Ecological Applications, 28(8), 2018, pp. 1948–1962

Eco-evolutionary rescue promotes host–pathogen coexistence

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Abstract. Emerging infectious pathogens are responsible for some of the most severe host mass mortality events in wild populations. Yet, effective pathogen control strategies are notoriously difficult to identify, in part because quantifying and forecasting pathogen spread and disease dynamics is challenging. Following an outbreak, hosts must cope with the presence of the pathogen, leading to host–pathogen coexistence or extirpation. Despite decades of research, little is known about host–pathogen coexistence post-outbreak when low host abundances and cryptic species make these interactions difficult to study. Using a novel disease-structured N-mixture model, we evaluate empirical support for three host–pathogen coexistence hypotheses (source–sink, eco-evolutionary rescue, and spatial variation in pathogen transmission) in a Neotropical amphibian community decimated by *Batrachochytrium dendrobatidis* (*Bd*) in 2004. During 2010–2014, we surveyed amphibians in Parque Nacional G. D. Omar Torríjos Herrera, Coclé Province, El Copé, Panama. We found that the primary driver of host–pathogen coexistence was eco-evolutionary rescue, as evidenced by similar amphibian survival and recruitment rates between infected and uninfected hosts. Average apparent monthly survival rates of uninfected and infected hosts were both close to 96%, and the expected number of uninfected and infected hosts recruited (via immigration/reproduction) was less than one host per disease state per 20-m site. The secondary driver of host–pathogen coexistence was spatial variation in pathogen transmission as we found that transmission was highest in areas of low abundance but there was no support for the source–sink hypothesis. Our results indicate that changes in the host community (i.e., through genetic or species composition) can reduce the impacts of emerging infectious disease post-outbreak. Our disease-structured N-mixture model represents a valuable advancement for conservation managers trying to understand underlying host–pathogen interactions and provides new opportunities to study disease dynamics in remnant host populations decimated by virulent pathogens.

Key words: *amphibians;* Batrachochytrium dendrobatidis; *chytrid; Dail-Madsen model; demography; enzootic; epidemiology; imperfect detection.*

Introduction

Emerging infectious diseases threaten human health, jeopardize food security, and imperil global biodiversity (Daszak et al. 2000, Jones et al. 2008, Holdo et al. 2009, Fisher et al. 2012, 2016, Lozano et al. 2013). To develop effective prevention and control options, wildlife managers need estimates of disease prevalence, mean infection intensity, transmission, and recovery rate parameters, which can be difficult to obtain from wild populations. Fungal pathogens, in particular, have led to the collapse of bat communities across North America (Blehert et al. 2009) and global amphibian mass mortality (Berger et al. 1998, Olson et al. 2013, Lips 2016). In each case, fungal pathogen emergence caused mass host mortality, where some species were extirpated while others persisted at low abundances (e.g., Crawford et al. 2010, Fisher et al. 2012, Langwig et al. 2012). Following an outbreak, persisting hosts must cope with the sustained presence of the fungal pathogen as it continues infecting hosts or as it occurs in environmental reservoirs (e.g., Johnson and Speare 2003, Hoyt et al. 2015). This leads to observed patterns of host–pathogen coexistence or extirpation post-outbreak (e.g., Anderson and May 1978, Thrall and Antonovics 1995, Briggs et al. 2010, Maslo et al. 2015, Knapp et al. 2016). While many studies have posited mechanisms for host–pathogen coexistence (Table 1), testing these hypotheses with field-derived empirical evidence is limited for populations that have experienced mass mortality events (e.g., Fisher et al. 2012, 2016, but see Frick et al. 2017) because low host abundance and cryptic species post-outbreak makes tracking individuals, estimating their demographic rates, and analyzing host–pathogen interactions difficult (e.g., Faustino et al. 2004, Pryde et al. 2005, Harmsen et al. 2011, Lachish et al. 2011).

Three hypotheses explain host–pathogen coexistence post-outbreak that may act alone or in tandem (Table 1; Fig. 1). First, *source–sink dynamics* characterize a system where host re-colonization via immigration or reproduction prevents extirpation as new individuals replace those lost from disease-induced mortality (e.g., Brown and Kodric-Brown

Manuscript received 4 June 2018; revised 12 September 2018; accepted 22 June 2018. Corresponding Editor: David S. Schimel.
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TABLE 1. Epidemiological literature review of the three hypotheses and mechanisms explaining host–pathogen coexistence.

Hypotheses, mechanisms, and pathogen system	Studies
Source–sink dynamics	
Demographic rescue (i.e., dispersal, animal migration, wildlife corridors, captive breeding and release programs, and translocation of individuals among populations)	
Applicable to multiple systems	Hess (1996), Altizer et al. (2011)
Chronic wasting disease	Coner and Miller (2004)
Mycoplasma gallisepticum	Hosseini et al. (2004)
Batrachochytrium dendrobatidis	Muths et al. (2011)
Irregular and spatially uncorrelated epidemics	
Measles, whooping cough	Rohani et al. (1999)
Vacuum effect (i.e., territorial boundaries are no longer defended, allowing an influx of new diseases and non-diseased animals to the area)	
Applicable to multiple systems	Killian et al. (2007)
Genetic rescue (i.e., selective advantage of hybrids produced by native and immigrant hosts)	
Applicable to multiple systems	Carlson et al. (2014)
Eco-evolutionary rescue	
Harvesting and density-dependent reproduction	
Applicable to multiple systems	Choisy and Rohani (2006)
Temporal variation in host density	
Applicable to multiple systems	Lloyd-Smith et al. (2005)
Mycobacterium bovis	Caley and Hone (2005)
Removing other stressors	
Applicable to multiple systems	Lafferty and Holt (2003)
White syndrome in corals	Bruno et al. (2007)
Pathogen genetic diversity and life history	
Myxoma virus	Best and Kerr (2000)
Host genetic diversity and life history	
Applicable to multiple systems	Altizer et al. (2003), Acevedo-Whitehouse and Cunningham (2006)
Batrachochytrium dendrobatidis	Savage and Zamudio (2011)
Ecological immunology	
Applicable to multiple systems	Hawley and Altizer (2011)
Selective culling or predation (top-down regulation)	
Applicable to multiple systems	Packer et al. (2003), Ostfeld and Holt (2004)
Chronic wasting disease	Wild et al. (2011)
Mesopredator release (top-down and bottom-up regulation)	
Toxoplasma gondii	Hollings et al. (2013)
Demographic compensation (i.e., decrease in natural mortality)	
Applicable to multiple systems	Tompkins and Begon (1999)
Tuberculosis	Jolles et al. (2006)
Avian malaria	Kilpatrick (2006)
Host microbiome	
Applicable to multiple systems	Belden and Harris (2007)
Batrachochytrium dendrobatidis	Jani and Briggs (2015)
Host age-structure	
Batrachochytrium dendrobatidis	Briggs et al. (2010), Vredenburg et al. (2010)
Species community composition changes through time	
Applicable to multiple systems	Streicker et al. (2013)
Seasonality (includes seasonal impacts on host social behavior, physiology, contact rates, pulses of host births and deaths, and changes in host immune defenses)	
Applicable to multiple systems	Altizer et al. (2006), Tompkins et al. (2011)
Spatial variation in pathogen transmission	
Spatial distribution of infected hosts	
Applicable to multiple systems	Hagenaars et al. (2004)
Sociality, aggregations, group size	
Small-mammal parasites	Perkins et al. (2009)
Pseudogymnoascus destructans	Langwig et al. (2012)
Sarcoptes scabiei	Almberg et al. (2015)

Table 1. (Continued)

Hypotheses, mechanisms, and pathogen system	Studies
Abiotic or biotic reservoirs (including microclimate variation)	
Cowpox virus	Begon et al. (1999)
Avian influenza viruses	Roche et al. (2009)
Applicable to multiple systems	Viana et al. (2014)
Batrachochytrium dendrobatidis	Savage et al. (2011), Becker et al. (2012)
Land-use change (e.g., fragmentation, urbanization, etc.)	
Microbotryum violaceum	Carlsson-Graner and Thrall (2002)
Nematodes	Gillespie and Chapman (2006)
Applicable to multiple systems	Bradley and Altizer (2007), Brearley et al. (2013)
Climate warming and disease risk	
Applicable to multiple systems	Harvell et al. (2004)
Superspreader individuals, species, environments	
Applicable to multiple systems	Paull et al. (2012)
Biodiversity–disease relationship	
Applicable to multiple systems	Keesing et al. (2006), Roche et al. (2012)
Resource provisioning	
Applicable to multiple systems	Becker and Hall (2014)
Behavioral susceptibility (i.e., the interaction between host movement and group size)	
Applicable to multiple systems	Cross et al. (2005)

Notes: Reviews and theoretical papers are indicated using the phrase "applicable to multiple systems" under the pathogen system column. Depending on spatial-temporal scale, some mechanisms are not mutually exclusive among hypotheses. Therefore, comparing across the hypotheses, mechanisms of source–sink dynamics involve processes occurring outside the metapopulation (e.g., immigration), mechanisms of eco-evolutionary rescue operate through time, and mechanisms of spatial variation in pathogen transmission occur solely within the metapopulation.

1977, Pulliam 1988, Hanski 1998, Whittaker and Fernandez-Palacios 2007, Carlson et al. 2014). In this case, the number of individuals entering the population increases population viability, resulting in little net change in host abundance over time. When source–sink dynamics lead to host–pathogen coexistence, the survival and recruitment rates of uninfected hosts are higher than that of infected hosts, leading to high host turnover but constant abundance. Second, *eco-evolutionary rescue* occurs when either evolutionary (i.e., local adaptation or natural selection of resistant/tolerant individuals) or ecological (i.e., reduced host density, changes in community composition, demographic compensation) mechanisms increase the fitness (i.e., survival and recruitment) of infected hosts post-outbreak, matching the fitness of uninfected hosts (i.e., Gomulkiewicz and Holt 1995, Kilpatrick 2006, Bell and Gonzalez 2009, Vander Wal et al. 2013, Carlson et al. 2014, Pillai et al. 2016). This may occur if hosts evolve resistance to the pathogen (defined as mechanisms that reduce the growth rate of the pathogen on the host and thereby mortality) or tolerance (defined as traits that enable the host to reduce disease without reducing the growth rate of the pathogen; Langwig et al. 2017). Alternatively, ecological changes, such as shifts in host density (Anderson and May 1978) or community composition (Streicker et al. 2013), may occur independently of changes in genetic variation or the capacity to rapidly evolve effective pathogen resistance, leading to a rescue effect at their population or community levels. Finally, abiotic or biotic features that correlate with infection risk (e.g., host density/pathogen prevalence, species richness, and/or microhabitat) may mediate host–pathogen coexistence by creating *spatial variation in pathogen transmission*. These areas may facilitate or inhibit pathogen survival and growth, becoming areas of high or low pathogen transmission, respectively (Paull et al. 2012). In turn, these areas are then sources of infected hosts that can disperse to less infected areas (Paull et al. 2012) or are environmental refugia that decrease host susceptibility or mortality to pathogen infection (i.e., Puschendorf et al. 2011, Becker et al. 2012). Note that the mechanisms operating *source–sink dynamics* involve processes occurring outside the metapopulation (e.g., immigration), whereas the mechanisms determining *eco-evolutionary rescue* operate temporally, and the mechanisms influencing *spatial variation in pathogen transmission* occur solely within the metapopulation. Collectively, these three hypotheses explain host–pathogen coexistence, but their relative importance and interactions are rarely estimated for host communities decimated by emerging infectious diseases.

Given limited ability to manipulate post-outbreak systems, estimating host demographic rates (e.g., survival, recruitment, infection, recovery) is one approach that shows promise to determine the mechanisms responsible for host–pathogen coexistence. Demographic rates are typically estimated using data on individually marked animals and associated capture–recapture models, which correct demographic rate estimates for bias induced by imperfect host detection (Kendall 2009, McClintock et al. 2010). However, capture–recapture models perform poorly when recapture rates are low, typical of populations with low abundances and cryptic species, generating high parameter uncertainty (e.g., Faustino et al. 2004, Pryde et al. 2005, Harmsen et al. 2011, Lachish et al. 2011). Recently developed N-mixture models provide a mechanistic framework that estimate host demographic rates without the need to track individuals by

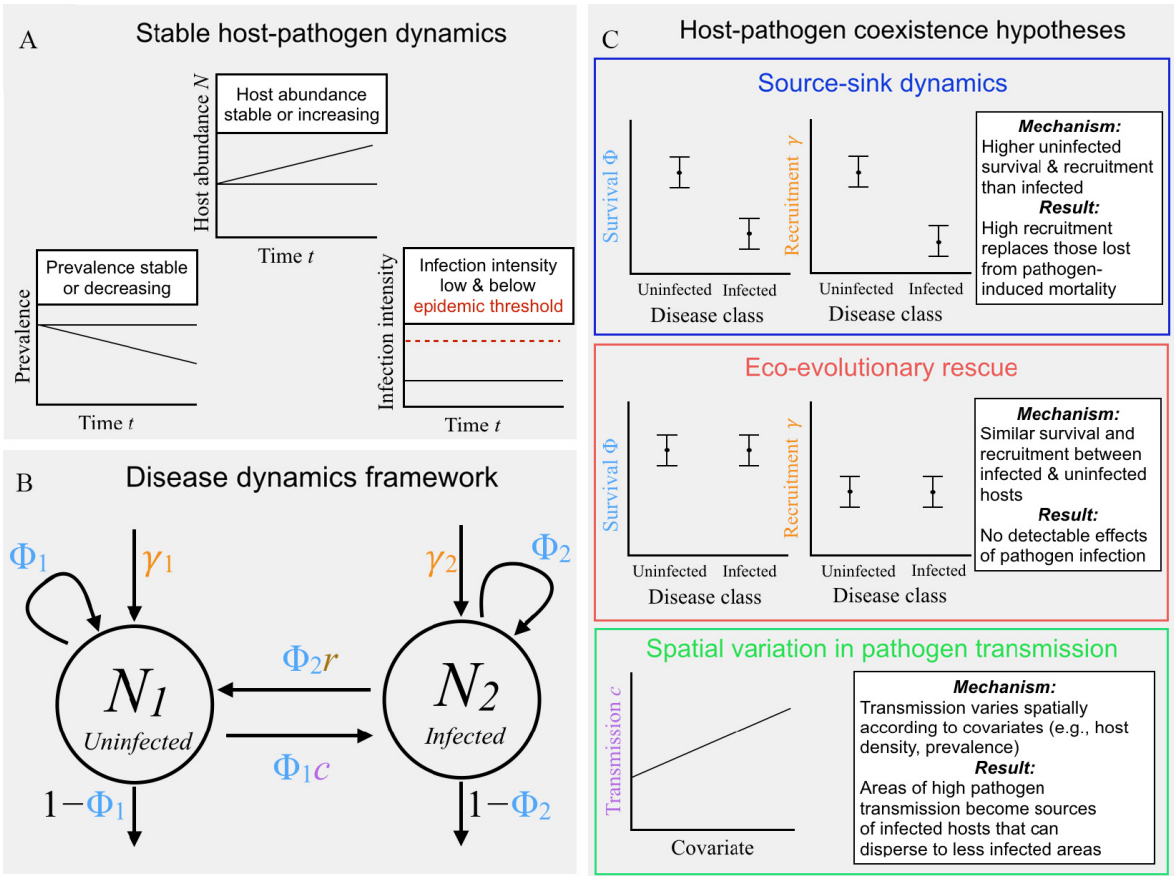

FIG. 1. To evaluate empirical evidence for host–pathogen coexistence: (A) First, we diagnose stable host–pathogen disease dynamics, where host abundance, pathogen prevalence, and infection intensity are maintained over time. (B) Then, we construct a model to estimate demographic parameters that would support or oppose each host–pathogen coexistence hypothesis: survival, recruitment, abundance, prevalence, and transmission risk. From time $t-1$ to t, each disease class (i.e., infected or uninfected) has individuals that survive (Φ), die ($1-\Phi$), transition between states (recover, r, or become infected, c), and arrive (γ; via immigration or reproduction). Demographic rates are estimated with count data using the disease-structured N-mixture model. (C) Finally, we determine which hypothesis (e.g., source–sink dynamics, eco-evolutionary rescue, or spatial variation in pathogen transmission) best explains host–pathogen coexistence by comparing infected and uninfected host demographic parameters.

taking advantage of the extra information gained from repeatedly surveying sites within a period of population closure (Dail and Madsen 2011, Zipkin et al. 2014a,b, Rossman et al. 2016).

Here, we evaluate support for the three host–pathogen coexistence hypotheses in promoting amphibian–*Batrachochytrium dendrobatidis* (hereafter *Bd*; Longcore et al. 1999) coexistence in El Copé, Panama. The amphibian community in El Copé was decimated by *Bd* in late 2004 (Lips et al. 2006). Typically, when *Bd* arrives in a naïve amphibian community, pathogen prevalence and host infection increase rapidly (Lips et al. 2006, Briggs et al. 2010, Crawford et al. 2010, Vredenburg et al. 2010), which often correlate with high host mortality and mass amphibian die-offs (e.g., Savage and Zamudio 2011, Heard et al. 2014, but see Reeder et al. 2012). Within months, the remaining amphibian community differs substantially from the original community in measures of host density, species richness, and community composition (e.g., Smith et al. 2009*a*, Crawford et al. 2010, Angeli et al. 2015, DiRenzo et al. 2016). The amphibian community in El Copé can be considered a metapopulation, because there is high gene flow among the streams studied and less dispersal to and from far away sites (Robertson et al. 2008). In this study, we extend the stage-structured N-mixture model (Zipkin et al. 2014a,b) to accommodate disease dynamics and estimate demographic rates, giving rise to new opportunities for conservation managers to understand disease dynamics of decimated populations and determine effective strategies to protect remnant populations.

Materials and Methods

Study site and surveys

From 2010 to 2014, we surveyed amphibians along four 200-m stream and three 400-m trail transects in Parque Nacional G. D. Omar Torríjos Herrera, Coclé Province, El Copé, Panama, that were established in 1998 as part of a long-term amphibian monitoring initiative (8°40′ N, 80°37′17″ W; Lips et al. 2003, 2006; for map, see Angeli et al. 2015). Prior to *Bd* arrival, this site had 74 amphibian species (Crawford et al. 2010). Within four years of *Bd* arrival, 30 species were extirpated, and nine species declined by 85% to 99% (Crawford et al. 2010). The park spans elevations between 500 and

1,000 m and is located on the continental divide. The study site has distinct dry (December to April) and wet (May to November) seasons, where the wet season experiences higher maximum daily temperatures and total monthly rainfall than the dry season (Appendix S1: Figs. S1–S3).

We divided each transect into 20-m adjacent sections (hereafter referred to as "sites") for a total of 40 stream and 59 trail sites. Within each primary sampling season (i.e., wet 2010, wet 2011, wet 2012, dry 2013, wet 2013, dry 2014), we surveyed each site one to eight times between 19:00 and 01:00 over 1–35 d (Appendix S1: Table S1). These surveys within primary seasons are referred to as secondary sampling periods. We assumed closed populations (i.e., no births, deaths, immigration, emigration, or disease state transitions) within primary sampling seasons (i.e., among secondary sampling periods; Appendix S1: Fig. S4) and open populations between primary sampling seasons. We did not detect any evidence of spatial autocorrelation in the amphibian count data across the sites (except for the last season 2014 dry; Appendix S1: Table S2), as many of the frog species used in the analysis tend to stay in the same location (Savage 2002, Köhler 2011).

Surveys were conducted by teams of two to six people slowly walking through each site, locating, and capturing amphibians within 2 m of the stream bank or trail. To estimate *Bd* infection status, we swabbed the skin of amphibians using a sterile cotton-tipped swab (Dry Swab MW113, Medical Wire & Equipment, Corsham, Wiltshire, UK) and stored the swab in a 2-mL capped tube with 30 μL of 70% ethanol (Hyatt et al. 2007). We used a fresh pair of latex powder-free gloves when handling each individual. We released all amphibians at the original point of capture.

Molecular analysis

We extracted the DNA on skin swabs using PrepMan Ultra (Thermo Fisher Scientific, Warrington, Cheshire, UK) to estimate *Bd* infection status. We tested swabs for *Bd* in singlicate using Taqman qPCR running 50 cycles (Boyle et al. 2004, Hyatt et al. 2007). We ran each plate using standards of the El Copé, Panama *Bd* isolate JEL 423 obtained during the 2004 outbreak ranging from 0.1 to 1,000 *Bd* zoospore genomic equivalents (ZGE) to determine *Bd* presence and infection intensity. To ensure that false-positives were negligible, we included negative controls on each qPCR plate. We categorized individuals as *Bd* positive if qPCR amplification occurred before cycle 50 (Briggs et al. 2010). Hereafter, we refer to *Bd* ZGE as host infection intensity.

Disease-structured N-mixture model

We planned on analyzing the amphibian-*Bd* data using a capture–mark–recapture framework to estimate host demographic rates and determine the relative support for each of the host–pathogen coexistence hypotheses (e.g., source–sink, rescue, spatial variation; Fig. 1), but low amphibian abundance and recapture rates generated nearly unidentifiable demographic estimates (Appendix S2: Table S1). Instead, we extended the generalized N-mixture model (Dail and Madsen 2011) to incorporate disease dynamics following the stage-structured modeling framework in Zipkin et al. (2014a,b) and focused our analysis on counts of unmarked infected and uninfected hosts to estimate demographic rates, while accounting for imperfect host and pathogen detection, pooling the data across species.

Pooling species data do not allow for species-level estimates of *Bd* infection, although it is well known that amphibian species vary in their susceptibility to *Bd* (e.g., Lips et al. 2003, Crawford et al. 2010, Searle et al. 2011a,b, Gervasi et al. 2013). Ultimately, this limits our ability to make inference on how and why particular species persist with pathogens. However, amphibians that persist following *Bd* outbreaks are typically more similar ecologically (e.g., Smith et al. 2009a) and genetically (e.g., Savage and Zamudio 2011, Savage et al. 2015) than the amphibian community pre-outbreak. This decrease in species heterogeneity may lead to lower variations in demographic rates among species (i.e., narrow credible intervals). Given that some species are more abundant than others, all demographic estimates reported are a weighted average across individuals of different species (i.e., more abundant species affect the demographic estimates more than rare species). Although there were insufficient data to run a species-specific analysis (Appendix S2: Table S1), we confirmed our results by running the model outlined below with the four most abundant species, representing both terrestrial and riparian habitats (i.e., *Espadarana prosoblepon*, *Pristimantis cerasinus*, *Pristimantis cruentus*, *and Sachatamia albomaculata*; Appendices S2 and S3). We present the pooled model results in the main text because all amphibian species in El Copé, Panama are hosts to *Bd*, and their presence may affect disease dynamics.

Parameters of the disease-structured N-mixture model are estimated by tabulating between-year variance as an increasing function of the survival probability, the expected number of individuals gained (via immigration and birth), disease transitions, and the number of years between samples, where greater turnover (via immigration, birth, and disease state transition) results in higher between-year variance (Dail and Madsen 2011, Zipkin et al. 2014a,b). The information to estimate disease transition probabilities comes from the between time-series Markovian dependence assumed by the model. Under reasonable models that impose Markovian dynamics between and within time-series of counts, the dependence structure provides the information about the dynamical state-specific parameters, which can be demonstrated analytically for simple cases (Dail and Madsen 2011). The modeling framework has also been validated via simulations with more complicated structures (e.g., Priol et al. 2014, Zipkin et al. 2014a,b, Bellier et al. 2016, Zhao et al. 2017).

Our interest lies in modeling $N_{i,j,t}$, the true amphibian abundance in disease state i at each site j during primary season t (hereafter referred to as "season"). We modeled the abundance of uninfected ($i = 1$) and infected ($i = 2$) amphibians at site j during the first season ($t = 1$) using a Poisson distribution

$$N_{i,j,1} \sim \text{Poisson}(\lambda_i)$$

such that mean host abundance, λ_i, differs by disease state i. We assume a Poisson distribution because the number of observed amphibians per 20 m site during the first season (wet 2010) was low (ranging from zero to nine) and had a mean/variance ratio of 0.68 (Appendix S1: Fig. S6), suggesting

only minor overdispersion in the data. Note that amphibians with infection intensities ranging between 1 and 10^6 ZGE are considered infected. Although parameter estimates likely vary between streams and trails, low host abundance and few sites made habitat-specific covariates effects unidentifiable.

We modeled subsequent seasons ($t \geq 2$) by considering the number of hosts that: survived in each disease state (S), transitioned between disease states (T), and were recruited via immigration and reproduction (G). To model the number of hosts that survived from season $t-1$ to t, we defined parameter Φ_i as the state-specific monthly apparent survival probability for uninfected ($i = 1$) and infected ($i = 2$) amphibians, such that

$$S_{i,j,t} \sim \text{Bin}\left(\text{N}_{i,j,t-1}, \Phi_i^{M_{j,t}}\right)$$

where $M_{j,t}$ is the total number of months between season $t-1$ to t. We estimated the monthly apparent survival probability because the number of months between the end of season $t-1$ to the start of season t varied between three and twelve and differed among sites. Similarly, we specified the number of hosts that transitioned from disease state i to ii at site j from season $t-1$ to t, $T_{i(ii),j,t}$, based on site-specific monthly transmission risk ($c_{j,t}$) and recovery probability ($r_{j,t}$)

$$T_{1(2),j,t} \sim \text{Bin}\left(S_{1,j,t},\ c_{j,t}^{M_{j,t}}\right)$$

$$T_{2(1),j,t} \sim \text{Bin}\left(S_{2,j,t},\ r_{j,t}^{M_{j,t}}\right).$$

With this specification, amphibians that transition between disease states first experience the survival probability associated with their disease state in season $t-1$ and then transition between disease states. Because we did not know a priori which transmission form to use (i.e., density or frequency dependent), we modeled transmission risk, $c_{j,t}$, as a function of a compound term, $\text{cov}_{j,t}$, and an indicator term, q, which identifies the transmission form (e.g., Smith et al. 2009b), where $\text{cov}_{j,t} = \frac{\text{N}_{2,j,t}}{\text{N}_{j,t}^q + 0.001}$. If q equals zero or one, then it suggests density- or frequency-dependent transmission, respectively. If q falls in between zero and one, then a mixture of density- and frequency- dependent processes is occurring (Smith et al. 2009b). We standardized and modeled the compound term ($\text{cov}_{j,t}$) using a logit link function, $\text{logit}(c_{j,t}) = \alpha 0 + \alpha 1 \times \text{cov}_{j,t}$. In either case of density- and frequency- dependent *Bd* transmission risk, we expected a positive value for $\alpha 1$.

Finally, we modeled the number of amphibians gained to each disease state i at site j from season $t-1$ to t, $G_{i,j,t}$

$$G_{i,j,t} \sim \text{Poisson}(\gamma_{i,j,t})$$

where $\gamma_{i,j,t}$ is the expected number of uninfected ($i = 1$) and infected ($i = 2$) hosts recruited (either by immigration or by reproduction) to site j between seasons. To accommodate differences in the number of months between seasons, we included the standardized number of months between seasons as a covariate, such that $\log(\gamma_{i,j,t}) = \beta 0_i + \beta 1 \times M_{j,t}$.

The state-specific host abundance for disease state i at site j during season t is then

$$\text{N}_{i,j,t} = G_{i,j,t} + S_{i,j,t} + T_{ii(i),j,t} - T_{i(ii),j,t}$$

the sum of the number of individuals that were gained at a site, survived at a site and remained there, and those that transitioned into disease state i minus those that transitioned out of disease state i.

We specified the observation model to account for imperfect host and pathogen detection during the sampling process. We adjusted for imperfect pathogen detection because infected hosts tend to be misidentified as uninfected when their infection intensities are low (e.g., Lachish et al. 2012, Miller et al. 2012) and low infection intensities are common post-outbreak (e.g., Briggs et al. 2010). Therefore, we modeled the number of misidentified infected hosts, $m_{j,k,t}$, at site j during secondary survey k and season t as a binomial random variable

$$m_{j,k,t} \sim \text{Bin}(g_{1,j,k,t}, 1 - \varphi_{j,k,t})$$

where $g_{1,j,k,t}$ is the field-observed number of uninfected hosts, and $\varphi_{j,k,t}$ is the average probability of detecting the pathogen on an individual given that it is infected at site j during survey k and season t. To calculate $\varphi_{j,k,t}$, we modeled the relationship between *Bd* detection probability and average site-specific *Bd* infection intensity, ZGE, which is reported on the log scale, following Miller et al. (2012), $\text{logit}(\varphi_{j,k,t}) = \delta 0 + \delta 1 \times \text{ZGE}_{j,k,t}$.

The corrected number of detected uninfected and infected hosts, $y_{i,j,k,t}$, in disease state i at site j during survey k and season t is then calculated by adjusting the number of field-observed hosts, $g_{i,j,k,t,}$ by the number of misidentified hosts, $m_{j,k,t}$

$$y_{1,j,k,t} = g_{1,j,k,t} - m_{j,k,t}$$

$$y_{2,j,k,t} = g_{2,j,k,t} + m_{j,k,t}.$$

We use $y_{i,j,k,t}$ to account for imperfect host detection and model true host abundance, $\text{N}_{i,j,t}$

$$y_{i,j,k,t} \sim \text{Bin}(\text{N}_{i,j,t}, p_{i,j,k,t})$$

where $p_{i,j,k,t}$ is the state-specific host detection probability at site j during survey k and season t. To account for seasonal and survey-specific effects on host detection probability, we included an indicator covariate for wet or dry season sampling, differing by disease state i, and the number of observers during each survey, which we assumed had the same effect on disease states. We included average *Bd* infection intensity as a covariate in the infected host detection model given that infection may change the probability of host capture (e.g., Poulin and Maure 2015)

$$\text{logit}(p_{1,j,k,t}) = \theta 0_1 + \theta 1_1 \cdot \text{wet}_t + \theta 2 \cdot \text{obs}_{j,k,t}$$

$$\text{logit}(p_{2,j,k,t}) = \theta 0_2 + \theta 1_2 \cdot \text{wet}_t + \theta 2 \cdot \text{obs}_{j,k,t} + \theta 3 \cdot \text{ZGE}_{j,k,t}.$$

Model fit

We fit our model using Markov chain Monte Carlo (MCMC) methods to estimate the posterior distributions for all parameters implemented in JAGS 4.0.0 in the R

environment (R Core Team 2015) and package jagsUI (Kellner 2016, Appendix S4). For parameters in logit link functions, except for the parameters associated with imperfect pathogen detection (δ0 and δ1), we used priors centered on zero with standard deviation of 2.71 following the recommendation by Lunn et al. (2012). For the indicator term q, we used a standard variable selection prior $q \sim$ Bernoulli (0.5) (Ntzoufras 2002). For all other parameters (i.e., $\beta 0_i$, $\beta 1$, $\log(\lambda_i)$), we used flat priors centered on zero with a standard deviation of 31.62 (i.e., precision of 0.001).

For δ0 and δ1, i.e., *Bd* detection rates in qPCR samples, we used informative priors provided by Miller et al. (2012), $\delta 0 \sim$ dunif(0.25, 1.32) and $\delta 1 \sim$ dunif(0.14, 0.51), because we did not collect the data to estimate these parameters (i.e., double swabbing or running multiple qPCR on a single sample) and it is reasonable to assume that qPCR detection is similar across studies. These parameters affect the detection probability of the pathogen on a host and correct for misidentifying individuals with low infection intensities as uninfected. We ran three separate runs of the model with different combinations of priors for the other parameters. We used normal priors centered on zero and varied the standard deviation using either 10 or 1,000. We found no difference in parameter estimation (Appendix S4: Fig. S1) and report results with a standard deviation of 1,000. We calculated a Bayesian P value to ensure that our model fit the data well (Appendix S4: Figs. S2 and S3; Kery and Schaub 2012). To determine the support for each of the host–pathogen coexistence hypotheses (e.g., source–sink, rescue, spatial variation), we compared the posterior distributions of parameters of interest (Fig. 1; Appendix S5). The complete model specification, including an assessment of model fit using a Bayesian P value approach, and data simulations with model analysis are presented in Data S1 and S2, respectively.

Results

Field summary

Over the six primary seasons, we captured and identified the disease state of 1,621 amphibians capture events representing 32 species (Appendix S2: Table S1) with 0–9 amphibians captured during any single secondary sampling period at a 20-m site. The number of observed individual amphibians ranged widely from 17 to 469 (Appendix S1: Fig. S7) over the six seasons, and we found very few tadpoles or juveniles of any species (Appendix S1: Fig. S8).

*Amphibian–*Bd *dynamics*

Amphibian abundance and *Bd* disease dynamics stabilized from 2010 to 2014 in El Copé, Panama, indicating an endemic disease state (model output: Fig. 2A; raw data: Appendix S1: Fig. S7). Total amphibian abundance increased from 134 individuals (95% CI: 90–175) in 2010 and remained at approximately 331 amphibians from 2012 to 2014 (Fig. 2; Appendix S5: Table S1). *Bd* prevalence and infection intensity were also steady over the same time period (Fig. 2). Infected host abundance was slightly greater than uninfected host abundance (Fig. 2A), with average *Bd* prevalence remaining just over 50% (Fig. 2B; range = 56% [95% CI, 49–64] in 2011 to 59% [95% CI, 42–75] in 2010). This is much higher than naïve *Bd* prevalence, which averaged around 22% across species (Appendix S1: Fig. S7). Most infected hosts (~97%) had estimated infection intensities <100 ZGE (Fig. 2C).

*Amphibian–*Bd *coexistence*

We found no negative consequence of *Bd* infection on host survival or recruitment as predicted by the eco-evolutionary rescue hypothesis (and contrary to the source–sink dynamics hypothesis; Figs. 1C and 3). Average apparent monthly survival probabilities of uninfected and infected hosts were both close to 96% (Fig. 3A; Table 2, S4; 95% CI, $\Phi_{\text{uninfected}}$ = 94.36–98.91%, Φ_{infected} = 94.86–98.01%), and the expected number of uninfected and infected hosts recruited (via immigration or reproduction) was less than one host per disease state per 20-m site every 8.5 months (Fig. 3B; Table 2, S4; 95% CI, $\gamma_{\text{uninfected}}$ = 0.30–0.61, γ_{infected} = 0.28–0.59). Average monthly recovery probability was also low at 19% (Table 2; 95% CI, 0.01–40.05). The high level of precision in our estimates of survival and recruitment (as demonstrated by relatively narrow credible intervals; Fig. 3) suggests that there is little unexplained variation across species, supporting the idea that the species in the post-outbreak amphibian community in El Copé, Panama may be experiencing similar population-level dynamics (Appendix S2).

Unexpectedly, we found support for negative density-dependent *Bd* transmission risk, where the indicator term, q, was close to zero (Fig. 4A; Table 2; q = 0.00; 95% CI, 0.00–0.00) and the slope term, $\alpha 1$, was negative (Fig. 4A; Table 2; $\alpha 1 = -3.05$; 95% CI, −5.1 to −1.29. This suggests that *Bd* transmission risk is density dependent, with the highest transmission probabilities at sites with low abundance. To understand the underlying driver of this unanticipated result, we conducted several post hoc correlation tests (function cor.test() in R; Spearman's correlation coefficient [ρ]) and additional model runs. First, to confirm the negative density-dependent *Bd* transmission risk detected by the model, we examined the relationship between observed host abundance during season t vs. the per capita change in the number of infected hosts between seasons $t - 1$ to t. We found the same negative correlation detected by the model in the observed data (Fig. 4B; Table 2; Spearman's correlation coefficient $\rho = -0.40$). Second, to determine whether changes in host abundance led to changes in pathogen exposure, we examined the correlation between observed host abundance and mean *Bd* infection intensity (i.e., Keesing et al. 2006). We found a negative correlation, suggesting that as host abundance increases, *Bd* exposure and infection intensity decreases (Fig. 4C; Table 2, Spearman's correlation coefficient $\rho = -0.35$).

We fit two additional models to determine the strength of negative density-dependent *Bd* transmission risk: a null and a random effects transmission model. We found that the null transmission model fit the data equally as well as the original model outlined above (Appendix S4: Figs. S4 and S5),

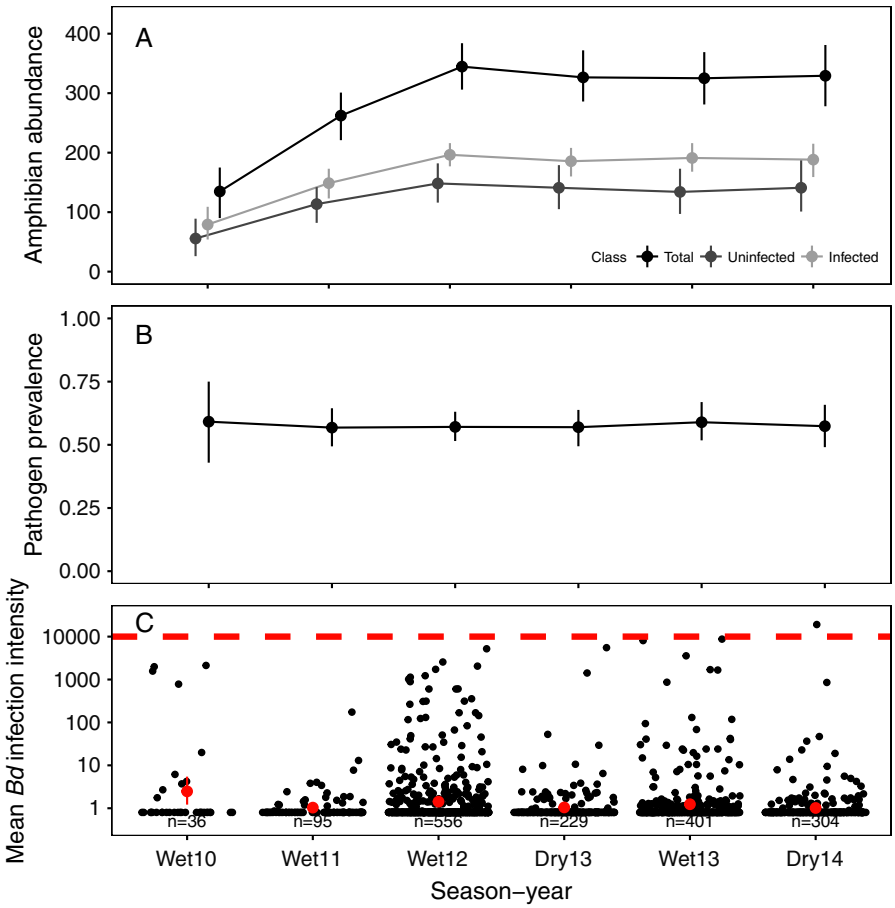

FIG. 2. Seasonal fluctuations in amphibian and *Batrachochytrium dendrobatidis* (*Bd*) abundance from 2010 to 2014 in El Copé, Panama. (A) Amphibian abundance, (B) pathogen prevalence, and (C) *Bd* infection intensity estimates from 2010 to 2014. In panels A and B, line ranges around points represent 95% credible intervals around the mean values (points). Each point represents an individual captured, and *n* represents number of hosts tested each year. The red points are seasonal mean infection intensity, and the point ranges are standard error estimates. The red dashed line represents the 10,000 zoospore threshold observed in the Sierra Nevada system, where amphibians experience chytridiomycosis epizootics (Vredenburg et al. 2010).

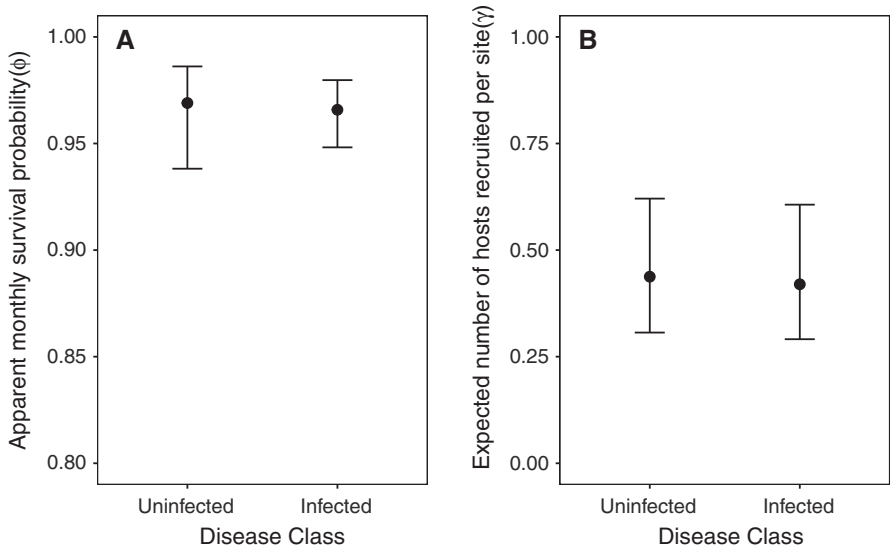

FIG. 3. Fitness parameters estimated for uninfected and infected amphibians in El Copé, Panama. (A) Apparent monthly survival probability of uninfected and infected hosts and (B) expected number of infected and uninfected hosts gained per site between seasons (shown for the average of 8.5 months). Ranges represent 95% credible intervals around the mean values (points).

Table 2. Summary of parameter estimates for disease-structured N-mixture model and Spearman's correlation tests.

Process, description, and parameter	Mean (95% CI)	Correlation coefficient ρ	*P*
Ecological			
Survival			
Φ_1	0.96 (0.93, 0.98)		
Φ_2	0.96 (0.94, 0.97)		
Recruitment			
$\beta 0_1$	0.43 (0.30, 061)		
$\beta 0_2$	0.41 (0.29, 060)		
$\beta 1$	1.80 (1.44, 2.27)		
Recovery			
r	0.16 (0.02, 0.46)		
Transmission			
q	0.01 (0.00, 0.00)		
$\alpha 0$	0.52 (0.13, 0.86)		
$\alpha 1$	0.04 (0.01, 0.21)		
Observational			
Pathogen detection			
$\delta 0$	0.73 (0.69, 0.76)		
$\delta 1$	0.62 (0.61, 0.63)		
Host detection			
$\theta 0_1$	0.06 (0.04, 0.08)		
$\theta 0_2$	0.03 (0.02, 0.04)		
$\theta 1_1$	0.32 (0.24, 0.39)		
$\theta 1_2$	0.27 (0.21, 0.35)		
$\theta 2$	0.56 (0.54, 0.58)		
$\theta 3$	0.57 (0.56, 0.58)		
Variables tested for correlation			
Change in per capita number of infected			
Host abundance		−0.40	<0.001
Mean *Bd* infection			
Host abundance		−0.35	<0.001

Notes: See *Methods* for complete parameter definitions. All model parameter values consist of mean and 95% credible interval. Parameter estimates are on the probability scale, except recruitment, which is numeric, quantifying the number of recruits per month.

indicating *Bd* transmission rates can be explained equally well as a fixed probability, suggesting the density-dependence detected is weak. In addition, the random effects transmission model suggested little variability in *Bd* transmission risk among sites (Appendix S4: Fig. S6; σ^2 mean = 0.13; 95% CI, σ^2 = 0.00–0.87), again suggesting that *Bd* transmission is fixed across the study area. Collectively, these two additional models show that the strength of density-dependent and the support for spatial variation in pathogen transmission is weak.

Amphibian–Bd *detection*

Both amphibians and *Bd* were detected imperfectly, although *Bd* detection probability was informed by estimates from Miller et al. 2012 (Table 2). The probability of correctly identifying an infected host as infected (φ) increased with average *Bd* infection intensity; likewise, the probability of detecting an infected host also increased with average *Bd* infection intensity (Table 2). Lastly, we found a positive effect of the number of observers on amphibian detectability (Table 2).

Discussion

The large negative consequences of *Bd* infection on amphibian survival and recruitment during the 2004 El Copé *Bd* outbreak (Lips et al. 2006, Crawford et al. 2010) are no longer evident in the amphibian community six years later, supporting the eco-evolutionary rescue hypothesis. We found weak support for the spatial variation in pathogen transmission hypothesis in the form of negative density-dependent *Bd* transmission, suggesting that areas with few individuals experience high *Bd* transmission risk, while areas of high amphibian abundance experience low levels of disease. Herein, we describe several evolutionary (i.e., host adaptation, attenuation in *Bd* virulence) and ecological (i.e., changes in community composition, decline in host density) mechanisms that may explain eco-evolutionary rescue in El Copé, Panama.

Evolutionary rescue, in the form of either changes in amphibian host susceptibility or *Bd* virulence, can explain amphibian–*Bd* coexistence in El Copé, Panama. This mechanism is supported by the growing evidence on the potential for amphibians to adapt to chytridiomycosis (e.g., McMahon et al. 2014, Ellison et al. 2015, Savage and Zamudio 2016) and observations that *Bd* virulence changes over time (e.g., Brem et al. 2013, Langhammer et al. 2013, Voyles et al. 2014). In some amphibian populations, *Bd* has driven rapid amphibian immunogenetic adaption (e.g., May et al. 2011, McMahon et al. 2014, Bataille et al. 2015, Savage and Zamudio 2016) and changes to amphibian innate and acquired immune responses (e.g., Savage and Zamudio 2011, Ellison et al. 2015) that decrease disease-induced host mortality. *Bd* infection no longer causes significant host mortality in several amphibian populations with endemic chytridiomycosis (e.g., *Rana muscosa* [Briggs et al. 2010], *Litoria rheocola* [Sapford et al. 2015], *Taudactylus eungellensis* [Retallick et al. 2004]; but see Murray et al. 2009, Longo and Burrowes 2010, Pilliod et al. 2010). There is growing evidence that *Bd* virulence attenuates over time, resulting in lower amphibian disease-induced mortality rates (e.g., Velo-Antón et al. 2012, Phillips and Puschendorf 2013), but in El Copé, Panama, Bd attenuation does not seem to be occurring based on comparisons of Bd virulence from historical and contemporary isolates (Voyles et al. 2018). A more likely evolutionary scenario would be that amphibians have evolved immunity to the chytrid fungus, contributing to host–pathogen coexistence.

Ecological rescue may also contribute to amphibian–*Bd* coexistence in El Copé, where a change in community composition mitigates disease-induced host mortality. Prior to *Bd* arrival in 2004, the El Copé amphibian community consisted of 74 species, including *Atelopus varius* (Crawford et al. 2010). This species harbors and sheds thousands to millions of infectious *Bd* zoospores that can infect a large number of hosts (i.e., an acute supershedder; DiRenzo et al. 2014). After *Bd*'s arrival, approximately 42 species were extirpated, and *Atelopus varius* was last seen in El Copé around 2009 (K. R. Lips, *unpublished data*). If *Atelopus varius* (and/or other species) was a primary transmitter of *Bd*, it is possible that following the extirpation of this species, *Bd* transmission rates decreased and persisting amphibians can cope with lower *Bd* transmission rates.

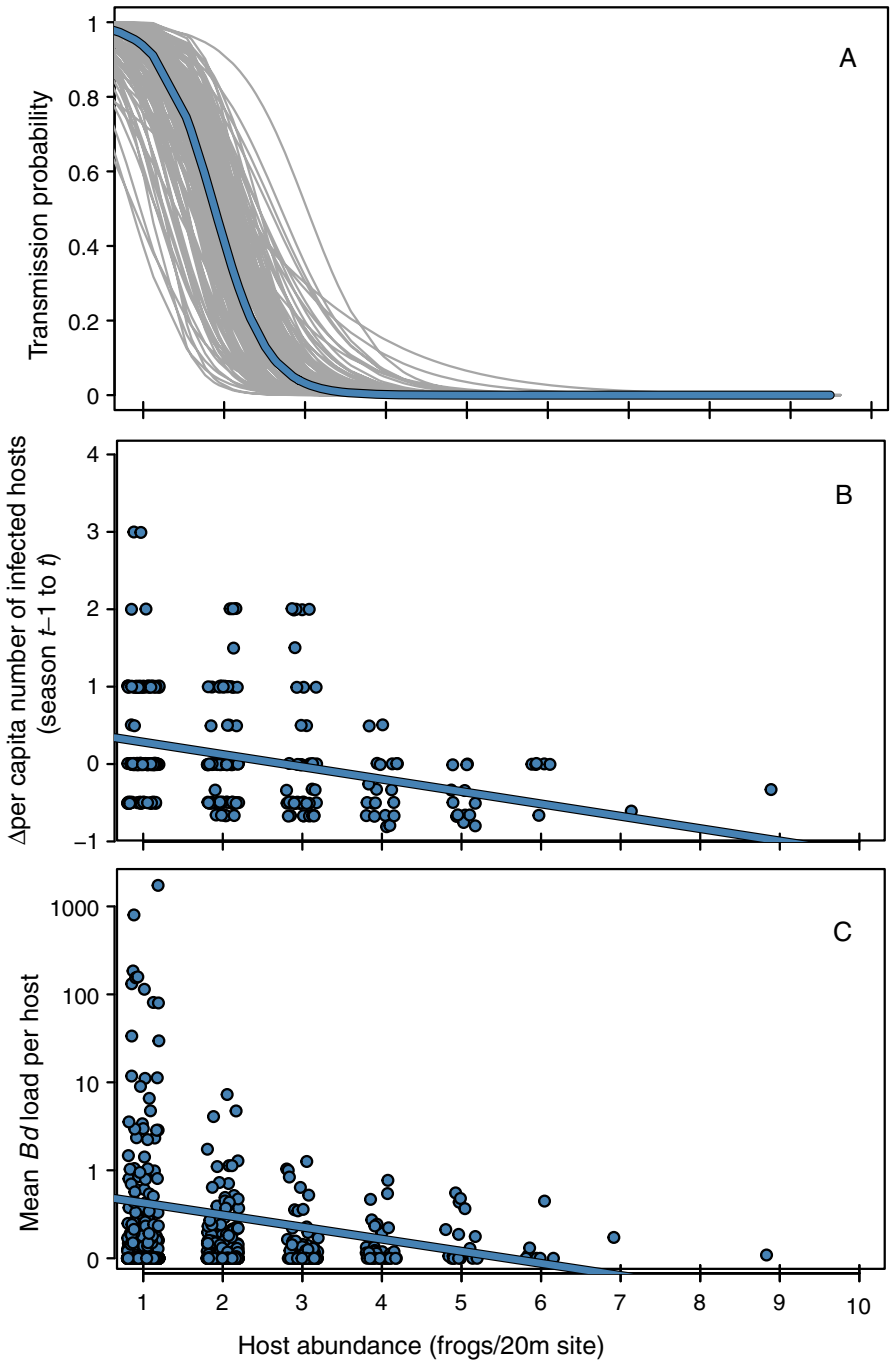

FIG. 4. The relationships between (A) *Bd* transmission risk and predicted host abundance, (B) observed host abundance during season t and the per capita change in the number of infected hosts between seasons ($t - 1$ to t), and (C) observed host abundance and mean *Bd* infection intensity. The dark line in A corresponds to the mean fitted line from the disease-structured N-mixture model results, while the light gray lines represent a random sample of size 200 from the posterior to visualize estimation uncertainty. All other thick lines in the proceeding panels correspond to the fit of Spearman's correlation.

In addition to declines in species richness, declines in amphibian abundance also decrease disease-induced host mortality if *Bd* transmission were density-dependent during the *Bd* outbreak (e.g., Rachowicz and Briggs 2007, Briggs et al. 2010). Under positive density dependence, lower amphibian density translates to lower contact rates and *Bd* transmission rates. The change from positive density-dependent transmission during the outbreak to negative density dependence post-outbreak could be the result of changes in *Bd* virulence, amphibian immunity, species richness, and host abundance. Present-day amphibian captures and species richness is at least 66% and 40% lower than pre-*Bd* estimates, respectively (K. R. Lips, *unpublished data*; Crawford et al. 2010). Using our field data, we cannot distinguish between the roles of community composition or host density because both metrics decreased following *Bd* arrival in El

Copé, but controlled experiments that manipulate community composition and density could disentangle these two processes (e.g., Becker et al. 2014).

In addition to eco-evolutionary rescue, we found that spatial variation in pathogen transmission may lead to host–pathogen coexistence. Specifically, we found that there was a weak signal of negative host-density-dependent *Bd* transmission. Negative host-density-dependent *Bd* transmission risk cannot be explained without assuming that *Bd* exists in environment reservoirs for long periods of time, given that *Bd* transmission risk is nearly 100% at sites where host abundance is one individual. Previous studies have demonstrated that *Bd* occurs in the environment; given that amphibians can become infected in areas that do not contain infected amphibians (i.e., Courtois et al. 2016, Fernández-Beaskoetxea et al. 2016, Voyles et al. 2018). However, without knowing if *Bd* can reproduce or how long it persists in the environment, we cannot support the implied assumptions of a *Bd* environmental reservoir. Without directly testing specific mechanisms for negative host-density-dependent *Bd* transmission, it is difficult to attribute this pattern to a single process (e.g., encounter reduction, susceptible host regulation, biotic or abiotic reservoirs; Keesing et al. 2006, Becker et al. 2014).

Given that survival and recruitment (via immigration or reproduction) rates were similar between infected and uninfected hosts, we found no support for the source–sink hypothesis explaining amphibian–*Bd* coexistence in El Copé, Panama. Several other studies show evidence for the source–sink hypothesis in different regions, where high amphibian recruitment compensates for low infected host survival (*Anaxyrus boreas* [Muths et al. 2011], *Litoria verreauxii alpine* [Scheele et al. 2015a,b], *Litoria rheocola* [Phillott et al. 2013]). In El Copé, male *Espadarana prosoblepon* move <3 m on average over two years, but this species is capable of long distance movement and genetic data showed that upland and lowland populations exchange individuals (Robertson et al. 2008). Unfortunately, little is known about migration and reproduction rates of most other Neotropical amphibian species found in El Copé, Panama. This detailed information could help to support or refute the feasibility of source–sink dynamics maintaining host abundance over time as a mechanism for host–pathogen coexistence.

Our model supports the assumption that persisting species have similar disease dynamics after the *Bd* outbreak, given that most parameter estimates had narrow credible intervals. Our original intent was to model species-specific disease dynamics and identify pathogen amplifiers (e.g., DiRenzo et al. 2014) or diluters (e.g., Searle et al. 2011a,b). However, we did not have the data for species-specific models given the limited number of detections per species (Appendix S2: Table S1). Single species models of the four most abundant species (*Espadarana prosoblepon*, *Pristimantis cerasinus*, *Pristimantis cruentus*, *and Sachatamia albomaculata*) performed similar to the community model albeit some credible intervals of parameter estimates were more imprecise because of small sample sizes (Appendix S2). Therefore, given the similarities in results between the species-specific and the pooled data models, we are confident in the results presented in the paper (Appendix S2). It is difficult to estimate species-specific disease dynamics in this diverse community, but future research may be able to differentiate species-specific contributions to host–pathogen coexistence as host abundance increases and data accumulates over time.

Emerging infectious diseases are challenging to forecast, which may be one impediment to development of optimal pathogen control strategies (Daszak et al. 2000, Jones et al. 2008, Fisher et al. 2012, but see Russell et al. 2017). One of the primary goals for the management of emerging infectious diseases is to minimize pathogen spread and their impacts on host populations (Smith et al. 2005, Bielby et al. 2008, Langwig et al. 2015). In amphibian communities where *Bd* is endemic, additional stressors including climate and land use change may compound pressures on amphibians struggling to persist (e.g., Scheele et al. 2016). These stressors have the potential to alter host population trajectories, putting species at higher risks of extinction. Amphibian declines are difficult to reverse, especially when the causes of decline are challenging to determine (e.g., disease, introduced species, climate change, and pollution). Thus far, the prospects for amphibian conservation and recovery in the face of record numbers of extirpations are grim (Wake and Vredenburg 2008). Yet, the results from our study indicate that the amphibian community in El Copé, Panama is stabilizing despite the ongoing presence of disease, providing a rare example of eco-evolutionary rescue occurring at an ecological time scale. It remains to be seen if eco-evolutionary rescue offers amphibians long-term persistence or only a short-term relief from a trajectory towards extinction. The advanced statistical framework and approach outlined here offers a guide for disease ecologists seeking to exploit unmarked organismal datasets and to address previously intractable questions at large spatial scales. Our approach should be useful for long-term datasets in small remnant populations devastated by emerging infectious diseases.

Acknowledgments

We thank the National Science Foundation (DEB #1120161 to K. R. Lips and K. R. Zamudio) for supporting this research. The authors thank N. Angeli, A. Cunha, C. Johnston, E. Kabay, C. Muletz, A. Novarro, J. Ray, S. Saunders, and T. Tunstall for help in the field and manuscript revisions. The authors thank M. Kéry and L. Browne for help with statistics. The authors also thank A. Marm Kilpatrick and two anonymous reviewers for greatly improving the quality of the manuscript. G. V. DiRenzo was supported by a National Science Foundation Graduate Research Fellowship and a grant from the Latin-American Studies office at the University of Maryland. This research was approved by the University of Maryland IACUC (Protocol #: R-12-05) and La Autoridad Nacional Del Ambiente (permit # SE/AH-3-12). We thank the Smithsonian Tropical Research Institute for logistical help. This is a contribution to the Amphibian Research and Monitoring Initiative (ARMI) of the U.S. Geological Survey.

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Supporting Information

Additional supporting information may be found online at: http://onlinelibrary.wiley.com/doi/10.1002/eap.1792/full

Data Availability

Data are available from the Dryad Digital Repository at https://doi.org/10.5061/dryad.90cg565; code is available on GitHub at https://doi.org/10.5281/zenodo.1042175.