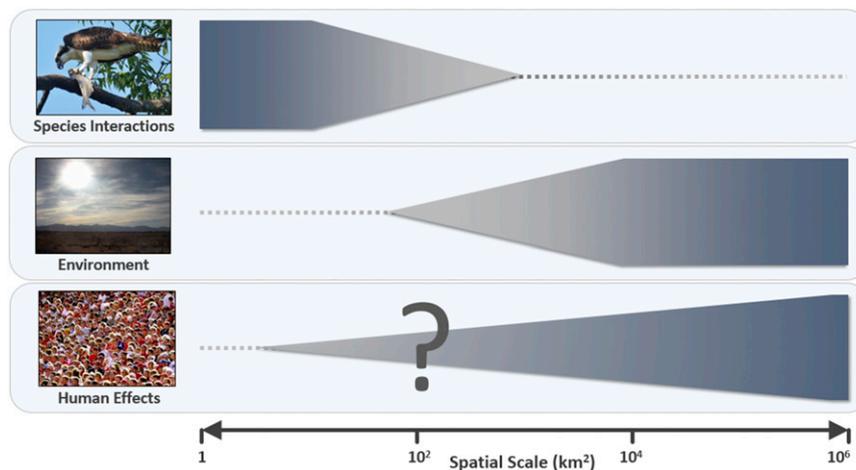


Fig. 1. How does spatial scale affect processes in ecology? Three processes are typically found to control the distribution of organisms: biotic interactions, environmental filtering, and dispersal. However, the extent to which each of these processes is relevant is expected to vary with spatial scale. The thickness of the blue bars represents the hypothesized importance of each process at different scales (horizontal axis). Biotic interactions are hypothesized to be important at local scales, and climate and dispersal are expected to be relevant at larger, regional scales. The question mark denotes that there are no established hypotheses regarding how scale affects the detection of human population density on distribution patterns. (Adapted from ref. 9.)

on dispersal) on the distributions of three emerging pathogens across seven spatial scales (quadrupling in area at each step; Fig. S1) spanning nearly five orders of magnitude. Two of these pathogens, West Nile virus (WNV) and *Borrelia burgdorferi*, the bacterium that causes Lyme disease, are responsible for ongoing human health crises (19, 20). The third pathogen, the chytrid fungus *Batrachochytrium dendrobatidis* (*Bd*), is considered one of the deadliest organisms on the planet because of its association with hundreds of amphibian extinctions in the last half century (21, 22). We chose to model the spatial factors affecting these pathogens because (i) spatially explicit datasets of their distributions were available (but were not available for other pathogens or other organisms in general; see *Methods*); (ii) they span a diversity of taxa (a virus, bacterium, and fungus) and transmission modes (WNV and Lyme are mosquito- and tick-borne, respectively, and *Bd* is a directly transmitted, water-borne pathogen), and infect various types of hosts (endothermic and ectothermic), increasing the generality of our findings; (iii) they are widespread generalists throughout the United States, providing a spatial extent great enough to conduct large-scale analyses; (iv) their abundances or prevalences appear to be partially controlled by a common biotic factor, the richness of potential hosts (19, 21, 23, 24), and by common abiotic factors, including climate and vegetation (20, 25, 26); and, finally, (v) understanding emerging diseases is of critical importance to biodiversity conservation and human health. Our goal was not to develop and put forth the best possible model to explain the spread of these diseases but rather to test whether spatial scale influences which types of ecological processes are important.

Because the abundance of all three pathogens has been shown previously to be affected by a common biotic factor, the richness of potential hosts (defined as the richness of all species that receive either successful or failed transmission attempts from a generalist pathogen or vector) (19, 21, 23, 24), we chose to use this factor in our models to represent the subset of biotic interactions that drive the processes causing dilution or amplification effects (5). We used total amphibian richness to predict the spread of *Bd*, avian richness for WNV, and mammalian richness for Lyme disease (we also initially tested the richness of other taxa for *B. burgdorferi*; see *Methods*). Additionally, for WNV we also tested models that included mosquito richness given that many mosquitoes can vector this virus (*Supporting Information*). In contrast, Lyme disease in the eastern United States is known to be vectored by only a single tick species, *Ixodes scapularis*,

found in every county where thorough sampling has been performed (*Supporting Information*). Thus, we did not include vector richness, prevalence, or abundance in our Lyme disease models. Importantly, because humans generally cannot be infected with WNV or *B. burgdorferi* unless they are bitten by an appropriate vector, modeling the distribution of these pathogens in humans implicitly integrates the effects of ecological processes on the pathogen as well as the vector. For our biotic factors, we hypothesized that potential host species richness would have the highest relative importance at local scales, inhibiting or promoting pathogen prevalence because of dilution and amplification effects (a negative or positive association between host richness and infections per host, respectively) (19). In contrast, we predicted that abiotic factors (climatic variables, altitude, and the normalized vegetation index; Table S1) would have the highest relative importance at regional scales.

Although biotic and abiotic variables have traditionally been the central focus of species-distribution models (11, 27), much attention recently has turned toward modeling the importance of human impacts on species distributions. Human activities can alter the dispersal of organisms (even for species not expanding their ranges; see *Supporting Information*) (25) both by facilitating long-distance movements of nonnative species (28) and emerging pathogens (25, 29) and by impeding spread by reducing habitat connectivity through habitat destruction and the construction of roads, canals, and buildings (30). Indeed, the distributions of all three pathogens have been reported to be affected by humans (20, 25, 29). Thus, we used human population density to represent the ways in which humans can affect pathogen transmission (e.g., through dispersal). We hypothesized that human impacts might be most important at regional scales because humans can homogenize biodiversity across large spatial scales.

Results and Discussion

For all three parasites, host richness was a statistically significant predictor of prevalence at local scales when controlling for the other factors in the model, and its relative importance declined as spatial scale increased (Fig. 2 and *Bd* in Table 1 and WNV and Lyme disease in Table S2). Hence, as hypothesized by several researchers (15, 16), the slope between host richness and prevalence became shallower as scale increased, suggesting that the controversy surrounding the relationship between host diversity and parasite abundance (i.e., the dilution effect) might partly be a product of the

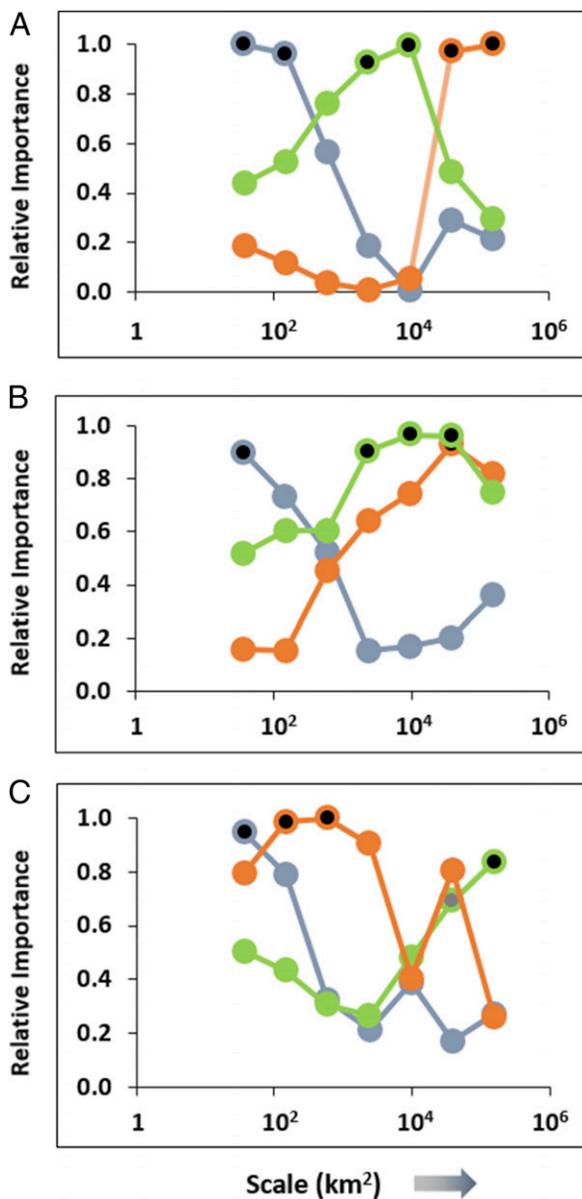


Fig. 2. Different processes control species distribution at different scales. Predictors for *Bd* (A), WNV (B), and Lyme disease (C) varied in their relative importance scores depending on the spatial scale of analysis (roughly 37–150,000 km²; horizontal axes). Blue lines represent host richness (a biotic process), green lines are abiotic factors (importance scores for abiotic factors that were statistically significant at any scale were averaged), and orange lines are human population density, a proxy for anthropogenic influences on organisms (e.g., effects on dispersal). Points with black circles indicate significance ($P < 0.05$) of a process at a given scale; gray points indicate significance for some but not all abiotic factors.

variation in the scales at which studies have been conducted (15, 16). In the multivariate WNV models, mosquito richness was not predictive of WNV distribution at any scale (Table S3), suggesting that the richness of hosts is more important than the richness of vectors in regulating WNV transmission.

Different abiotic factors were important for different host–parasite systems (see *Bd* in Table 1 and WNV and Lyme disease in Table S2). Nevertheless, for all three parasites and when controlling for the other factors in the model, abiotic factors were statistically significant and of high relative importance only at scales larger than those at which biotic factors were important.

Finally, human population density was significantly (negatively) related to all three parasites at scales much larger than the scales at which host richness was important (Table 1 and Table S2)—this generally was at regional spatial scales ($\sim 10^4$ – 10^5 km²) but at intermediate to regional scales ($\sim 10^3$ – 10^4 km²) for Lyme disease. This result was not surprising, because *Bd* and WNV are found throughout the United States, whereas Lyme disease is, for the most part, restricted to a comparatively narrower geographic range because of habitat requirements (26), limiting the influence of humans to smaller scales (31). When significant, different abiotic factors were generally important at the same scales as one another (Supporting Information).

Importantly, several supplemental analyses support the robustness of our results. First, single regions of the country did not tend to influence the results of our *Bd* models heavily (Fig. 3), although we did see some variation in space for WNV and Lyme models (Fig. S2), possibly because of extreme predictor values in specific areas (Supporting Information). Second, null model randomization tests (Supporting Information and ref. 18) confirmed that our results were not a statistical artifact of the structure of the predictor data (Fig. S3). Moreover, our findings were consistent across a bacterium, virus, and fungus, invasive (WNV and *Bd*) and native species, pathogens that infect endothermic and ectothermic hosts, and pathogens that are and are not transmitted by vectors. Despite the robustness of these results, they should not be taken to suggest that abiotic factors or richness cannot predict species distributions at local or regional scales, respectively; rather, they only show that at these scales these factors are generally less important than the other factors considered.

We conducted several additional analyses to provide insights into the statistical and ecological mechanisms for our findings. Univariate models revealed that biotic factors were significant only at local scales, climate was generally scale independent, and human population density was significant only at regional scales,

Table 1. Results of multimodel inference analyses predicting the prevalence of *Bd*

Scale/predictor	Estimate	SE	<i>P</i> value
0.0625 degree			
Intercept	0.599	0.025	<0.001
Richness	−0.164	0.028	<0.001
Factor one	−0.011	0.020	0.575
Factor two	−0.021	0.029	0.470
Factor three	0.019	0.025	0.450
Population	0.002	0.010	0.782
0.5 degree			
Intercept	0.060	0.026	<0.001
Richness	−0.021	0.049	0.646
Factor one	−0.083	0.031	0.008
Factor two	−0.095	0.033	0.004
Factor three	0.070	0.033	0.035
Population	0.002	0.002	0.993
4 degrees			
Intercept	0.587	0.021	<0.001
Richness	−0.002	0.015	0.928
Factor one	−0.005	0.015	0.720
Factor two	−0.006	0.017	0.739
Factor three	0.013	0.028	0.646
Population	−0.177	0.034	<0.001

Models used host richness, three abiotic factors, and human population density as predictors in the analysis. The scales shown are the smallest, intermediate, and largest scales used. See the legend of Table S1 for interpretation of the factors and Table S2 for results for WNV and *Borrelia burgdorferi*. Statistically significant ($P < 0.05$) predictors are in bold.

Spatial scale

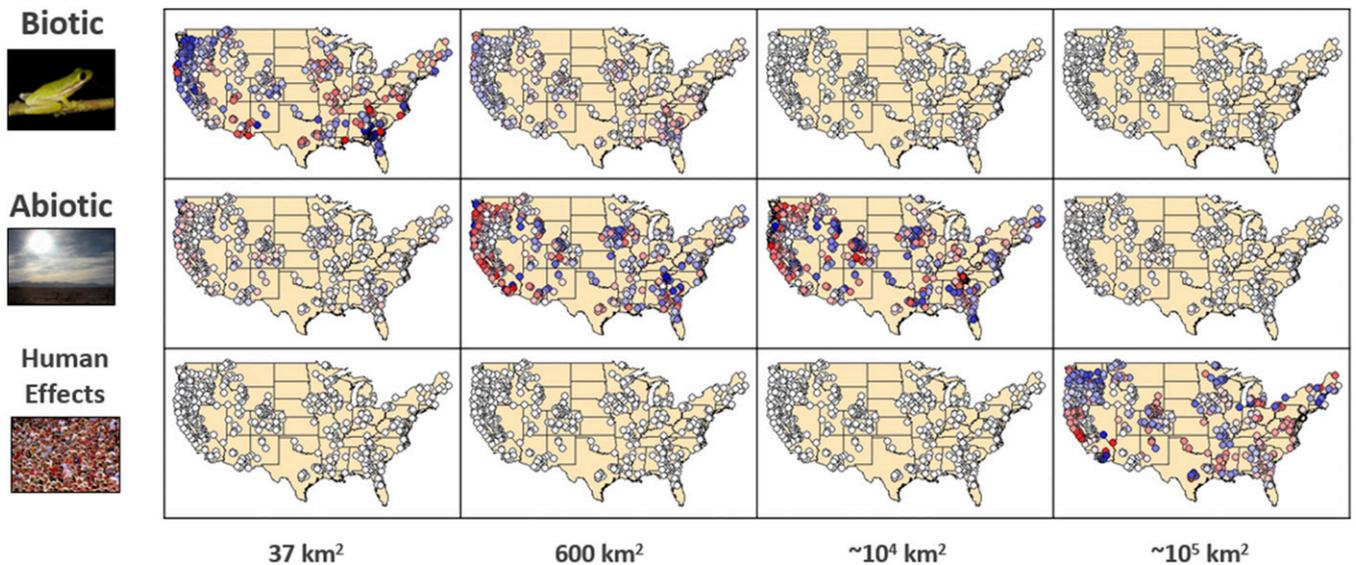


Fig. 3. Generality of scale-dependent processes in space. The maps indicate the contribution of each of three processes as predictors of *Bd* distribution in models. Points represent physical locations with *Bd* prevalence data and are colored based on the magnitude of the change in their residual after the given process was added to a model predicting *Bd* distribution. Blue, white, and red points indicate the process decreased, had no effect, or increased the magnitude of the residuals, respectively. Maps with many colored points indicate that a given process was highly important at a given scale; maps with mostly white points signify that it was unimportant. See Fig. S2 for equivalent maps for WNV and Lyme disease.

providing a statistical explanation for the pattern observed in relative importance scores (*Supporting Information* and Fig. S4). Correlograms of spatial autocorrelation revealed that biotic factors varied most at local scales, whereas climatic factors varied more at regional scales (*Supporting Information* and Fig. S5). These results support the traditionally hypothesized ecological mechanism for scale-dependent variation in the importance of biotic and abiotic variables: Factors should be most important at the scales at which they vary the most, because it will be difficult to find a statistically significant correlation when independent variables have low variance (8).

Intermediate scales are commonly used in an attempt to minimize scale effects by accounting for both ends of the scale spectrum (8, 18), with the assumption that significant processes at either small or large scales will also be detectable along the spectrum. However, in our analyses, host species richness was never significant at the same scale as abiotic factors or human population density. Therefore, our results add to existing evidence (discussed in ref. 18) that rarely is there a single scale at which all three processes are important. Rather, our results support domains or sections of the scale spectrum at which processes operate stably (independent of scale), separated by abrupt transitional regions in which variables rapidly gain or lose importance. For instance, for all three parasites, host richness was relatively important below 150 km², declined abruptly in importance thereafter, and remained unimportant at all higher spatial scales (Fig. 2). Identifying domains could improve predictions and management at untested scales and simplify the selection of scales for future analyses (8).

One of the most important challenges in ecology is to determine what dictates the abundance and distribution of species. Here we show that biotic factors vary most and seem to drive distributional patterns at more local scales, whereas abiotic factors vary most and seem to drive patterns at regional scales, providing support for a long-held but undertested hypothesis in spatial ecology. Importantly, multiple regression models at a single scale almost

always would have shown only one ecological process to be important, erroneously implying that the others were of low relevance. As humans continue to modify species composition, dispersal, and climate across scales, it is critical that we understand the full spectrum of consequences of these changes. Without thorough multi-scale analyses, scientists are likely to misestimate the impacts of anthropogenic modifications on biodiversity and the environment.

Methods

Predictor Data. We used the total species richness of amphibians, birds, and mammals to predict the distribution of *Bd*, WNV, and *B. burgdorferi*, respectively. Richness of potential hosts was used instead of richness of known hosts because noncompetent hosts can dilute pathogen prevalence in the area by wasting bites from a vector or infection attempts from a parasite, resulting in failed transmission events. Geographic ranges for all species within each taxon were downloaded from the International Union for the Conservation of Nature Red List website (www.iucnredlist.org) as polygons and were used to create richness rasters (*Supporting Information*). We considered using the richness of birds and reptiles to predict the distribution of Lyme disease as well, but these factors were not significant in preliminary models. We used a human population density grid from the Center for International Earth Science Information Network's Global Rural-Urban Mapping Project (GRUMPv1). We log-transformed population data because they were right-skewed. Rasters containing data for the following abiotic variables were downloaded from WorldClim (www.worldclim.org): 50-y means of precipitation; mean, minimum, and maximum monthly temperatures; diurnal temperature range; annual temperature range; and altitude. We also collected the average monthly Normalized Difference Vegetation Index (NDVI) data from the National Oceanic and Atmospheric Administration (www.ospo.noaa.gov/Products/land/gvi/NDVI.html). We reduced our eight abiotic variables to three (>90% of the total variation) using a factor analysis (factanal function in statistics package, R 3.0.1, fitting four factors; Table S1). Factor one was heavily influenced by mean, minimum, and maximum temperatures. Factor two was primarily based on precipitation and the NDVI. Factor three consisted mainly of temperature variability (diurnal temperature range) and altitude data. Given that *Bd* is a freshwater pathogen and mosquitos require freshwater to breed, we also tested whether water as a fraction of land cover was predictive of these two pathogens. It was not a significant positive predictor in preliminary models and thus was not

included in our final models (see [Supporting Information](#) for additional details). In addition, we tested whether species richness for vectors (mosquitos) was predictive of WNV prevalence ([Supporting Information](#)). We chose not to examine the temporal dispersal of the pathogens because temporal resolution was insufficient for a robust examination of temporal dynamics.

Creation of Rasters at Multiple Scales. All Geographic Information Systems data processing was done using the raster package in R v. 3.0.1 unless otherwise indicated. To produce rasters at each of our targeted resolutions, we first masked, or cropped, rasters to the United States or the eastern United States (mask function, raster package), depending on the pathogen, as discussed below. The smallest scale we could achieve with all available predictors was 0.0625×0.0625 degree (~ 37 km²), so we adjusted all rasters up to this size and removed any geographic projections (aggregate and projectRaster functions, raster package). This scale served as the smallest in our analyses. From there, we up-scaled rasters (aggregate function) to take the mean (abiotic factors and human density) or sum of unique values (richness) of each 2×2 group of cells in the smaller scale, forming one new cell at the larger scale and quadrupling the area at each step. This process was repeated six times until we had rasters with cell sizes of 4×4 degrees ($\sim 1.5 \times 10^5$ km²).

Species ranges were clipped (i.e., cropped using the clip function, raster package) to the border of the United States or eastern United States using ArcMap 10.2 and were converted from spatial polygons to rasters in R ([SI Methods](#)). All predictors were again standardized via conversion to z-scores so that predictors had a mean of zero and SD of one at every scale. See [Table S4](#) for correlations between predictors at all scales.

Parasite Data. On March 21, 2014 we downloaded a compilation of spatially explicit chytrid data from *Bd* Maps (www.bd-maps.net) containing records obtained by swabbing animals for infection in the field. We calculated arcsine-transformed prevalence at each location where amphibians were tested. We obtained WNV and *B. burgdorferi* data through the county-level disease monitoring program (diseasemaps.usgs.gov) of the Centers for Disease Control and Prevention (CDC). Total human cases were averaged across years for *B. burgdorferi* (1992–2011) and WNV (2001–2012 beginning with the first year in which cases were reported in a particular county to account for the rapid spread) and were adjusted to prevalence per 10,000 people using 2010 US county-level census data (www.census.gov). If we did not adjust the Lyme and WNV data by population density, the distribution simply would match the human population distribution. Any significant effects of human population density for these pathogens thus indicate that the effect of humans is greater or less than a linear proportional function. To produce spatial points for our analysis, we converted the centroid of each county to a point containing that county's data (gCentroid function, rgeos package). However, because counties in the western United States often were larger than the cells in our fine-grain rasters (~ 37 km²), we limited our analysis of these two pathogens to the states east of the Mississippi River ([Fig. S2](#)). All response data were in the form of spatial points. We attempted to find spatially explicit prevalence data for other pathogens as well, but could not ([Supporting Information](#)).

Generalized Least Squares Models. We fit generalized least squared (GLS) multiple regression models (glis function, nlme package, full maximum likelihood fit, accounting for spatial autocorrelation using corExp function) (32) using extracted values (extract function, raster package) of the five

continuous predictors (pathogen-specific host richness, population density, and three abiotic factors) for each pathogen data point in space. We did not test for interactions between predictors, as explained in [Supporting Information](#). GLS models were fit for the same response data at every scale for each pathogen by using predictors generated for that scale.

Multimodel Inference. We did not want to rely on any single model for our conclusions. Therefore we used multimodel inference (MuMIn package), a procedure that fits models using all possible combinations of predictors and weights them by Akaike Information Criterion (AIC) (dredge function). This procedure entailed generating AIC values and Akaike weights for each candidate model (which were limited to three predictors or less). We then computed relative importance scores by summing the Akaike weights of all of the models in which each predictor appeared (33, 34). Next, we computed model-averaged parameter estimates with and without shrinkage using all possible models. We considered all possible models with three or fewer predictors because models with large Δ AIC contribute extremely little to the model-averaged parameter estimate because they have very small Akaike weights (33, 34) and because models with four or all five predictors would have overwhelmed the averaged models and swamped out relative importance scores.

Randomization Tests. We tested whether the observed changes in the importance of biotic, abiotic, and human density variables across scales were spuriously driven by correlations among these predictors using a randomization test (500 iterations). For each iteration, we randomly reshuffled chytrid prevalence data among the observations (thus preserving the correlation structure of the predictors) and repeated our statistical analysis.

Univariate Models. For all pathogens, we ran univariate GLS models with every predictor at each scale to test whether predictors changed in importance across scales (in multivariate models) on their own or because of changes in importance for other predictors.

Spatial Correlograms. To test the hypothesis that biotic factors were more variable at smaller scales than climate factors, we created correlograms [Moran's I vs. distance plots; ncf package, correlog function; 0.0625° scale (~ 37 km²)] to evaluate spatial autocorrelation as a function of distance, with the expectation that at small scales biotic factors would have smaller Moran's I values than climatic factors.

The root mean square errors (RMSE) for the model-averaged predictions for each parasite at each scale are shown in [Table S5](#). The lists of models incorporated into each averaged model, along with their respective weights, are presented in [Table S6](#). In addition, we have presented model averaged outputs without shrinkage in [Table S7](#).

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