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LETTER

Resistance, tolerance and environmental transmission dynamics determine host extinction risk in a load-dependent amphibian disease

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Abstract

While disease-induced extinction is generally considered rare, a number of recently emerging infectious diseases with load-dependent pathology have led to extinction in wildlife populations. Transmission is a critical factor affecting disease-induced extinction, but the relative importance of transmission compared to load-dependent host resistance and tolerance is currently unknown. Using a combination of models and experiments on an amphibian species suffering extirpations from the fungal pathogen *Batrachochytrium dendrobatidis* (Bd), we show that while transmission from an environmental Bd reservoir increased the ability of Bd to invade an amphibian population and the extinction risk of that population, Bd-induced extinction dynamics were far more sensitive to host resistance and tolerance than to Bd transmission. We demonstrate that this is a general result for load-dependent pathogens, where non-linear resistance and tolerance functions can interact such that small changes in these functions lead to drastic changes in extinction dynamics.

Keywords

Batrachochytrium dendrobatidis, chytridiomycosis, density-dependent transmission, frequency-dependent transmission, integral projection models, macroparasite, microparasite, *Rana muscosa*, *Rana sierrae*.

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INTRODUCTION

Disease-induced extinction of a host population is considered rare (De Castro & Bolker 2005; Smith *et al*. 2006; McCallum 2012). This is because in many systems disease transmission is an increasing function of the density of infected hosts (i.e. density-dependent transmission) such that decreasing host density reduces disease transmission and prevents disease-induced extinctions (McCallum & Dobson 1995; Gerber *et al*. 2005). Theoretical models suggest that to drive a host population extinct, a disease needs to have alternative transmission dynamics such that declining host density does not prevent further disease transmission (De Castro & Bolker 2005; Smith *et al*. 2006; McCallum *et al*. 2009). For example, frequency-dependent transmission, in which hosts have a density-independent number of contacts with other hosts per unit time (McCallum *et al*. 2001), or abiotic/biotic reservoirs for the pathogen are two transmission scenarios that can lead to disease-induced host extinction. In both cases, decreasing host density does not necessarily lead to a decrease in disease transmission. Despite the rarity of disease-induced host extinction (Smith *et al*. 2006), a number of wildlife diseases, such as chytridiomycosis in amphibians, white-nose syndrome in bats, and facial tumour disease in Tasmanian devils, have recently been identified as the causative agents of host declines and population extinctions (Skerratt *et al*. 2007; Blehert *et al*. 2008; McCallum *et al*. 2009).

While the characteristics of the transmission function in these emerging infectious diseases may ultimately determine whether a population experiences disease-induced extinction (McCallum 2012), extinction dynamics will also be influenced by how resistant (i.e. the ability of a host to reduce or eliminate a pathogen conditional on exposure; Boots *et al*. 2009; Medzhitov *et al*. 2012) and/or tolerant (i.e. the ability of a host to persist with a pathogen load that is typically lethal for non-tolerant individuals; Roy & Kirchner 2000; Medzhitov *et al*. 2012) a host is to the pathogen. Therefore, when managing disease-induced declines and extinctions, it may be important to manage not only for the transmission dynamics, but also the level of host tolerance and resistance in a population (Kilpatrick 2006; Langwig *et al*. 2015, 2017; Epstein *et al*. 2016). However, the conditions under which it might be more effective to manage for resistance and tolerance instead of transmission are currently unknown.

Understanding the relative importance of resistance and tolerance compared to transmission in driving extinction dynamics has important implications for managing the emerging amphibian disease chytridiomycosis. Chytridiomycosis is caused by the amphibian chytrid fungus *Batrachochytrium dendrobatidis* (Bd) and has resulted in widespread amphibian declines and extinctions (Daszak *et al*. 2003; Skerratt *et al*. 2007). Bd is a cutaneous fungus that disrupts the osmoregulatory ability of amphibian skin, leading to the potentially fatal disease chytridiomycosis (Voyles *et al*. 2007, 2009). While a

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number of transmission-related factors, including an environmental pool of Bd zoospores and biotic reservoirs, are hypothesised to contribute to disease-induced extinction of amphibian populations (Rachowicz & Briggs 2007; Mitchell *et al*. 2008; Briggs *et al*. 2010; McCallum 2012; Doddington *et al*. 2013), few studies have attempted to quantify the transmission function itself (but see Rachowicz & Briggs (2007) and Bielby *et al*. (2015)). Quantifying the transmission function is important when considering disease-induced extinction because it determines the ability of a pathogen to invade a population as well as drive a host population extinct (De Castro & Bolker 2005; Gerber *et al*. 2005).

In addition to the transmission function, extinction dynamics in amphibian-Bd systems also depend on the dynamics of Bd load on an amphibian host (Briggs *et al*. 2010). Varying Bd load dynamics among amphibian populations, potentially induced by varying resistance and tolerance mechanisms, can promote population-level persistence following epizootics (Retallick *et al*. 2004; Briggs *et al*. 2010; Grogan *et al*. 2016; Savage & Zamudio 2016). This variation in resistance and tolerance could be due to a number of different mechanisms including innate and acquired immune responses (Ellison *et al*. 2015), differences in host susceptibility (Knapp *et al*. 2016), variation in the amphibian microbiome (Harris *et al*. 2009; Jani & Briggs 2014), temperature-dependent Bd growth (Forrest & Schlaepfer 2011; Knapp *et al*. 2011), and variable virulence in Bd strains (Rosenblum *et al*. 2013; Jenkinson *et al*. 2016). Load dynamics are important in Bd systems because disease-induced mortality of amphibians is highly load-dependent, with survival probability sometimes decreasing rapidly at high Bd loads (Stockwell *et al*. 2010; Vredenburg *et al*. 2010). This attribute of load-dependent survival leads to a simple, but largely untested hypothesis in host-pathogen systems: host populations that are either able to prevent large increases in pathogen load (via resistance mechanisms) or tolerate high pathogen loads (via tolerance mechanisms), will experience reduced disease-induced extinction risk, even when the transmission rate is high. This is a general hypothesis for load-dependent wildlife diseases and amphibian-Bd interactions provide an ideal system in which to test it.

The above hypothesis can be phrased as the following question: How important is transmission compared to host tolerance and resistance for mitigating disease-induced extinction? Answering this question requires quantifying the transmission function, something rarely done in amphibian-Bd systems (Kilpatrick *et al*. 2010). Moreover, understanding the role of this transmission function in the ability of Bd to invade an amphibian population will be important for accurately understanding any subsequent Bd-induced extinctions (Gerber *et al*. 2005). Therefore, we also ask two additional questions: What is the nature of the transmission function in amphibian-Bd systems? How does this transmission function affect the ability of Bd to invade an amphibian population? We use a combination of experiments and dynamical models to show that empirical patterns of Bd transmission are best modelled using an environmental Bd pool and that this pool significantly increases the ability of Bd to invade a population and the population-level extinction risk. However, despite this large effect of the environmental pool, we show that host resistance and tolerance are far more influential on Bd-induced extinction dynamics than transmission. This is likely a general property of load-dependent diseases in which non-linear resistance and/or tolerance functions interact such that managing for resistance and tolerance can more effectively mitigate disease-induced extinction than managing for transmission.

METHODS

To answer the questions posed above, we focused on Bd-induced extinction dynamics in the mountain yellow-legged frog complex (*Rana muscosa* and *Rana sierrae*, henceforth *R. muscosa*). *R. muscosa* are native to California's Sierra Nevada mountains and have experienced significant Bd-induced population declines and extinctions over the last four decades (Briggs *et al*. 2005; Vredenburg *et al*. 2010; Briggs *et al*. 2010; Knapp *et al*. 2016). Using this host-parasite system, the *Methods* section is organised as follows.

First, we used a laboratory experiment to quantify the well-known importance of temperature-dependent Bd growth dynamics on *R. muscosa* (Andre *et al*. 2008; Wilber *et al*. 2016). Second, we used a mesocosm experiment to quantify the nature of the transmission function in the *R. muscosa*-Bd system, testing for both density-dependent transmission, frequency-dependent transmission, and transmission from an environmental zoospore pool. Third, we used the results from these experiments to build a discrete-time, host-parasite Integral Projection Model (IPM) and derived R_0 with an environmental zoospore pool. We used this result to explore the effects of the zoospore pool on Bd invasion. Finally, to answer our primary question regarding the relative importance of transmission compared to resistance and tolerance on extinction risk, we extended our model to consist of a within-year component in which Bd transmission and disease-induced amphibian mortality occurred and a between-year component in which *R. muscosa* demographic transitions occurred (Fig. 1). Using this hybrid model, we explored the sensitivity of Bd-induced extinction to transmission, resistance and tolerance.

Laboratory and mesocosm experiments

We used laboratory and mesocosm experiments to quantify the temperature-dependent load dynamics and the transmission dynamics in the *R. muscosa*-Bd system. The laboratory experiment is fully described in Wilber *et al*. (2016) and consisted of 15 adult frogs housed at three different temperatures (4, 12, 20 °C; 5 frogs per temperature). Wilber *et al*. (2016) used this experiment to parameterise four functions relating to Bd load dynamics: a load-dependent host survival function and a temperature-dependent Bd growth function, loss of infection function, and initial infection function (Appendix Fig. S1, see Table 1 for function descriptions).

To quantify the nature of the transmission function in this system, we performed a mesocosm experiment that consisted of four different density treatments: 1, 4, 8 and 16 uninfected adult frogs per mesocosm (volume $\approx$ 1 m^3). Each treatment was replicated four times for a total of 16 mesocosms (see

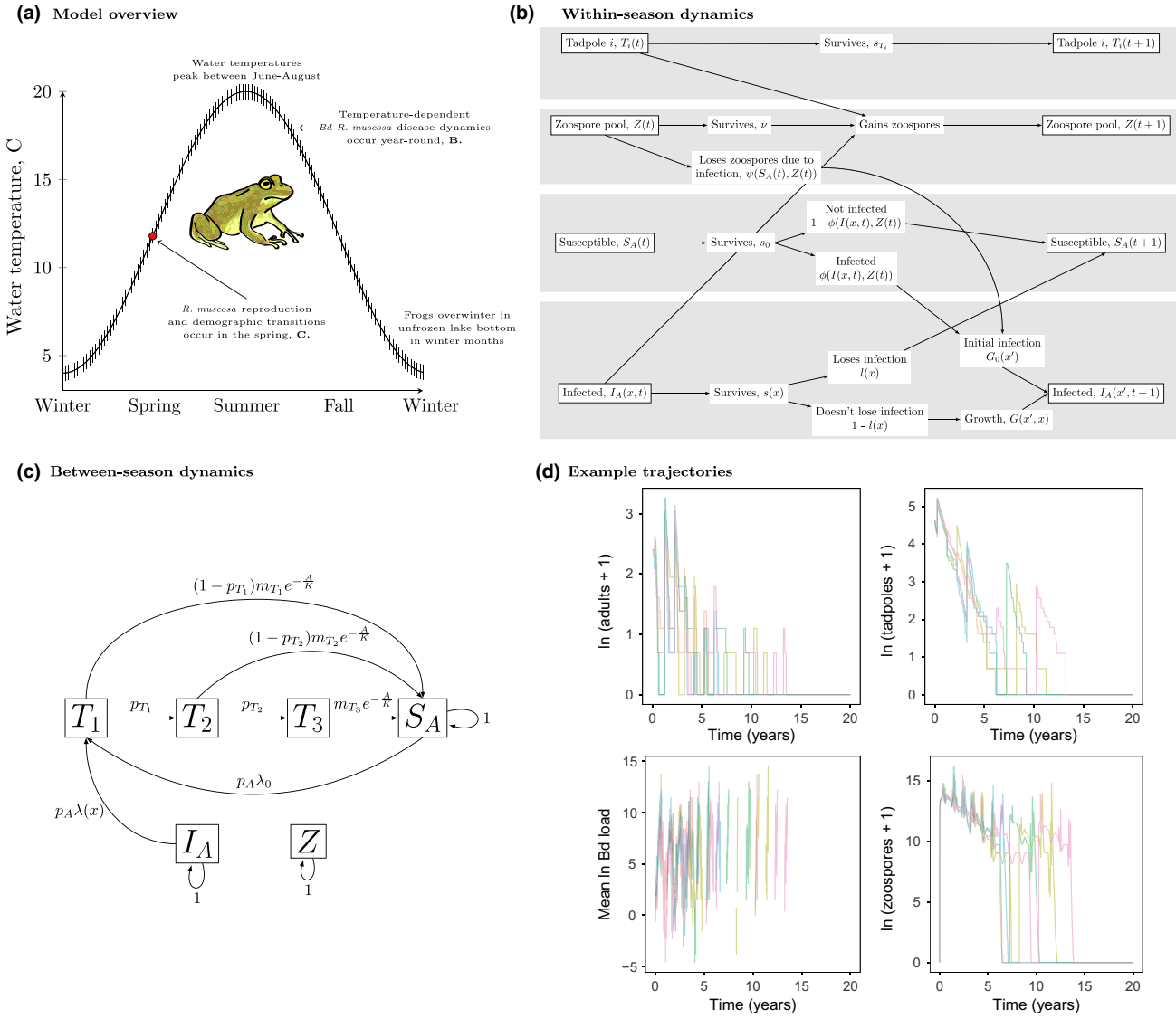

Figure 1 (a) Diagram showing the temporal dynamics of the hybrid model of *R. muscosa*-Bd. Reproduction and demographic transitions occur once a year in the spring (red dot and (c).). Disease dynamics are temperature-dependent and are updated every 3 days (vertical dashes and (b).) over the course of the entire year. (b) The within-season dynamics of *R. muscosa* and Bd. (c) The between season demography of *R. muscosa*. Note that survival probability of susceptible adults (S_A), infected adults (I_A) and Bd zoospores in the environmental pool (Z) is one because their survival probabilities are already accounted for in the within-season model. (d) Representative trajectories of adult, tadpole and zoospore pool population sizes from the hybrid model with a density-dependent transmission function and infection from a dynamic zoospore pool. Five stochastic trajectories are shown from the hybrid model (coloured lines). The mean ln Bd load, conditional on infection, is also shown. Gaps in trajectories for the mean ln Bd load indicate that no infected individuals were in the population at those time points.

Appendix S1). In addition to the uninfected adults, each mesocosm started with five infected tadpoles, which could release Bd zoospores into the environment and subsequently infected adults. All of the adults in a mesocosm were uniquely identifiable by pit tags, but the five tadpoles were not. The experiment ran for 74 days and every 4–8 days all adults and tadpoles in a mesocosm were swabbed and the zoospore load on each was determined using quantitative PCR (Boyle *et al.* 2004). Frogs and tadpoles within a mesocosm were always swabbed on the same day.

To estimate the transmission function, we measured the load transitions on all adult frogs from time t to $t + \Delta t$ over the first 32 days of the experiment (Δt = 4–8 days depending on the time between swabs in the experiment). We only used the first 32 days of the experiment as after this time point all amphibians experienced an unexplained decline in zoospore loads (see Appendix Fig. S2). However, because the load trajectories over these first 32 days were consistent with other experiments (e.g. Wilber *et al.* 2016) and transitions from uninfected to infected tended to occur before day 32, we felt confident in estimating transmission dynamics from only the first 32 days. Moreover, we replicated the experiment *in silico* to demonstrate that we could recover known transmission functions over the first 32 days of the experiment (Appendix S1). As transmission is the probability of an uninfected individual gaining an infection in a time step, we only

Table 1 Parameters used in the *Rana muscosa*-Bd hybrid model

Description	Functional form	Parameters	Details of parameterisation
Infected survival function, $s(x)$: Probability of host survival from t to $t+1$ with load x	$\text{logit}[s(x)] = b_{0,0} + b_{1,0}x$	$b_{0,0} = 5.295$; $b_{1,0} = -2.595$	*Likelihood* Bernoulli($s(x)$), x was z-transformed Appendix Fig. S1b.
Growth function, $G(x',x)$: Probability density of host transitioning from load x to load x' at time $t+1$	$\mu(x,T) = b_{0,1} + b_{1,1}x + b_{2,1}T$ $\sigma^2(x) = v_{0,1} \exp(2c_{0,1}x)$	$b_{0,1} = 0.012$; $b_{1,1} = 0.799$; $b_{2,1} = 0.092$; $v_{0,1} = 5.92$; $c_{0,1} = -0.049$	*Likelihood* Normal($\mu(x,T),\sigma^2(x)$) Appendix Fig. S1a.
Loss of infection function, $l(x)$: The probability of host having infection of load x at t and losing it by $t+1$	$\text{logit}[l(x,T)] = b_{0,2} + b_{1,2}x + b_{2,2}T$	$b_{0,2} = 1.213$; $b_{1,2} = -0.472$; $b_{2,2} = -0.151$	*Likelihood* Bernoulli($l(x,T)$) Appendix Fig. S1c.
Initial infection burden function, $G_0(x')$: Probability density of being uninfected at t and gaining an infection of x' at $t+1$	$\mu(T) = b_{0,3}+b_{1,3}T$ $\sigma^2(T) = v_{0,3} \exp(2c_{0,3}T)$	$b_{0,3} = 0.642$; $b_{1,3} = 0.137$; $v_{0,3} = 0.59$; $c_{0,3} = 0.063$	*Likelihood* Normal($\mu(T),\sigma^2(T)$) Appendix Fig. S1d.
Transmission function, ϕ: The probability of an uninfected host gaining an infection at time $t+1$	Functional forms vary	See Table 2	See Table 2
Uninfected adult survival probability over three day time step, s_0	Constant	$s_0 = 0.999$	Yearly survival from Briggs *et al.* (2005) converted to a three day time scale
Temperature-dependent zoospore survival probability, v	$v = f(T)$	Non-parametric	Cubic smoothing spline based on data from Woodhams *et al.* (2008) Appendix Fig. S1e.
Proportion of zoospores contributed to Z by infected adult	Constant	$\mu_A = 1$	Likely a conservative estimate of how infected adults contribute to the zoospore pool
Mean tadpole zoospore load, μ_{T_i}	Constant	$\mu_{T_i} = 1487.036$	Mean zoospore load of tadpoles in mesocosm experiment described in text
Probability of tadpole i surviving a three day time step	Constant	$s_{T_1} = 0.987$; $s_{T_2} = 0.997$; $s_{T_3} = 0.997$	Yearly survival from Briggs *et al.* (2005) converted to a three day time scale
Probability of tadpole i not metamorphosing, p_{T_i}	Constant	$p_{T_1} = 1$; $p_{T_2} = 0.5$; $p_{T_3} = 0$	Briggs *et al.* (2005)
Probability of tadpole i surviving metamorphosis, m_{T_i}	Constant	$m_{T_1} = 0.9$; $m_{T_2} = 0.9$; $m_{T_3} = 1.0$	Briggs *et al.* (2005)
Probability of adult reproducing, p_A	Constant	$p_A = 0.25$	Briggs *et al.* (2005)
Mean adult reproductive output, λ	Constant	$\lambda(x) = \lambda_0 = \lambda = 50$	Leads to realistic population-level growth rate of $\lambda_{\text{growth rate}} \approx 1.46$ in the disease-free, density-independent model (Briggs *et al.* 2005)
Carrying capacity parameter, K	Constant	$K = 5$	Leads to equilibrium adult densities between 10-15 adults per m^3 in disease-free model

All b and c parameters had a Normal prior with mean 0 and standard deviation 5. All v parameters had a half-Cauchy prior from 0 to ∞ with scale parameter 1. For all statistical models, convergence was assessed using traceplots and ensuring that the Gelman-Rubin statistic was < 1.05 (Gelman *et al.* 2014). *logit* specifies a logistic link, x is ln zoospore load, and T is temperature. All probabilities are over a three day time step.

included transitions where Bd load was 0 at time t (n = 333). If the load at time $t + \Delta t$ was positive we assigned this data point a value of 1 (infected) and if the load was still zero we assigned it a value of 0 (uninfected).

Uninfected frogs can acquire Bd infection through contact with other infected frogs and through contact with zoospores in an environmental Bd pool (Courtois *et al.* 2017). To account for these different pathways, we fit two sets of transmission models to the data. The first set of models assumed a constant level of infection from the zoospore pool and either density-dependent or frequency-dependent transmission from conspecifics (Table 2). The second set of models allowed transmission to be a function of how many zoospores were in the zoospore pool at time t in addition to either density-dependent or frequency-dependent transmission. In Appendix S1, we describe how we defined and fit our transmission models with a dynamic zoospore pool. In short, we used the transmission function $\phi(t) = 1 - \exp(-\Lambda(Z(t), I(t))\Delta t)$ and allowed for the zoospore pool $Z(t)$ at time t to be an unobserved, dynamic variable that lost zoospores due to environmental decay and gained zoospores due to production from infected adults and tadpoles at every time step. $I(t)$ is the number of infected adults at time t. Table 2 gives the transmission functions and the resulting fits to the data from the mesocosm experiment.

The host-parasite IPM and R_0

The host-parasite IPM

Using the aforementioned laboratory and mesocosm experiments, we parameterised a host-parasite Integral Projection Model (IPM) where Bd load on an individual frog was the continuous trait being modelled (Fig. 1b; Metcalf *et al.* 2015; Wilber *et al.* 2016). Bd load on a frog is estimated as the number of copies of Bd DNA detected on standardised skin swabs via quantitative PCR (Boyle *et al.* 2004) and provides a continuous measure of infection intensity between 0 (uninfected) and an arbitrarily large Bd infection. The IPM is a discrete time model and here a single time step is three days. This time step is on the same scale as the generation of time of Bd, which ranges between 4–10 days depending on temperature (Piotrowski *et al.* 2004; Woodhams *et al.* 2008). We used the discrete-time IPM because it is easily parameterised from laboratory data which is collected at discrete time intervals.

This IPM tracks two discrete stages at time t: the density of susceptible adults $S_A(t)$ in the population and the density of zoospores in the environment $Z(t)$. This model also tracks a continuous, infected stage $I_A(x, t)$ where x is ln Bd load and $\int_{L_x}^{U_x} I_A(x,t)dx$ gives the density of adult frogs with a ln Bd load between a lower bound L_x and an upper bound U_x at time t. This continuous, infected stage tracks the distribution of Bd loads at any time t in the population.

Considering these discrete and continuous stages, the amphibian-Bd IPM can be written as follows (Fig. 1b)

$$S_A(t+1) = S_A(t)s_0(1-\phi) + \int_{L_x}^{U_x} I_A(x,t)s(x)l(x)dx \quad (1)$$

$$I_A(x', t+1) = \int_{L_x}^{U_x} I_A(x,t)s(x)(1 - l(x))G(x',x)dx + S_A(t)s_0\phi G_0(x') \quad (2)$$

$$Z(t+1) = Z(t)\nu + \mu_A \int_{L_x}^{U_x} \exp(x)I_A(x,t)dx - \psi(S_A(t), Z(t)) \quad (3)$$

$S_A(t + 1)$ describes the density of susceptible adults at time $t + 1$ and is determined by the number of adults that survive and do not become infected in a time step (first term in eqn 1) and the number of infected adults that survive and lose their infection in a time step (second term in eqn 1). $I_A(x',t + 1)$ describes the density of infected adults with a ln Bd load x' at time $t + 1$ and is determined by infected adults who survive with load x, do not lose their load x, and experience a change in load from x to x' in a time step (first term in eqn 2) and from uninfected adults who survive, become infected, and gain an initial Bd load of x' in a time step (second term in eqn 2). The vital rate functions contained in eqns 1–3 are described in Fig. 1b and Table 1.

The equation $Z(t + 1)$ gives the density of zoospores in the zoospore pool at time $t + 1$. $Z(t + 1)$ depends on three distinct terms: the survival probability of the zoospores in the environment from time t to $t + 1$ (ν), contribution of zoospores from infected adults where μ_A is the proportion of total zoospores on adults contributed to the zoospore pool over a time step, and removal of zoospores from the zoospore pool by frogs transitioning from uninfected to infected. This removal term $\psi(S_A(t),Z(t))$ had very little effect on the dynamics of the system and we do not consider it further.

Based on the laboratory experiment described above and known Bd life history (Woodhams *et al.* 2008), we allowed various vital rate functions to be temperature-dependent (e.g. the survival of free-living zoospores, Table 1, Appendix Fig. S1).

R_0 with an environmental reservoir

Using the IPM described in eqns 1–3, we calculated R_0 to quantify how temperature and the transmission dynamics affected the ability of Bd to invade a *R. muscosa* population – a necessary condition for Bd-induced population declines and extinction. R_0 describes the average number of secondary infections produced over the lifetime of an average infected agent (Diekmann *et al.* 1990; Dietz 1993). When $R_0 \leq 1$, a pathogen cannot invade a fully susceptible host population. When $R_0 > 1$, a pathogen can invade a fully susceptible host population with probability $1-(1/R_0)$ (Gerber *et al.* 2005; Allen 2015).

In Appendix S2 we show that, consistent with continuous-time disease models (Rohani *et al.* 2009), R_0 for discrete-time IPMs with an environmental reservoir is composed of transmission from host contact and the environment. We use this result in combination with our fully parameterised host-parasite IPM to calculate the temperature-dependent R_0 for *R. muscosa*-Bd systems with and without infection from the environmental zoospore pool.

The hybrid model

The model described by eqns 1–3 is sufficient to describe the dynamics of an initial epizootic, but to examine Bd-induced extinction dynamics in *R. muscosa* populations a number of additions need to be made. We briefly describe the hybrid model that accounts for the within-year Bd dynamics as well as the between year demography of *R. muscosa*. Fig. 1 gives a visual representation of the hybrid model and Appendix S3 gives a full description.

The within-year component (Fig. 1b.), is identical to the IPM given in eqns 1–3 with the addition of three tadpole stages. The tadpole stage of *R. muscosa* is likely important in generating enzootic dynamics in *R. muscosa* populations (Briggs *et al.* 2005, 2010). We assumed all tadpoles were immediately infected with Bd and had a constant mean contribution to the zoospore pool (Table 1). This is justified by the observation that most tadpoles in *R. muscosa* populations carry high fungal loads, even in enzootic populations (Briggs *et al.* 2010). *R. muscosa* tadpole survival is not affected by Bd infection. Therefore, the within-season dynamics of the tadpole stages were simply given by the probability of a tadpole surviving from time t to $t + 1$. Infected tadpoles also contributed to the zoospore pool at each time step (Fig. 1b).

R. muscosa populations also experience seasonal temperature fluctuations in which winter lake temperatures drop to *c.* 4 °C in the winter (in the unfrozen portion of a lake where the frogs overwinter) and reach *c.*20 °C in the summer (Knapp *et al.* 2011). We accounted for this seasonal variability by imposing a deterministically fluctuating environment on the *R. muscosa*-Bd IPM (Fig. 1a). At each discrete time point within a season, a new temperature was calculated and the temperature-dependent vital rate functions were updated accordingly.

The between-year component of the hybrid model accounted for yearly maturation and metamorphosis of the tadpole stages as well as reproduction of adults (Fig. 1c). We assumed that the recruitment of metamorphed tadpoles into the adult stage was density-dependent and that all tadpoles entered the adult stage as uninfected (i.e. all individuals are infected as tadpoles, but lose their infection at metamorphosis, Briggs *et al.* 2010). Because we have no empirical evidence for Bd-induced fertility reduction in *R. muscosa*, we assumed that reproduction in uninfected and infected adults was the same.

Simulating the hybrid model

After parameterising the hybrid model using the above experiments, we used the model to make predictions about the probability of disease-induced host extinctions. Because demographic stochasticity is important when predicting extinction for small populations (Lande *et al.* 2003), we included it into the hybrid model (Caswell 2001; Schreiber & Ross 2016). To do this, we first discretised the within-season IPM using the mid-point rule and 30 mesh points (Easterling *et al.* 2000) and then determined the transition of an individual frog or zoospore to another state (including death) as a draw from a multinomial distribution with probabilities given by the discretised hybrid model at that time step (Appendix S4). In addition, we assumed that both the production of tadpoles that occurs once a year in the spring and the number of zoospores shed into the zoospore pool at each time step followed a Poisson distribution (Appendix S4).

To answer our question regarding the importance of transmission, resistance, and tolerance on Bd-induced extinction, we performed two analyses. First, we examined how different transmission functions parameterised from our mesocosm experiment affected extinction risk. Using the three transmission functions with a dynamic zoospore pool described in Table 2 and the parameter values given in Table 1, we performed 500 stochastic simulations of the hybrid model to generate time-dependent extinction curves over a 25 year period. All simulations were started with 10 uninfected adult frogs, 85 year-one tadpoles (T_1), 12 year-two tadpoles (T_2), and 3 year-three tadpoles (T_3). The relative proportions of adult frogs and tadpoles were assigned based on the stable stage distribution in the Bd-free model. While the initial conditions necessarily affect the absolute time to extinction, they do not affect the shapes of the extinction curves for different transmission functions relative to each other. All simulations started in the winter at 4 °C, with reproduction occurring in the first spring at 12 °C (Fig. 1a). Given our analysis of R_0 in the previous section, we assumed that Bd could invade with a probability of one, such that tadpoles were immediately infected with Bd and began contributing to the zoospore pool $Z(t)$ (see Appendix S4). For each simulation, we calculated time-dependent extinction curves as the mean probability of going extinct in a given time step over all 500 simulations.

Second, we performed a sensitivity analysis on the hybrid model to assess the relative importance of transmission compared to resistance and tolerance. Transmission was determined by the parameters in the transmission function ϕ, resistance was determined by the parameters in the growth function $G(x',x)$, the loss of infection function $l(x)$, and the initial infection burden function $G_0(x')$, and tolerance was determined by the parameters in the survival function $s(x)$. To perform the sensitivity analysis, we ran 1000 simulations using the parameter values given in Table 1 and the initial conditions described above. For each simulation we recorded whether or not a *R. muscosa* population went extinct in $\leq$ 8 years, as this was where extinction probability was *c.*50% with the default parameter values.

On each run of the simulation we perturbed sixteen lower-level transmission, resistance and tolerance parameters by, for each parameter, drawing a random number from a lognormal distribution with median 1 and dispersion parameter $\sigma_{\text{sensitivity}} = 0.3$ and multiplying the given parameter by this random number (Sobie 2009). Our results were robust to our choice of σ and our method of perturbation (Appendix Fig. S3). For each simulation, we saved the perturbed parameter values and stored them in a 1000 by 16 parameter matrix. Upon completion of the simulation, we used both regularised logistic regression and a Random Forest classifier in which our response variable was whether or not a given simulation went extinct and our predictor variables were the scaled (i.e. z-transformed)

matrix of perturbed predictors (Harper *et al*. 2011; Pedregosa *et al*. 2011; Lee *et al*. 2013). Using this approach, we could then identify the relative importance of each parameter in the vital rate functions in predicting whether or not extinction occurred (Sobie 2009). Moreover, we also built a pruned regression tree to visualise the interactive effects of transmission, resistance, and tolerance parameters on host extinction risk (Harper *et al*. 2011). All the code necessary to replicate the analyses is provided at https://github.com/mqwilber/host_extinction.

RESULTS

Question 1: What is the structure of the transmission function?

Accounting for the dynamics of the environmental zoospore pool resulted in significantly better transmission models compared to those that did not. The transmission model with density-dependent host to host transmission as well as transmission from a dynamic zoospore pool was a better model than all other transmission models considered (Table 2). In addition to being a better model in terms of WAIC, the density-dependent transmission model also captured the marginal pattern of increasing probability of infection with increasing density of infected hosts (Appendix Fig. S4).

Question 2: How does the transmission function affect the ability of Bd to invade?

Using the temperature-dependent vital rate functions described in Table 1 and the best-fitting density-dependent transmission function with an environmental zoospore pool (Table 2), we examined how host density and temperature affected the ability of Bd to invade a *R. muscosa* population. When transmission was density-dependent, but did not depend on the environmental zoospore pool, Bd was able to invade *R. muscosa* populations over a large range of densities and temperatures, though there was a slight protective effect of low temperatures and low densities (Fig. 2a). Including transmission from the environmental zoospore pool substantially increased the region in which Bd could invade and invasion was highly probable for most temperatures and host densities (Fig. 2b and c).

Question 3: How sensitive is disease-induced extinction to transmission, resistance and tolerance?

The time-dependent probability of extinction was similar between the three transmission functions that included a dynamic zoospore pool (Appendix Fig. S5, Table 2). The similarity between these curves was due to the overwhelming influence of the infection probability from the zoospore pool, which swamped out the well-known differences between frequency-dependent and density-dependent transmission functions. Drastically decreasing zoospore survival probability below what has been observed in laboratory experiments (Woodhams *et al*. 2008), led to an expected reduction in extinction risk as the transmission probability then declined with decreasing host density (given density-dependent transmission, Appendix Fig. S5).

A sensitivity analysis of Bd-induced host extinction to transmission, host resistance, and host tolerance showed that, regardless of the transmission function used, *R. muscosa* extinction was more sensitive to the parameters relating to host resistance and tolerance than to parameters relating to transmission (Fig. 3). In particular, the most important parameter across all transmission functions was the slope of the growth function $b_{1,1}$, which is a parameter affecting host resistance. For a given temperature, the logistic regression analysis showed that decreasing this parameter, which roughly corresponds to decreasing the mean Bd load on a host for a given temperature, decreased the probability of disease-induced extinction for all transmission functions (Fig. 3a–c). Bd-induced *R. muscosa* extinction was also sensitive to the parameters of the survival function, particularly the intercept of the survival function $b_{0,0}$. This parameter can be thought of as the threshold at which Bd-induced mortality begins to occur given a fixed slope in the survival function. The logistic regression analysis showed that increasing this parameter, which corresponds to increasing the threshold at which *R. muscosa* begins to suffer load-dependent Bd mortality, decreased the probability of extinction (Fig. 3a–c).

Resistance and tolerance parameters also showed significant interactions when affecting host extinction risk. Random forests and pruned regression trees showed the importance of the slope of the growth function as well as the importance of the interaction between this parameter and the intercept of

Table 2 The results of fitting transmission functions of the form $\phi=1-\exp(-\Lambda)$ to the *R. muscosa*-Bd mesocosm experiment. I is the total number of infected adults in a mesocosm at the beginning of a time interval, A is the total number of adults in a tank, Z is the number of zoospores in the mesocosm at the beginning of the time interval as estimated from a latent zoospore pool model (Appendix S1), and Δt is the time between swabbing events in the experiment (between 4 and 8 days). All β parameters had a half-Cauchy prior from 0 to ∞ with scale parameter equal to 1. Models with lower WAICs and higher weights are better models. The bold value indicates the lowest WAIC.

Name	Function	Parameters	WAIC (weight)
Constant zoospore pool	$\Lambda = (\beta_0)\Delta t$	$\beta_0 = 8.07 \times 10^{-2}$ day^{-1}	401.1 (0)
Density-dependent w/ constant zoospore pool	$\Lambda = (\beta_0+\beta_1 I)\Delta t$	$\beta_0 = 4.18 \times 10^{-2}$, $\beta_1 = 5.25 \times 10^{-2}$	336.7 (0)
Frequency-dependent w/ constant zoospore pool	$\Lambda = (\beta_0 + \beta_1 \frac{I}{A})\Delta t$	$\beta_0 = 4.28 \times 10^{-2}$, $\beta_1 = 0.551$	336.6 (0)
Dynamic zoospore pool	$\Lambda = (\beta_0 \ln(Z + 1))\Delta t$	$\beta_0 = 1.09 \times 10^{-2}$	345.32 (0)
Density-dependent w/ dynamic zoospore pool	$\Lambda = (\beta_0 \ln(Z + 1)+\beta_1 I)\Delta t$	$\beta_0 = 5.29 \times 10^{-3}$, $\beta_1 = 7.52 \times 10^{-2}$	**301.18** (0.99)
Frequency-dependent w/ dynamic zoospore pool	$\Lambda = (\beta_0 \ln(Z+1) + \beta_1 \frac{I}{A})\Delta t$	$\beta_0 = 5.77 \times 10^{-3}$, $\beta_1 = 0.627$	311.06 (0.01)

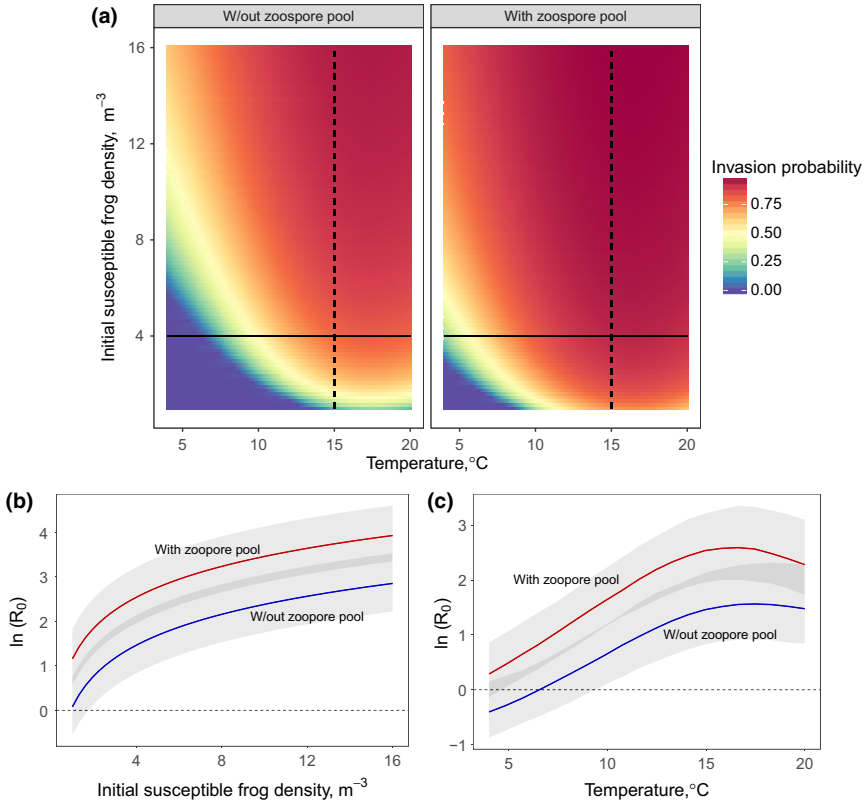

Figure 2 R_0 and the invasion probability of Bd ($1 - \frac{1}{R_0}$) for different temperatures and host densities with and without an environmental zoospore pool. This calculation of R_0 uses the parameters given in Table 1 and the 'Density dependent w/ dynamic zoospore pool' transmission function in Table 2. While R_0 will inevitably decrease without transmission from a zoospore pool (i.e. when β_0=0; see Appendix S2), the magnitude of that decrease depends on the estimated transmission coefficient from the zoospore pool. (a) Gives the invasion probability of Bd. The dashed, vertical lines in a. correspond to the curves shown in (b), where ln (R_0) is plotted against initial adult density when temperature is 15 °C. The solid, horizontal lines in a. correspond to the curves shown in (c) where ln (R_0) is plotted against temperature when initial adult density is four adults per m^3. The grey regions give the 95% credible intervals. The dashed lines in (b) and (c) correspond to R_0 = 1 (ln (R_0) = 0), below which Bd cannot invade.

the survival function (a tolerance parameter) and the temperature-dependency in the growth function (a resistance parameter) (Fig. 3a–c; Appendix Fig. S6a–c).

DISCUSSION

Wildlife conservation in the face of disease emphasises the importance of the transmission function in extinction risk (McCallum 2012). This is a reasonable emphasis as the transmission function is ultimately the most important aspect of disease-induced extinction: if a host does not get infected with a disease it will not suffer disease-induced mortality. In amphibian-Bd systems it has been hypothesised that both amphibian density and an environmental pool of zoospores can affect transmission (Rachowicz & Briggs 2007; Briggs *et al.* 2010; Courtois *et al.* 2017), but the nature of this transmission has rarely been quantified. We experimentally quantified the transmission function in the *R. muscosa*-Bd system and used these results, in combination with a dynamic model, to predict how the environmental zoospore reservoir affected the ability of Bd to invade an amphibian population. Consistent with previous theory (Godfray *et al.* 1999; Rohani *et al.* 2009), we found that including an environmental zoospore pool substantially increased R_0 for *R. muscosa*-Bd systems, such that Bd was able to invade a *R. muscosa* population for most realistic temperatures and host densities. To the best of our knowledge, this is the first estimation of R_0 in an amphibian-Bd system (but see Woodhams *et al.* 2011, for a discussion of R_0 in amphibian-Bd systems), and the large value of R_0 across all temperatures and densities is consistent with field observations that temperature and density have little protective effect in the *R. muscosa*/*sierrae* system (Knapp *et al.* 2011, R. A. Knapp *et al.*, unpublished). These results suggest that attempting to prevent Bd invasion into a system may be largely futile and management should be focused on mitigating post-invasion Bd impacts (Langwig *et al.* 2015).

Conditional on Bd invasion, we used our parameterised model to explore the importance of the transmission function on Bd-induced amphibian extinction and found that the extinction dynamics were similar between all transmission models with a dynamic zoospore pool. This was due to the large number of zoospores shed by infected amphibians combined with the laboratory-estimated decay rate of zoospores outside the host, leading to a zoospore pool that remained large even for rapidly declining host populations (Fig. 1d). Only considering this result, we would then expect *R. muscosa* populations to be at substantial risk of disease-induced extinction given that the persisting zoospore pool prevents a

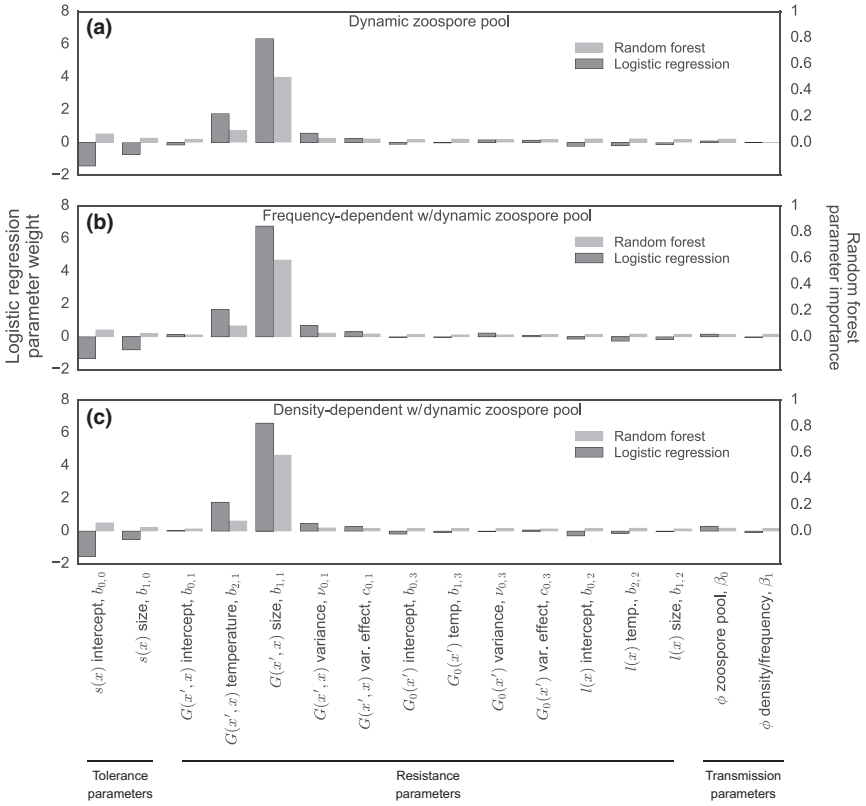

Figure 3 (a–c) The sensitivity of *R. muscosa* extinction probability to parameters dictating transmission, resistance and tolerance of Bd for the three transmission functions used in the hybrid model. The dark grey bars give the weights of the various parameters when logistic regression is used to classify whether or not a simulation trajectory experienced extinction. The absolute height of the bar shows the relative importance of that parameter and the direction specifies what happens to the extinction probability when that parameter is increased. For example, increasing the $G(x',x)$ parameter $b_{1,1}$ increases the probability of extinction. The light grey bars give the relative importances of each parameter in predicting the extinction of a simulation when a Random Forest classifier was used to account the interactions between parameters on extinction probability. These values are all between zero and one and the height of a bar indicates the relative importance of a transmission, resistance, or tolerance parameter.

decrease in transmission rate with declining host density (Anderson & May 1981; Godfray *et al.* 1999; De Castro & Bolker 2005). This finding is consistent with a number of other studies that have found that the dynamics of the Bd zoospore pool are critical for determining Bd-induced amphibian extinctions (Mitchell *et al.* 2008; Briggs *et al.* 2010; Doddington *et al.* 2013). If abiotic or biotic factors such as temperature, stream flow, water chemistry, and/or zoospore consumption by aquatic organisms are able to substantially increase zoospore death rate beyond the values seen in the lab (Tunstall 2012; Strauss & Smith 2013; Venesky *et al.* 2013; Heard *et al.* 2014; Schmeller *et al.* 2014), then we might expect a reduction, though not an elimination, of Bd invasion probability and amphibian extinction risk.

However, considering only the transmission function ignores the fact that, conditional on infection, increasing resistance or tolerance to a disease can also reduce disease-induced mortality and thus provide alternative mechanisms by which to manage disease-induced extinction risk (Kilpatrick 2006; Vander Wal *et al.* 2014; Langwig *et al.* 2015). Using our model, we found that Bd-induced extinction risk was far more sensitive to host resistance and tolerance than to the transmission dynamics of Bd. In particular, extinction risk of *R. muscosa* populations was most sensitive to the vital rate functions dictating the growth rate of Bd on a host, the load-dependent survival probability, and the interaction between these two functions.

This result highlights the importance of accounting for the load-dependent nature of vital rate functions when considering extinction risk in load-dependent diseases such as chytridiomycosis. In this study, consistent with results observed in the field (Vredenburg *et al.* 2010), the survival function of Bd was strongly non-linear such that above ≈9 ln zoospores =8103 zoospores the survival probability of *R. muscosa* rapidly declined (Appendix Fig. S1b). When the survival function is load-dependent and highly non-linear, as observed in some amphibian-Bd systems (Stockwell *et al.* 2010; Vredenburg *et al.* 2010, but see Clare *et al.* 2016), small changes in host resistance or tolerance can lead to abrupt changes in survival probability. In particular, non-linearities in the survival function (i.e. tolerance) need to be considered in the context of the shape of the growth function (i.e. resistance) of a parasite on its host.

To illustrate the generality of this result, consider the following graphical argument. Take a pathogen growth function ($G(x', x)$) that predicts a static mean pathogen load near the threshold at which the survival function predicts a drastic decrease in survival probability (Fig. 4, i.e. a non-linear dose-

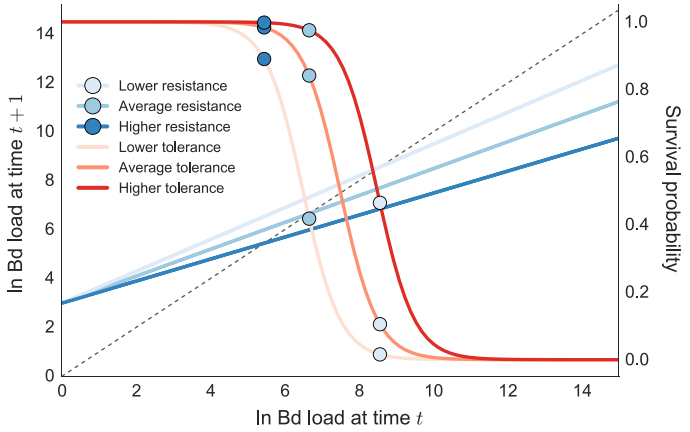

Figure 4 The interaction between the growth function determining host resistance (blue lines) and the survival function determining host tolerance (red lines) has large impacts on host survival probability. The solid blue lines of different shades give three different growth functions that describe how Bd load changes from time step t to time step $t + 1$. The growth functions have different slopes representing different levels of resistance. When one of the growth functions crosses the dashed 1:1 line, this indicates that the Bd load at time t will be the same as the Bd load at time $t + 1$ (i.e. stasis). The red lines of different colours specify different survival functions with different levels of tolerance. The corresponding blue coloured circle on one of the red survival curves gives the probability of a host surviving a time step with the given Bd load at stasis. Each red survival curve has three different blue dots for each of the three growth functions. Because of the strong non-linearity of the survival function, changes in the Bd load at stasis can lead to disproportionate changes in survival probability. However, the direction and magnitude of these changes depends on the degree of tolerance represented in the survival curve.

response curve; Dwyer *et al.* 1997; Handel & Rohani 2015; Louie *et al.* 2016). Slightly shifting the slope (or the intercept) of the growth function (i.e. changing resistance) up or down will increase or decrease the static mean pathogen load and move a host into the region of the survival curve where either mortality or survival is almost certain (Fig. 4). Similarly, holding the growth function constant and altering the survival function (i.e. changing tolerance) will change how close the static mean pathogen load is to the survival function threshold (Fig. 4). This suggests that identifying how the growth function of a pathogen changes in resistant host populations, whether by decreasing the slope, decreasing the intercept or by transitioning from a linear to a non-linear function (Langwig *et al.* 2017), is important for understanding the sensitivity of extinction risk to both the growth function (resistance) and the survival function (tolerance). Identifying whether or not a disease system shows this strong interaction between resistance and tolerance can help determine whether disease mitigation should focus on reducing parasite loads via strategies such as inducing acquired immunity, microbial treatments, or selecting for resistance (Harris *et al.* 2009; Langwig *et al.* 2015) or decreasing parasite transmission via strategies such as culling and/or treating the disease reservoir (Cleaveland *et al.* 2001).

The importance of host resistance and tolerance for our model's predictions of disease-induced extinction indicates that these host strategies could promote population persistence in *R. muscosa*-Bd populations, as they have in other species of amphibians suffering from chytridiomycosis, bats suffering from white-nose syndrome, and Tasmanian devils suffering from facial tumour disease (Hoyt *et al.* 2016; Savage & Zamudio 2016; Epstein *et al.* 2016; Langwig *et al.* 2017). In fact, a recent study showed that many populations of *R. sierrae* that experienced Bd-induced population declines over the last four decades are recovering in the presence of Bd, but with reduced Bd loads relative to naive populations (Knapp *et al.* 2016). This result is consistent with resistance mechanisms reducing Bd load and thus increasing host survival probability. While changes in resistance mechanisms, and not tolerance mechanisms, are putatively responsible for persistence in a number of load-dependent diseases (Savage & Zamudio 2011; Epstein *et al.* 2016; Langwig *et al.* 2017), our results show that the shape of the tolerance function is critical for understanding the effects of resistance on host persistence (Fig. 4). An important future direction will be to explore how heterogeneities in host resistance, tolerance, and/or transmission functions can promote host persistence (Boots *et al.* 2009; Langwig *et al.* 2015; Brunner *et al.* 2017).

While our study suggests that an interaction between resistance and tolerance promotes population persistence in *R. musocsa*-Bd populations, additional mechanisms that we do not consider here are likely important in other amphibian-Bd systems. For example, laboratory studies have shown that Bd can evolve increased or reduced virulence in as few as 50 generations (less than one year, Langhammer *et al.* 2013; Voyles *et al.* 2014; Refsnider *et al.* 2015). If Bd virulence attenuates over the course of an epizootic, these changes could augment host persistence, without any changes in host resistance or tolerance. In reality, the evolution of both the pathogen and the host affects population persistence (Vander Wal *et al.* 2014) and developing load-dependent models that incorporate both of these processes is an open challenge in wildlife epidemiology.

The emergence of a number of diseases of conservation concern have highlighted the importance of considering disease-induced extinction in the context of load-dependent parasite dynamics. We show that simultaneously considering transmission, resistance, and tolerance, in conjunction with load-dependent dynamics, provides novel insight regarding how to best manage emerging infectious diseases.

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AUTHORSHIP

C.B., M.T. and R.K. designed and implemented the laboratory and mesocosm experiments. M.W. and C.B. designed

and performed the analyses. M.W. drafted the manuscript and all authors contributed to revisions.

DATA ACCESSIBILITY

Data supporting the results are available from the Dryad Digital Repository: http://dx.doi.org/10.5061/dryad.p614h

REFERENCES

Allen, L.J.S. (2015). *Stochastic Population and Epidemic Models: Persistence and Extinction*. Springer International Publishing, London.

Anderson, R.M. & May, R.M. (1981). The population dynamics of microparasites and their invertebrate hosts. *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, 291, 451–524.

Andre, S.E., Parker, J. & Briggs, C.J. (2008). Effect of temperature on host response to Batra- chochytrium dendrobatidis infection in the mountain yellow-legged frog (*Rana muscosa*). *J. Wildl. Dis.*, 44, 716–720.

Bielby, J., Fisher, M.C., Clare, F.C., Rosa, G.M. & Garner, T.W.J. (2015). Host species vary in infection probability, sub-lethal effects, and costs of immune response when exposed to an amphibian parasite. *Sci. Rep.*, 5, 1–8.

Blehert, D.S., Hicks, A.C., Behr, M., Meteyer, C.U., Berlowski-Zier, B.M., Buckles, E.L. *et al.* (2008). Bat white-nose syndrome: an emerging fungal pathogen? *Science*, 323, 227.

Boots, M., Best, A., Miller, M.R. & White, A. (2009). The role of ecological feedbacks in the evolution of host defence: what does theory tell us? *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, 364, 27–36.

Boyle, D.G., Boyle, D.B., Olsen, V., Morgan, J.A.T. & Hyatt, A.D. (2004). Rapid quantitative detection of chytridiomycosis (*Batrachochytrium dendrobatidis*) in amphibian samples using real-time Taqman PCR assay. *Dis. Aquat. Organ.*, 60, 141–8.

Briggs, C.J., Knapp, R.A. & Vredenburg, V.T. (2010). Enzootic and epizootic dynamics of the chytrid fungal pathogen of amphibians. *Proc. Natl Acad. Sci. USA*, 107, 9695–9700.

Briggs, C.J., Vredenburg, V.T., Knapp, R.A. & Rachowicz, L.J. (2005). Investigating the populationlevel effects of chytridiomycosis: an emerging infectious disease of amphibians. *Ecology*, 86, 3149–3159.

Brunner, J.L., Beaty, L., Guitard, A. & Russell, D. (2017). Heterogeneities in the infection process drive ranavirus transmission. *Ecology*, 98, 576–582.

Caswell, H. (2001). *Matrix Population Models: Construction, Analysis, and Interpretation*. 2nd edn. Sinauer, Sunderland, MA.

Clare, F., Daniel, O., Garner, T. & Fisher, M. (2016). Assessing the ability of swab data to determine the true burden of infection for the amphibian pathogen *Batrachochytrium dendrobatidis*. *EcoHealth*, 13, 360–367.

Cleaveland, S., Hess, G.R., Dobson, A.P., Laurenson, M.K., McCallum, H.I., Roberts, M.G. & Woodroffe, R. (2001). The role of pathogens in biological conservation. In: *The Ecology of Wildlife Diseases* (eds Hudson, P.J., Rizzoli, A., Grenfell, B., Heesterbeek, H. & Dobson, A.). Oxford University Press, Oxford, pp. 139–150.

Courtois, E.A., Loyau, A., Bourgoin, M. & Schmeller, D.S. (2017). Initiation of *Batrachochytrium dendrobatidis* infection in the absence of physical contact with infected hosts - a field study in a high altitude lake. *Oikos*, 126, 843–851.

Daszak, P., Cunningham, A.A. & Hyatt, A.D. (2003). Infectious disease and amphibian population declines. *Divers. Distrib.*, 9, 141–150.

De Castro, F. & Bolker, B. (2005). Mechanisms of disease-induced extinction. *Ecol. Lett.*, 8, 117–126.

Diekmann, O., Heesterbeek, J.A.P. & Metz, J.A.J. (1990). On the definition and the computation of the basic reproduction ratio R0 in models for infectious diseases in heterogeneous populations. *J. Math. Biol.*, 28, 365–382.

Dietz, K. (1993). The estimation of the basic reproduction number for infectious diseases. *Stat. Methods Med. Res.*, 2, 23–41.

Doddington, B.J., Bosch, J., Oliver, J.A., Grassly, N.C., Garcia, G., Schmidt, B.R. *et al.* (2013). Context-dependent amphibian host population response to an invading pathogen. *Ecology*, 94, 1795–1804.

Dwyer, G., Elkinton, J.S. & Buonaccorsi, J.P. (1997). Host heterogeneity in susceptibility and disease dynamics: tests of a mathematical model. *Am. Nat.*, 150, 685–707.

Easterling, M.R., Ellner, S.P. & Dixon, P.M. (2000). Size-specific sensitivity: applying a new structured population model. *Ecology*, 81, 694–708.

Ellison, A.R., Tunstall, T., Direnzo, G.V., Hughey, M.C., Rebollar, E.A., Belden, L.K. *et al.* (2015). More than skin deep: functional genomic basis for resistance to amphibian chytridiomycosis. *Genome Biol. Evol.*, 7, 286–298.

Epstein, B., Jones, M., Hamede, R., Hendricks, S., McCallum, H., Murchison, E.P. *et al.* (2016). Rapid evolutionary response to a transmissible cancer in Tasmanian devils. *Nat. Commun.*, 7, 12684.

Forrest, M.J. & Schlaepfer, M.A. (2011). Nothing a hot bath won't cure: infection rates of amphibian chytrid fungus correlate negatively with water temperature under natural field settings. *PLoS ONE*, 6, e28444.

Gelman, A., Carlin, J.B., Stern, H.S., Dunson, D.B., Vehtari, A. & Rubin, D.B. (2014). *Bayesian Data Analysis*. 3rd edn. Taylor & Francis Group, LLC, Boca Raton.

Gerber, L.R., McCallum, H., Lafferty, K.D., Sabo, J.L. & Dobson, A. (2005). Exposing extinction risk analysis to pathogens: is disease just another form of density dependence? *Ecol. Appl.*, 15, 1402–1414.

Godfray, H.C.J., Briggs, C.J., Barlow, N.D., O'Callaghan, M., Glare, T.R. & Jackson, T.A. (1999). A model of insect-pathogen dynamics in which a pathogenic bacterium can also reproduce saprophytically. *Proc. Royal Society B: Biol. Sci.*, 266, 233–240.

Grogan, L.F., Phillott, A.D., Scheele, B.C., Berger, L., Cashins, S.D., Bell, S.C.*et al.* (2016). Endemicity of chytridiomycosis features pathogen overdispersion. *J. Anim. Ecol.*, 85, 806–816.

Handel, A. & Rohani, P. (2015). Crossing the scale from within-host infection dynamics to between-host transmission fitness: a discussion of current assumptions and knowledge. *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, 370, 20140302.

Harper, E.B., Stella, J.C. & Fremier, A.K. (2011). Global sensitivity analysis for complex ecological models: a case study of riparian cottonwood population dynamics. *Ecol. Appl.*, 21, 1225–1240

Harris, R.N., Brucker, R.M., Walke, J.B., Becker, M.H., Schwantes, C.R., Flaherty, D.C. , (2009). Skin microbes on frogs prevent morbidity and mortality caused by a lethal skin fungus. *ISME J.*, 3, 818–824.

Heard, G.W., Scroggie, M.P., Clemann, N. & Ramsey, D.S.L. (2014). Wetland characteristics influence disease r Wetland characteristics influence disease risk for a threatened amphibian. *Ecol. Appl.*, 24, 650–662.

Hoyt, J.R., Langwig, K.E., Sun, K., Lu, G., Parise, K.L., Jiang, T. *et al.* (2016). Host persistence or extinction from emerging infectious disease: insights from white-nose syndrome in endemic and invading regions. *Proc. Biol. Sci.*, 283, 20152861.

Jani, A.J. & Briggs, C.J. (2014). The pathogen *Batrachochytrium dendrobatidis* disturbs the frog skin microbiome during a natural epidemic and experimental infection. *Proc. Natl Acad. Sci.*, 111, E5049–E5058.

Jenkinson, T.S., Betancourt Román, C.M., Lambertini, C., Valencia-Aguilar, A., Rodriguez, D., Nunes- De-Almeida, C.H.L. *et al.* (2016). Amphibian-killing chytrid in Brazil comprises both locally endemic and globally expanding populations. *Mol. Ecol.*, 25, 2978–2996.

Kilpatrick, A.M. (2006). Facilitating the evolution of resistance to avian malaria in Hawaiian birds. *Biol. Cons.*, 128, 475–485.

Kilpatrick, A.M., Briggs, C.J. & Daszak, P. (2010). The ecology and impact of chytridiomycosis: an emerging disease of amphibians. *Trends Ecol. Evol.*, 25, 109–118.

Knapp, R.A., Briggs, C.J., Smith, T.C. & Maurer, J.R. (2011). Nowhere to hide: impact of a temperature-sensitive amphibian pathogen along an elevation gradient in the temperate zone. *Ecosphere*, 2, art93.

Knapp, R.A., Fellers, G.M., Kleeman, P.M., Miller, D.A.W., Vredenburg, V.T., Rosenblum, E.B. *et al.* (2016). Large-scale recovery of an endangered amphibian despite ongoing exposure to multiple stressors. *Proc. Natl Acad. Sci.*, 113, 11889–11894.

Lande, R., Engen, S. & Saether, B.-E. (2003). *Stochastic Population Dynamics in Ecology and Conser- vation*. Oxford University Press, Oxford.

Langhammer, P.F., Lips, K.R., Burrowes, P.A., Tunstall, T., Palmer, C.M. & Collins, J.P. (2013). A fungal pathogen of amphibians, *Batrachochytrium dendrobatidis*, attenuates in pathogenicity with in vitro passages. *PLoS ONE*, 8, 1–9.

Langwig, K.E., Hoyt, J., Parise, K., Frick, W., Foster, J. & Kilpatrick, A.M. (2017). Resistance in persisting bat populations after white-nose syndrome invasion. *Philos. Trans. R. Soc. Lond., B, Biol. Sci.*, 372, 20160044.

Langwig, K.E., Voyles, J., Wilber, M.Q., Frick, W.F., Murray, K.A., Bolker, B.M. *et al.* (2015). Context-dependent conservation responses to emerging wildlife diseases. *Front. Ecol. Environ.*, 13, 195–202.

Lee, Y.-S., Liu, O.Z., Hwang, H.S., Knollmann, B.C. & Sobie, E.A. (2013). Parameter sensitivity analysis of stochastic models provides insights into cardiac calcium sparks. *Biophys. J.*, 104, 1142–1150.

Louie, A., Song, K.H., Hotson, A., Thomas Tate, A. & Schneider, D.S. (2016). How many parameters does it take to describe disease tolerance? *PLoS Biology*, 14, e1002435.

McCallum, H. (2012). Disease and the dynamics of extinction. *Philos. Trans. R. Soc. Lond., B, Biol. Sci.*, 367, 2828–39.

McCallum, H., Barlow, N. & Hone, J. (2001). How should pathogen transmission be modelled? *Trends Ecol. Evol.*, 16, 295–300.

McCallum, H. & Dobson, A. (1995). Detecting disease and parasite threats to endangered species and ecosystems. *Trends Ecol. Evol.*, 10, 190–194.

McCallum, H., Jones, M., Hawkins, C., Hamede, R., Lachish, S., Sinn, D.L. *et al.* (2009). Transmission dynamics of Tasmanian devil facial tumor disease may lead to disease-induced extinction. *Ecology*, 90, 3379–3392.

Medzhitov, R., Schneider, D.S. & Soares, M.P. (2012). Disease tolerance as a defense strategy. *Science*, 335, 936–941.

Metcalf, C.J.E., Graham, A.L., Martinez-Bakker, M. & Childs, D.Z. (2015). Opportunities and challenges of Integral Projection Models for modelling host-parasite dynamics. *J. Anim. Ecol.*, 85, 343–355.

Mitchell, K.M., Churcher, T.S., Garner, T.W.J. & Fisher, M.C. (2008). Persistence of the emerging pathogen *Batrachochytrium dendrobatidis* outside the amphibian host greatly increases the probability of host extinction. *Proc. R. Soc. B*, 275, 329–334.

Pedregosa, F., Varoquaux, G., Gramfort, A., Michel, V., Thirion, B., Grisel, O. *et al.* (2011). Scikit-learn: machine learning in python. *J. Mach. Learn. Res.*, 12, 2825–2830.

Piotrowski, J.S., Annis, S.L. & Longcore, J.E. (2004). Physiology of *Batrachochytrium dendrobatidis*, a chytrid pathogen of amphibians. *Mycologia*, 96, 9–15.

Rachowicz, L.J. & Briggs, C.J. (2007). Quantifying the disease transmission function: effects of density on *Batrachochytrium dendrobatidis* transmission in the mountain yellow-legged frog *Rana muscosa*. *J. Anim. Ecol.*, 76, 711–21.

Refsnider, J.M., Poorten, T.J., Langhammer, P.F., Burrowes, P.A. & Rosenblum, E.B. (2015). Genomic correlates of virulence attenuation in the deadly amphibian chytrid fungus, *Batrachochytrium dendrobatidis*. *G3 (Bethesda)*, 5, 2291–2298.

Retallick, R.W.R., McCallum, H. & Speare, R. (2004). Endemic infection of the amphibian chytrid fungus in a frog community post-decline. *PLoS Biol.*, 2, e351.

Rohani, P., Breban, R., Stallknecht, D.E. & Drake, J.M. (2009). Environmental transmission of low pathogenicity avian influenza viruses and its implications for pathogen invasion. *Proc. Natl Acad. Sci.*, 106, 10365–10369.

Rosenblum, E.B., James, T.Y., Zamudio, K.R., Poorten, T.J., Ilut, D., Rodriguez, D. *et al.* (2013). Complex history of the amphibian-killing chytrid fungus revealed with genome resequencing data. *Proc. Natl Acad. Sci.*, 110, 9385–90.

Roy, B.A. & Kirchner, J.W. (2000). Evolutionary eynamics of pathogen resistance and tolerance. *Evolution*, 54, 51–63.

Savage, A.E. & Zamudio, K.R. (2011). MHC genotypes associate with resistance to a frog-killing fungus. *Proc. Natl Acad. Sci.*, 108, 16705–16710.

Savage, A.E. & Zamudio, K.R. (2016). Adaptive tolerance to a pathogenic fungus drives major histocompatibility complex evolution in natural amphibian populations. *Proc. R. Soc. B*, 283, 20153115.

Schmeller, D.S., Blooi, M., Martel, A., Garner, T.W.J., Fisher, M.C., Azemar, F. *et al.* (2014). Microscopic aquatic predators strongly affect infection dynamics of a globally emerged pathogen. *Curr. Biol.*, 24, 176–180.

Schreiber, S.J. & Ross, N. (2016). Individual-based integral projection models: the role of size-structure on extinction risk and establishment success. *Methods Ecol. Evol.*, 7, 867–874.

Skerratt, L.F., Berger, L., Speare, R., Cashins, S., McDonald, K.R., Phillott, A.D. *et al.* (2007). Spread of chytridiomycosis has caused the rapid global decline and extinction of frogs. *EcoHealth*, 4, 125–134.

Smith, K.F., Sax, D.F. & Lafferty, K.D. (2006). Evidence for the role of infectious disease in species extinction and endangerment. *Conserv. Biol.*, 20, 1349–1357.

Sobie, E.A. (2009). Parameter sensitivity analysis in electrophysiological models using multivariable regression. *Biophys. J.*, 96, 1264–1274.

Stockwell, M.P., Clulow, J. & Mahony, M.J. (2010). Host species determines whether infection load increases beyond disease-causing thresholds following exposure to the amphibian chytrid fungus. *Anim. Conserv.*, 13, 62–71.

Strauss, A. & Smith, K.G. (2013). Why does amphibian chytrid (*Batrachochytrium dendrobatidis*) not occur everywhere? An exploratory study in missouri ponds. *PLoS ONE*, 8, e76035.

Tunstall, T.S. (2012). *Characteristics of the emergent disease* Batrachochytrium dendrobatidis *in* Rana muscosa *and* Rana sierrae *species complex*. Ph.D. thesis, University of California, Berkeley.

Vander Wal, E., Garant, D., Calmé, S., Chapman, C.A., Festa-Bianchet, M., Millien, V. *et al.* (2014). Applying evolutionary concepts to wildlife disease ecology and management. *Evol. Appl.*, 7, 856–868.

Venesky, M.D., Liu, X., Sauer, E.L. & Rohr, J.R. (2013). Linking manipulative experiments to field data to test the dilution effect. *J. Anim. Ecol.*, 83, 557–565.

Voyles, J., Berger, L., Young, S., Speare, R., Webb, R., Warner, J., Rudd, D., Campbell, R. & Skerratt, L. (2007). Electrolyte depletion and osmotic imbalance in amphibians with chytridiomycosis. *Dis. Aquat. Organ.*, 77, 113–118.

Voyles, J., Johnson, L.R., Briggs, C.J., Cashins, S.D., Alford, R.A., Berger, L. *et al.* (2014). Experimental evolution alters the rate and temporal pattern of population growth in *Batrachochytrium dendrobatidis*, a lethal fungal pathogen of amphibians. *Ecol. Evol.*, 4, 3633–3641.

Voyles, J., Young, S., Berger, L., Campbell, C., Voyles, W.F. & Dinudom, A. (2009). Pathogenesis of chytridiomycosis, a cause of catastrophic amphibian declines. *Science*, 326, 5–8.

Vredenburg, V.T., Knapp, R.A., Tunstall, T.S. & Briggs, C.J. (2010). Dynamics of an emerging disease drive large-scale amphibian population extinctions. *Proc. Natl Acad. Sci.*, 107, 9689–94.

Wilber, M.Q., Langwig, K.E., Kilpatrick, A.M., Mccallum, H.I. & Briggs, C.J. (2016). Integral Projection Models for host-parasite systems with an application to amphibian chytrid fungus. *Methods Ecol. Evol.*, 7, 1182–1194.

Woodhams, D.C., Alford, R.A., Briggs, C.J., Johnson, M. & Rollins-Smith, L.A. (2008). Life-history trade-offs influence disease in changing climates: strategies of an amphibian pathogen. *Ecology*, 89, 1627–1639.

Woodhams, D.C., Bosch, J., Briggs, C.J., Cashins, S., Davis, L.R., Lauer, A. *et al.* (2011). Mitigating amphibian disease: strategies to maintain wild populations and control chytridiomycosis. *Front. Zool.*, 8, 8.

SUPPORTING INFORMATION

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