# When chytrid fungus invades: integrating theory and data to understand disease-induced amphibian declines

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**Title**: When chytrid fungus invades: integrating theory and data to understand disease-induced amphibian declines

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# Lay summary

The emerging amphibian fungal pathogen *Batrachochytrium dendrobatidis* (Bd) has led to severe amphibian declines around the globe. One of the challenges when attempting to mitigate the effects of Bd on amphibian populations is that different amphibian populations can show drastically divergent outcomes following Bd invasion. These include an increase in amphibian population density, no discernible change in population density, a decrease in density, and even population-level extinction. Here we integrate extensive data from amphibian-Bd systems and epidemiological theory to build a framework for predicting when and why amphibian populations might show different population-level trajectories upon Bd invasion. This framework allows us to place seemingly disparate population-level responses following Bd invasion in terms of known disease ecology theory to better understand and manage amphibian declines and recoveries.

# Abstract

Amphibian populations around the globe are experiencing declines, many of which are driven by the fungal pathogen *Batrachochytrium dendrobatidis* (Bd). However, different species of amphibians, as well as divergent populations of the same species of amphibian, can show drastically different responses to Bd invasion. In this chapter we answer three questions: 1) What are the potential trajectories of amphibian host populations following Bd invasion? 2) How are each of these trajectories influenced by both the transmission dynamics and load dynamics governing an amphibian-Bd system? 3) How do ecological, evolutionary, and environmental factors affect both Bd transmission and Bd load dynamics, which in turn influence the population-level outcome of amphibian hosts? We build a general framework that identifies eight population-level trajectories that amphibian populations can take upon Bd invasion that are a result of five different branch points. Each of these branch points is affected by either the transmission dynamics or the load dynamics underlying the system. By integrating relevant disease ecology theory as well as empirical data, this framework can be used to guide context-dependent management strategies for amphibian populations infected with Bd. While this framework is motivated by amphibian-Bd systems, we anticipate that it will also provide a useful lens through which to view the relative importance of transmission and load dynamics in other host-pathogen systems.

## 12.1 Introduction

Globally, amphibian populations are experiencing unprecedented declines (Stuart et al. 2004; Skerratt et al. 2007). While there are many contributing factors including habitat loss, environmental contamination, and commercial harvesting, emerging infectious disease is a major cause of these declines (Daszak

et al. 2003; Stuart et al. 2004; Skerratt et al. 2007). Of particular concern is the pathogen *Batrachochytrium dendrobatidis* (Bd), an aquatic fungus that infects the skin of amphibians and leads to the disease chytridiomycosis (Box 12.1; Longcore et al. 1999; Voyles et al. 2009). Chytridiomycosis can lead to drastic population declines and, in some cases, species extinction (Daszak et al. 2003). Bd has been identified in over 500 species of amphibians across six continents (Fisher et al. 2012), making it one of the most widespread and devastating vertebrate pathogens in documented history (Skerratt et al. 2007).

The widespread and generalist nature of Bd has resulted in a variety of different epidemiological outcomes in response to infection. Different species of amphibians have shown population-level outcomes ranging from extirpation to little or no impact (Kilpatrick et al. 2010; James et al. 2015). Moreover, different populations of the same amphibians species can show variable outcomes in response to Bd invasion (Briggs et al. 2005; Doddington et al. 2013; Savage & Zamudio 2016). In parts of the world, Bd is still invading and in some cases leading to epizootics (i.e. epidemic in a non-human system) of chytridiomycosis (Lips et al. 2008; Vredenburg et al. 2010; Bletz et al. 2015; Clare et al. 2016), while in other areas Bd has been present for decades, or longer, and is currently persisting with amphibian hosts in an enzootic state (Briggs et al. 2010; Knapp et al. 2016; Scheele et al. 2017). Understanding when the invasion of Bd into an amphibian population will lead to extirpation and when it will have negligible effects is an important conservation question for mitigating Bd-induced amphibian declines (Woodhams et al. 2011).

[Box 12.1 here]

Identifying the characteristics of host-parasite systems that allow for parasite invasion and host regulation is a central goal in epidemiology (Anderson & May 1991; Anderson 1995; Diekmann & Heesterbeek 2000; Tompkins et al. 2002; Gerber et al. 2005). Much of this work has focused on microparasites, pathogens such as bacteria and viruses that reproduce within their host and often invoke a strong immune response (Anderson & May 1979), for which identifying properties such as pathogen transmission, pathogen pathogenicity, and host growth rate generally allows one to characterise different population-level disease trajectories (Anderson & May 1991; Diekmann & Heesterbeek 2000). However, Bd and other fungal pathogens typically categorized as microparasites, also exhibit characteristics of macroparasites, e.g. helminths and ectoparasites that do not directly reproduce within/on a host (Anderson & May 1979). This is because many critical epidemiological parameters, such as pathogen-induced mortality rate, are highly dependent on the amount of Bd on a given host (Vredenburg et al. 2010; Woodhams et al. 2011; DiRenzo et al. 2014). This is similar to macroparasite systems where the number of parasites within a host needs to be explicitly modeled to capture load-dependent pathology (Anderson & May 1978; Dobson & Hudson 1992). In general, host-microparasite models tend to focus on how transmission dynamics affect population-level outcomes, but rarely focus on pathogen load. Because of the nature of Bd infections (see Box 12.1), both transmission dynamics and load dynamics must be considered, and

thus, one also needs to elucidate the factors that affect fungal load on individual hosts (Briggs et al. 2010; Fisher et al. 2012; Grogan et al. 2016). This makes amphibian-Bd systems an ideal case study for building a framework that synthesises how both transmission and load dynamics affect different host population-level outcomes upon pathogen invasion.

In this chapter we address three questions regarding different population-level outcomes in amphibian-Bd systems. First, what are the potential trajectories of amphibian host populations following Bd invasion? Second, how are each of these trajectories influenced by both the transmission dynamics and load dynamics governing an amphibian-Bd system? Third, how do ecological, evolutionary, and environmental factors affect both transmission and load dynamics, which in turn influence the population-level outcome of an amphibian-Bd system? We define transmission dynamics as the processes by which an amphibian acquires a Bd infection, while Bd-load dynamics are the processes that affect the growth of Bd on an individual host, conditional on infection. To answer these questions, we build a general framework that simplifies the different population-level trajectories of amphibian-Bd systems into a series of branch points (Figure 12.2). Each of these branch points is affected by either the transmission dynamics or the load dynamics underlying an amphibian-Bd system. By integrating relevant disease ecology theory as well as empirical data on amphibian-Bd systems, this framework provides a unified approach to consider variable population-level trajectories across amphibian-Bd systems. Ultimately, knowledge of the factors that determine which trajectory an amphibian population takes at each branch point may help guide the development of effective mitigation strategies to positively change the outcome of Bd invasion and protect threatened amphibians from population declines and disease-induced extinction.

## 12.2 A framework for different population-level outcomes in amphibian-Bd systems

We begin our discussion of this framework by considering a naive amphibian population (i.e. not yet exposed to Bd) that is persisting at a stable density (Fig. 12.2). From this starting point, an amphibian population is then exposed to Bd and the resulting population-level trajectory is determined by a series of branch points where amphibian-Bd trajectories can diverge (circles in Fig. 12.2). The trajectory taken at any branch point is dictated by either the transmission dynamics of the system, the Bd-load dynamics of the system, or both. Multiple ecological, evolutionary, environmental, and demographic factors affect the transmission and load dynamics at a given branch point, such that they in turn influence the trajectory taken by the amphibian-Bd system.

[Figure 12.2 here]

In the following sections, we discuss each of these branch points and give empirical examples of when different amphibian systems have taken different trajectories at these branch points. We highlight

general epidemiological theory that suggests when a host-pathogen system will follow a given trajectory and explore how this theory has been used to inform us about the different population-level outcomes in amphibian-Bd systems.

### 12.2.1 Branch point 1: Does Bd invade an amphibian host-population?

The first branch determines whether or not Bd successfully invades an amphibian population. While there are thousands of examples of Bd successfully invading amphibian populations (Skerratt et al. 2007), there are far fewer documented examples of Bd failing to invade a system. This is often the case for infectious disease as pathogen-specific monitoring usually occurs after a pathogen has already invaded and impacted a host population (Lloyd-Smith et al. 2005a). An example of both failed and successful Bd invasions is seen in populations of the mountain yellow-legged frog complex (*Rana muscosa* and *Rana sierrae*) (Box 12.1). As Bd has invaded the thousands of lakes and streams supporting *R. muscosa/sierrae* populations (Vredenburg et al. 2010), monitoring efforts have detected populations that transitioned from Bd-negative to Bd-positive and back to Bd-negative, all without a Bd epizootic occurring (R.A. Knapp et al., unpublished). While often undetected, it is likely that failed Bd invasions occur in other amphibian species. Here we discuss how *transmission dynamics* affect the ability of Bd, and pathogens in general, to invade a naive host population.

#### 12.2.1.1 Transmission dynamics and $R_0$

Epidemiological theory tells us that the probability of a pathogen invading a system is a function of the basic reproduction number $R_0$ (Allen 2015). $R_0$ is the average number of secondary cases a single infected individual produces in an entirely susceptible population and is an important parameter in understanding disease dynamics (Dietz 1993). Particularly, for a population with a single infected host, the probability $b$ that a pathogen invades is approximately given by (Gerber et al. 2005; Allen 2015)

$$b = \begin{cases} 1 - \frac{1}{R_0} & R_0 > 1 \\ 0 & R_0 \leq 1 \end{cases} \tag{1}$$

For $R_0 > 1$ an infected host more than replaces itself during an infectious period and there is a non-zero probability that a pathogen will successfully invade a host population. Because invasion success is probabilistic, given multiple replicate populations (or the same population being invaded multiple times) we would expect, by chance alone, some of these invasions to fail even if $R_0 > 1$ (Fig. 12.3). Given this probabilistic nature of pathogen invasion, it is challenging to determine whether a failed invasion is due to the system being not invasible (i.e. $R_0 \leq 1$) or being invasible ($R_0 > 1$) but stochastically experiencing a failed invasion (Lloyd-Smith et al. 2005a). Despite this challenge, it is clear that to even attempt to predict the trajectory of an amphibian-Bd system after the first branching point, it is important

to calculate $R_0$. The mathematical methods to calculate $R_0$ are well-established (e.g. Dietz 1993; Van Den Driessche & Watmough 2002; Klepac & Caswell 2011) and one of the challenges is specifying the ecological, evolutionary, environmental, and demographic details of a specific amphibian-Bd system.

[Figure 12.3 here]

Because $R_0$ describes the number of infected hosts "produced" by a currently infected host, it is inherently tied to the transmission dynamics within a system (Dietz 1993). Transmission dynamics describe the per capita rate at which susceptible hosts become infected (i.e. the force of infection, $f(I)$). While many factors such as host behaviour, host susceptibility, host-pathogen compatibility, pathogen infectivity, community composition, and temperature affect the force of infection (Combes 2000; Diekmann & Heesterbeek 2000; Dobson 2004; Mordecai et al. 2013; McCallum et al. 2017), one of the most fundamental factors that affects this rate is how the rate of contacts between infected and uninfected hosts changes with host density (Diekmann & Heesterbeek 2000; McCallum et al. 2001; Begon et al. 2002). This is important for directly-transmitted diseases because contact between an infected host and an uninfected host is necessary for transmission.

A common assumption in wildlife disease models is that the rate of contacts per host increases linearly with increasing host density (McCallum et al. 2001; Begon et al. 2002; Lloyd-Smith et al. 2005a). One potential mechanism leading to this relationship is if individuals move and contact each other randomly in an area (Begon et al. 2002). This is known as density-dependent transmission (McCallum et al. 2001; Begon et al. 2002). Another common assumption is that the rate of contacts per host is constant as host density increases. One potential mechanism leading to this relationship is if individuals only interact with individuals in a social group and the group size does not change with density (McCallum et al. 2001; Begon et al. 2002). This is known as frequency-dependent transmission. More complex functions relating the rate of contact to changing host density can also be considered (McCallum et al. 2001).

Given a simple Susceptible-Infected-Susceptible (SIS) model with density-dependent transmission (Fig. 12.2A), $R_0 = \frac{\beta H}{\alpha+\gamma}$. In contrast, with frequency-dependent transmission $R_0 = \frac{\beta'}{\alpha+\gamma}$. The crucial difference between these two types of transmission is that for density-dependent transmission $R_0$ scales with total population density $H$ and for frequency-dependent transmission it does not. This suggests that if, for example, the management goal was to try and reduce the probability of Bd invading a naive amphibian population (i.e. decrease $R_0$), reducing population density via culling would be a theoretically effective strategy given density-dependent transmission, but would be a completely ineffective given frequency-dependent transmission. Thus, characterizing the transmission function has important implications for managing Bd invasions (Woodhams et al. 2011).

Wilber et al. (2017) sought to characterise the transmission function for the mountain yellow-legged frog-Bd system (Box 12.1; see also Rachowicz & Briggs 2007). They set up mesocosms with four different densities of uninfected adult frogs (each density was replicated four times), placed 5 infected

tadpoles into the mesocosms, and monitored the transmission dynamics over the course of 74 days by measuring Bd load on all frogs and tadpoles in a mesocosm every four to seven days. They then fit both frequency-dependent and density-dependent models to the transmission data and found that the experimental data were best described by a density-dependent transmission function. Note that while a component of transmission in the mountain yellow-legged frog-Bd system might be well-described by density-dependent contacts, we do not yet know the general role of density-dependent versus frequency-dependent transmission across different amphibian-Bd systems.

[Box 12.2 here]

While characterising whether infected amphibians contact susceptible amphibians in a density- or frequency-dependent manner is an important aspect of Bd transmission (Rachowicz & Briggs 2007; Courtois et al. 2017), susceptible individuals also become infected by contacting Bd zoospores in the environment (Briggs et al. 2010; Courtois et al. 2017). In the aforementioned experiment, Wilber et al. (2017) found that including an environmental Bd reservoir along with density-dependent host contact provided the best fit to the transmission experiment. Incorporating this transmission function into a dynamic model (Box 12.2), they found that including the environmental zoospore pool significantly increased $R_0$ and therefore the probability of a pathogen successfully invading a host population (Fig. 12.5; Godfray et al. 1999; Rohani et al. 2009; Wilber et al. 2017). While we discuss the importance of the environmental zoospore pool more thoroughly in the following sections, we stress that future mesocosm and laboratory studies attempting to quantify Bd transmission should also measure the dynamics of the zoospore pool and potential factors affecting these dynamics (detailed below). This will help amphibian ecologists better quantify the transmission function and improve our understanding of the conditions under which Bd will successfully invade a host population.

[Figure 12.5 here]

### 12.2.2 Branch point 2: Does an infected amphibian population decline?

Once Bd has successfully invaded an amphibian host population (branch point 1), the next branch point determines whether or not Bd invasion leads to population decline (Fig. 12.2). For example, Savage & Zamudio (2016) examined different populations of the lowland leopard frog *Lithobates yavapaiensis* and found that while all populations were infected with Bd (i.e. Bd had successfully invaded), some populations were experiencing greater Bd-induced mortality than others. Because this study did not control for the time since Bd invasion, we cannot immediately tell if the different frog populations are actually just at different time points along the same trajectory. However, Savage et al. (2015) hypothesised that innate genetic differences in the hosts led to different trajectories of these amphibian populations upon Bd invasion.

In another example, Bd successfully invaded populations of the Mallorcan midwife toad *Alytes*

*muletensis*, but these populations did not suffer severe Bd-induced declines (though individual-level Bd-induced mortality was still observed, Doddington et al. 2013). Unlike the previous example, one of the reasons for the lack of severe Bd-induced declines in these populations was that they are infected with a strain of Bd that has been demonstrated to have relatively low virulence (Farrer et al. 2011; Doddington et al. 2013). These examples illustrate that properties of both the host and the pathogen dictate whether or not Bd invasion results in amphibian population declines.

The population trajectory at this branch point depends on the *load dynamics* of Bd. This is because Bd-induced host mortality, which is the most obvious outcome of Bd invasion that leads to population-level host declines, is highly load-dependent (Voyles et al. 2009; Vredenburg et al. 2010). A number of field and laboratory studies have documented that when the Bd load on a host exceeds some approximate species-specific threshold, the probability of host survival declines rapidly (Vredenburg et al. 2010; Stockwell et al. 2010; DiRenzo et al. 2014; Wilber et al. 2016). Some amphibian species are able to prevent Bd from reaching this threshold and are thus able to persist with high Bd prevalence, but lower mean loads (Stockwell et al. 2010). Similarly, particular strains of Bd are less virulent, which can correlate with reduced Bd loads (e.g. Doddington et al. 2013). Determining why different species and/or populations of amphibians show different load dynamics as well as why different Bd strains show different levels of virulence, is important for predicting both whether or not an amphibian population will experience a Bd-induced decline and the magnitude of that decline.

#### 12.2.2.1 Resistance, tolerance, and pathogen virulence

We discuss the load dynamics of Bd through the lens of resistance and tolerance – two distinct mechanisms that can affect Bd load-dynamics and the population-level trajectory at branch point 2. Resistance is the ability of a host to reduce or eliminate pathogen load, conditional on pathogen exposure (Medzhitov et al. 2012). In contrast, tolerance does not affect pathogen load, but rather reduces the effect of a given load on host fitness (Råberg et al. 2009; Medzhitov et al. 2012). Resistance is often defined as the inverse of maximum infection load and tolerance as the slope of the relationship between infection load and some measure of host fitness (Råberg et al. 2009). Pathogen virulence is implicit in the definitions of resistance and tolerance and is defined as the effect of a pathogen at some load on the fitness of a host (Råberg et al. 2009). Many mechanisms underly both resistance and tolerance (e.g. host innate and acquired immunity, behaviour, tissue repair, etc.; Medzhitov et al. 2012), but it is often easier to experimentally measure resistance and tolerance as defined above and relate them to population-level outcomes (Råberg et al. 2007).

To make these concepts more concrete, consider two epidemiological functions of an amphibian-Bd interaction: the pathogen growth function $G(x', x)$ and the host survival function $s(x)$. The pathogen growth function describes how the Bd load on an amphibian changes from $x$ to $x'$ in a time step $t$ to $t+1$

(Fig. 12.6). Assume the mean Bd load at $t+1$ given a load of $x$ at time $t$ is given by $x(t+1) = b_0 + b_1 x$. If the slope $b_1$ increases, Fig. 12.6A shows that the equilibrium Bd load also increases. Therefore, one way to classify more resistant amphibian individuals (or populations) are those with lower slopes in the growth function (Fig. 12.6A). The host survival function $s(x)$ describes the probability of a host with a load of $x$ surviving from time $t$ to time $t+1$. Assume that $s(x)$ can be described by $\text{logit}(s(x)) = a_0 - a_1 x$ where logit specifies the log-odds survival probability (Fig. 12.6B). Tolerance could be defined by the slope $a_1$, where an increased $a_1$ corresponds to a smaller decrease in the log-odds survival probability per unit increase in Bd load and thus a higher tolerance (Fig 12.6B; Råberg et al. 2009). In this example, pathogen virulence could be defined as the effect of the pathogen on host survival at the equilibrium level of Bd load (i.e. $a_1 \frac{b_0}{1-b_1}$) and is thus a product of the pathogen growth function determining host resistance and the survival function determining host tolerance.

[Figure 12.6 here]

Both increased resistance and tolerance can reduce or eliminate population declines. For example, increasing resistance by decreasing the slope $b_1$ of $G(x', x)$ reduces the mean Bd load on an amphibian host and thus increases survival probability. Similarly, increasing tolerance by increasing $a_1$ would also increase survival probability for a given load. In some cases, the mechanisms that affect resistance and/or tolerance are genetically-based (Roy & Kirchner 2000). For example, the difference in load dynamics on the lowland leopard frogs mentioned above was hypothesised to be due to heritable, genetic differences in immune function (Savage et al. 2015; Savage & Zamudio 2016). However, changes in host resistance can be driven by a host's behavior (Adams et al. 2017), a host's environment (Raffel et al. 2012), and/or the strain of Bd infecting a host (Farrer et al. 2011). In the following sections we focus on how two particular factors affect host resistance (i.e. Bd load dynamics) that can augment or prevent Bd-induced population declines: variability in Bd virulence and changes in temperature.

#### 12.2.2.2 Variability in Bd virulence

As described above, the virulence of a particular Bd strain can have important implications for whether or not an amphibian population declines following Bd invasion. Experimental infection studies have identified that Bd exhibits a large amount of variation in virulence across different strains (Berger et al. 2005; Farrer et al. 2011; Doddington et al. 2013; Becker et al. 2017). In these studies, amphibian hosts are infected with different Bd strains and, if a host dies, the time of host death is recorded. Strains that kill amphibian hosts more quickly are considered more virulent. Note that this definition of virulence does not explicitly consider Bd load. In addition to examining the time of death, studies should also measure Bd load over the time course of these infection experiments (e.g. Doddington et al. 2013). This would provide a straightforward way to place Bd virulence in the context of how a given Bd load affects the probability of survival, which is consistent with defining virulence as a product of host tolerance

and host resistance (Råberg et al. 2009). Moreover, this would help highlight that Bd load *per se* is not necessarily a consistent predictor of virulence across different strains of Bd. This is because morphological characteristics of Bd, such as zoosporangium size (Fisher et al. 2009), can interact with Bd load such that amphibians infected with similar loads do not experience the same fitness consequences.

Variability in Bd virulence has a strong genetic component (Fisher et al. 2009; Farrer et al. 2011; Rosenblum et al. 2013; Refsnider et al. 2015; Lambertini et al. 2016). Of the five currently identified Bd lineages, one particular lineage, the Global Panzootic Lineage (BdGPL), is consistently more virulent in experimental infection studies (Farrer et al. 2011; Doddington et al. 2013; Becker et al. 2017) and has been implicated in Bd-induced amphibian declines around the world (Farrer et al. 2011; Rosenblum et al. 2013; James et al. 2015). However, within the BdGPL, particular strains are not consistently virulent to all amphibian species and particular amphibian species are not consistently affected by all strains (Rosenblum et al. 2013; Becker et al. 2017). It is important to understand variable virulence in Bd strains because amphibian populations that are able to persist in the presence of one Bd strain can still be highly susceptible to even closely related strains (Becker et al. 2017).

To explore the importance of variable strain virulence on population-level trajectories of amphibians, Doddington et al. (2013) built a dynamic model of Mallorcan midwife toad populations. Using experimental infections, they estimated the virulence of two different Bd strains, one within the virulent BdGPL lineage and the other within the less virulent BdCape lineage. They then incorporated these estimates into a dynamic model parameterized from additional laboratory experiments and field observations. Doddington et al. found that upon the invasion of the more virulent BdGPL strain, an epizootic ensued and amphibian populations declined. However, in their model Bd tended to go extinct before driving the toad populations to extinction. In contrast, when the populations were invaded with the less virulent BdCape strain that was actually infecting the populations in the field, the model predicted that subsequent population declines were less severe and toads could often coexist with the less virulent Bd strain. This was consistent with their observations that Mallorcan toad populations were generally persisting with the BdCape strain in the field.

#### 12.2.2.3 Temperature and Bd load

There are a number of different environmental variables that can affect the load dynamics of Bd, such as moisture, hydrological dynamics, and temperature (Woodhams et al. 2011; Murray et al. 2011; Tunstall 2012; Raffel et al. 2012, 2015; Adams et al. 2017). Temperature is one of the most frequently studied abiotic variables affecting the load dynamics of Bd because of it potential to determine amphibian population trajectories following Bd invasion (e.g. Piotrowski et al. 2004; Pounds et al. 2006; Kriger & Hero 2007; Woodhams et al. 2008; Kilpatrick et al. 2010; Rohr & Raffel 2010; Knapp et al. 2011; Doddington et al. 2013; Cohen et al. 2017). However, predicting the effects of temperature on disease

risk in general is difficult given the complex interactions between temperature and other biotic and abiotic variables (Lafferty & Kuris 2009; Rohr et al. 2011; Altizer et al. 2013; Paull & Johnson 2013). To address this challenge, it is critical to understand how processes underlying infection, such as the activation of the host immune response and the growth of the pathogen, respond to changes in temperature.

Important immunological processes of amphibians, such as the production of lymphocytes, nuetrophils, and antibody synthesis, are influenced both positively and negatively by changes in temperature (Maniero & Carey 1997; Raffel et al. 2006), and often in a non-linear way (Plytycz & Jozkowicz 1994). Similarly, Bd survival, growth, and reproduction are highly temperature-dependent. *In vitro*, Bd growth rates are highest between 17-25 °C, with a marked decrease in growth above and below these temperatures (Piotrowski et al. 2004). This increased growth rate is the result of a trade-off between faster maturation times of zoosporangia and fewer zoospores being produced per zoosporangium at higher temperatures (Woodhams et al. 2008). Per capita zoospore death rate also increases with temperature (Woodhams et al. 2008), but the faster maturation time with increasing temperature still allows population-level growth rate to increase with increasing temperature.

The effect of temperature on Bd infection and resulting chytridiomycosis is a product of the interaction between these temperature-dependent infection processes of amphibians and Bd (Raffel et al. 2012). For example, while *in vitro* Bd shows optimal growth between 17-25 °C, *in vivo* temperature-dependent Bd growth is highly host-dependent (Kilpatrick et al. 2010). On the host *Rana muscosa*, Bd shows increasing growth rates between 4-20 °C (Wilber et al. 2016) and likely decreasing growth rates after about 20 °C (Andre et al. 2008). In contrast, Bd shows increased growth on red-spotted newts (*Notophthalmus viridescens*) when temperatures are reduced from 25 to 15 °C (Raffel et al. 2015). Similar patterns of reduced growth with increasing temperature are seen for the Cuban tree frog (*Osteopilus septentrionalis*) (Raffel et al. 2012).

Given that Bd load dynamics are highly temperature dependent, how might this temperature-dependence affect whether or not Bd infection leads to population-level declines? Using the same model for Mallorcan midwife toad populations described in the previous section, Doddington et al. (2013) sought to understand why a single invaded toad population was experiencing a population-level decline, while all other invaded toad populations were either stable or increasing. Doddington et al. used their model to show that the different population level-trajectories could be largely explained by an empirically estimated, temperature-dependent increase in the rate of a toad losing a Bd infection. This study illustrates that temperature-dependent changes in Bd load dynamics can have significant implications on amphibian population trajectories. Future work should try to link both absolute changes in temperature as well as temperature variability to population-level models of amphibian-Bd dynamics (Rohr & Raffel 2010; Raffel et al. 2012; Cohen et al. 2017).

### 12.2.3 Branch point 3: Does Bd directly drive the amphibian population extinct?

Once an amphibian population has experienced Bd-induced population declines, branch point 3 determines whether Bd directly drives an amphibian population extinct or whether an amphibian population can persist with Bd at a reduced density in an enzootic state (Fig. 12.2). While we distinguish this branch point from branch point 4 in which Bd indirectly results in host extinction via either small population forces or sub-lethal effects of Bd (see next section), in practice these two branch points are difficult to distinguish and the underlying processes may even work synergistically to cause amphibian extinction (Smith et al. 2006; McCallum 2012). Some canonical examples of Bd-induced population-level extinctions include *Rana muscosa/sierrae* in North America (Vredenburg et al. 2010), multiple species in the genus *Atepolus* in Central and South America (Marca et al. 2005), species in the genus *Litoria* in eastern Australia (Laurance et al. 1996; Skerratt et al. 2007), and the common midwife toad *Alytes obstetricans* in Spain (Bosch et al. 2001). Some populations of these same species have also avoided extinction and now persist at reduced densities in an enzootic state (Retallick et al. 2004; Briggs et al. 2005; Perez et al. 2014).

Disease-induced extinction theory highlights that *transmission dynamics* ultimately determine whether or not a pathogen can drive a host population extinct (De Castro & Bolker 2005; McCallum 2012). The general criterion for a pathogen to drive a host population to extinction is that the force of infection does not decrease to zero with decreasing density of infected hosts (De Castro & Bolker 2005). This criterion can be met via a number of transmission mechanisms including frequency-dependent transmission and/or environmental reservoirs for the pathogens (McCallum 2012). Because we have discussed frequency-dependent transmission above, we focus on how abiotic reservoirs and biotic reservoirs and sinks in the ecological community affect whether or not an amphibian population experiences Bd-induced extinction.

#### 12.2.3.1 Abiotic reservoirs

Generally, if a pathogen is able to reproduce and/or persist outside of the host then decreasing host density will not necessarily lead to a decreased transmission rate as hosts will continue to encounter the pathogen in the environment. The importance of an abiotic reservoir in pathogen transmission will depend on a number of characteristics of the pathogen, such as how it persists and reproduces outside the host (Anderson & May 1981; Godfray et al. 1999; Rohani et al. 2009; Almberg et al. 2011).

Host-pathogen models show that when pathogen death rate in the environment is low and the rate of increase of the environmental pool of pathogens is high, the threshold host density that a pathogen needs to persist is reduced (Anderson & May 1981; Godfray et al. 1999). In other words, given a long-lived, constantly replenished environmental reservoir via infected hosts or saprophytic growth (i.e. growth

on decaying organic material), there is a substantial risk of disease-induced extinction as uninfected hosts will to continue to encounter the pathogen in the environment even though they are no longer encountering infected hosts. To account for the effect of the environmental reservoir on extinction dynamics, it is important to characterise the average lifetime of a pathogen in the environment, the rate at which infected hosts contribute pathogens to the environment, the reproductive rate of the pathogen in the environment, and the contact between hosts and the environmental pathogen pool. Because the Bd environmental pool is a critical component in amphibian-Bd dynamics (Mitchell et al. 2008; Kilpatrick et al. 2010; Briggs et al. 2010; Doddington et al. 2013), numerous studies have sought to quantify these four characteristics in amphibian-Bd systems.

Regarding environmental persistence, studies have shown that Bd zoospores can persist for up to seven weeks in sterilized (autoclaved) lake water (Johnson & Speare 2003) and up to twelve weeks in sterilized moist sand (Johnson & Speare 2005). Laboratory experiments have also shown the ability of Bd to persist outside the host, with zoospore death rates ranging from between 2.7 x $10^{-3}$ - 4.1 x $10^{-2}$ hour$^{-1}$, depending on temperature (Woodhams et al. 2008). Moreover, Bd has been detected in water samples from aquatic habitats and in moist terrestrial environments (Kirshtein et al. 2007; Chestnut et al. 2014; Kolby et al. 2015).

While these studies indicate that Bd can persist in the abiotic environment, there is currently limited empirical evidence on how Bd persistence affects Bd-induced extinction and understanding the details of Bd persistence in the field is still an important area of research. For example, aquatic filter feeders such as *Daphnia* or tadpoles may reduce the Bd persistence time in the environment by ingesting Bd zoospores during feeding (Buck et al. 2011; Hamilton et al. 2012; Venesky et al. 2013). Similarly, other microorganisms in the environment may compete with or consume Bd (Bletz et al. 2013; Schmeller et al. 2014), reducing its persistence time in the environment and subsequently the risk of Bd-induced extinction (Godfray et al. 1999).

Infected amphibian hosts can also potentially produce large number of infective zoospores that contribute to the environmental pool (Box 12.1; Briggs et al. 2010; DiRenzo et al. 2014). The number of zoospores produced per zoosporangium varies with temperature and one study found it to be between 161 at lower temperatures (10 C) and 65 at higher temperatures (23 C) (Woodhams et al. 2008). However, linking this single zoosporganium production to the production of zoospores by an infected amphibian in the field is still very much a work in progress. Similarly, while zoospore saprophytic growth of Bd in the environment is possible, there is not yet any evidence that this is occurring.

Finally, the environmental zoospore pool is only important if amphibian hosts actually come in contact with it. To experimentally address the importance of the environmental pool in transmission, Courtois et al. (2017) performed a field experiment in an alpine lake in which uninfected common midwife toads *Alytes obstetricans* were either in contact with or not in contact with other infected toads. Uninfected

toads not in contact with other infected toads still became infected with Bd, indicating that infection was occurring through contact with zoospores in the environment (Courtois et al. 2017). The importance of the environmental zoospore in Bd infection was also demonstrated in the stream dwelling green-eyed tree frog *Litoria serrata* (Hagman & Alford 2015).

While these experiments demonstrate that contact with the zoospore pool is occurring, contact will vary with the life history and behavior of amphibian species. For example, if adult amphibians are primarily terrestrial (e.g. Darwin's frog *Rhinoderma darwinii*, Valenzuela-Sánchez et al. 2015) or actively avoid zoospores (e.g. McMahon et al. 2014), then this will limit contact with the zoospore pool and transmission will have to be driven by other mechanisms. Moreover, host behavior can interact with the motility of Bd zoospores, which is typically less than two centimeters (Piotrowski et al. 2004). For example, largely sedentary hosts might have lower contact rates with zoospores in the environment than more vagile hosts. On the other hand, hydrological dynamics can drastically increase the distance zoospores can travel (Hagman & Alford 2015) and may increase rate at which sedentary hosts contact zoospores.

Including these characteristics of the zoopore pool into population-level models has helped identify when amphibian-Bd populations will show Bd-induced extinction versus enzootic dynamics. Briggs et al. (2010) developed an individual-based model to explore when *R. muscosa*-Bd systems exhibited Bd-induced extinction and when they could persist in an enzootic state with Bd (Box 12.3). Briggs et al. (2010) included host demography and stage-structure as well as a dynamic zoospore pool in which zoospores were added at some rate from infected frogs and removed from the environmental pool based on 1) the death rate of the zoospores in the environment and 2) the rate of zoopores in the environment encountering and encysting on an amphibian host (Box 12.3). Importantly, Briggs et al. explicitly tracked the Bd load on each individual frog so that infected frogs with more zoosporangia contributed proportionally more zoospores to the environmental pool.

[Box 12.3 here]

This model produced results consistent with previous theory on environmental reservoirs and highlighted additional complexities in amphibian-Bd systems. For example, Drawert et al. (2017) used the model to show that reducing amphibian density (e.g. via culling) had little net positive effect on mitigating Bd-induced amphibian extinction. While reducing host density via culling is a possible strategy for managing density-dependent wildlife diseases (Lachish et al. 2010; Woodhams et al. 2011), the ineffectiveness of simulated culling in amphibian-Bd systems is consistent with theory showing that pathogens with long-lived environmental stages and a high rates of production of pathogens via hosts will be able to persist in a host population even when host density is quite low (Anderson & May 1981). In place of the importance of host density in determining population-level outcomes, Briggs et al. (2010) found that density-independent characteristics of zoospores, such as the rate at which zoospores reinfected

the same amphibians after being released from the zoosporangia, could determined whether or not an amphibian population experienced Bd-induced extinction or persisted enzootically with Bd. Similarly, experimentally-parameterised models exploring disease-induced extinction in the European common toad *Bufo bufo* and the Mallorcan midwife toad *Alytes muletensis* found that host extinction was sensitive to the persistence and reproduction of Bd in the environment (Mitchell et al. 2008; Doddington et al. 2013). Taken together, these studies show that differences in zoospore pool dynamics can determine whether one population experiences Bd-induced extinction or enzootic persistence following disease-induced population decline.

#### 12.2.3.2 Biotic reservoirs and sinks

Biotic reservoirs and composition of the amphibian community also play an important role in determining whether or not disease can drive a host population extinct (McCallum 2012). We loosely define a biotic reservoir as an alternative host for the pathogen that is generally more tolerant than the focal host. The simplest way that a biotic reservoir can increase the risk of disease-induced extinction is by providing an alternative host on which a pathogen can reproduce and persist, independent of the density of the focal host. Similar to pathogen reproduction in the environment, an alternative biotic reservoir would allow the density of a focal host to decrease without decreasing the force of infection.

Intra-specific and inter-specific biotic reservoirs have been identified in amphibian-Bd systems. In some frog species, long-lived tadpoles do not suffer from chytridiomycosis and can provide biotic reservoirs in which Bd can persist and replicate (Briggs et al. 2010). The aforementioned model by Briggs et al. (2010) (Box 12.3) showed that the presence of a tadpole reservoir could help maintain Bd in *R. muscosa* populations. Tadpoles can also be sinks for Bd zoospores. In some species of anurans, such as the African clawed frog (*Xenopus laevis*) and Eastern narrowmouth toads (*Gastrophryne carolinensis*), tadpoles can reduce the abundance of Bd zoospores by filtering them out of the environment (E. Wilson personal communication, Venesky et al. 2013). If tadpoles both increase zoospore density in the environment by providing a reservoir and decrease zoospore density by filtering, the net effect of tadpoles on Bd transmission and resulting Bd-induced amphibian declines will depend on the relative rates of these two processes.

Both amphibian and non-amphibian reservoirs of Bd have abeen identified. Bd has been detected on water fowl (Garmyn et al. 2012), crayfish (McMahon et al. 2013), zebrafish (Liew et al. 2017), and reptiles (Kilburn et al. 2011). Of these, only crayfish and zebrafish have been shown to maintain Bd infections (McMahon et al. 2013; Liew et al. 2017) and only crayfish have been shown to transmit this infection to amphibian hosts (McMahon et al. 2013). Within a community of amphibians, it is not uncommon for some species to be at high risk of Bd-induced declines and others to be relatively tolerant of Bd (Stockwell et al. 2016; Scheele et al. 2017). In this case, Bd can replicate on tolerant host species,

enter the environmental pool, infect susceptible host species, and drive them to extinction (McCallum 2012). For example, Pacific chorus frogs (*Pseudacris regilla*) are a relatively tolerant of Bd and may contribute to Bd-induced declines of mountain yellow-legged frogs by functioning as a reservoir for Bd (Reeder et al. 2012). Moreover, it is possible that some species of amphibians within a community could be "supershedders" that release a disproportionately large number of zoopsores into the environment over the course of Bd infection (DiRenzo et al. 2014). Similar to "superspreaders" (Lloyd-Smith et al. 2005b; Streicker et al. 2013), "supershedders" could significantly increase the severity of epizootics and the Bd-induced extinction risk for other amphibian species in the community by increasing both the force of infection as well as the zoospore dose upon initial infection.

Alongside their potential as reservoirs, other amphibian species may function as 'sinks' for infection, raising the question of how changes in amphibian community composition and diversity are likely to influence overall transmission. It is well-established that changing host diversity *per se* can have a variety of impacts on host-parasite dynamics, including shifts in susceptible host density, in the encounter probability between host and parasite, and in the persistence or virulence of an infection (e.g. Keesing et al. 2006; Johnson et al. 2015). In particular, the reduction of pathogen transmission with increased host diversity (i.e., the dilution effect hypothesis) has received substantial empirical support in many different disease systems (Keesing et al. 2010; Ostfeld & Keesing 2012; Civitello et al. 2015). Whether diversity is likely to increase or decrease infections will depend strongly on the order in which amphibian species assemble: if highly susceptible species tend to be replaced by more resistant species as diversity increases, then dilution effects are likely (see Johnson et al. 2013). If, however, resistant species are instead replaced by susceptible or tolerant taxa at higher richness – or if overall host density grows with diversity – amplification effects may occur. Thus far, experimental studies focused on amphibian-Bd interactions have found evidence consistent with a dilution effect, such that increasing amphibian community diversity decreased Bd abundance and prevalence, after controlling for confounding effects of host density (Searle et al. 2011; Venesky et al. 2013; Becker et al. 2014). In some cases, the effects of particular amphibian taxa on infection have been extended to field-based patterns of infection (e.g. Venesky et al. 2013), lending further evidence to the potential importance of specific species on transmission.

### 12.2.4 Branch point 4: Does Bd indirectly drive the amphibian population extinct?

Branch point 3 illustrates that direct Bd-induced extinction is a result of both the transmission dynamics driving the system (branch point 3) as well Bd-induced mortality (branch point 2 and 3). However, Bd can also indirectly hasten the extinction of amphibian populations by two distinct mechanisms: through sub-lethal effects of Bd on amphibian fitness and through forces that hasten the extinction of small populations (Fig 12.2, Lande 1993; Lande et al. 2003; Garner et al. 2009). Many of the empirical

examples of Bd-induced population extinction mentioned in the previous section were likely augmented by these indirect effects of Bd on amphibian populations.

There are instances where the *transmission dynamics* and the *load dynamics* of an amphibian-Bd system are such that direct, Bd-induced extinction is unlikely (Briggs et al. 2010; Doddington et al. 2013). For example, if Bd is highly virulent and zoospores only persist for a short time in the environment relative to the dynamics of the infection on an amphibian, then Bd invasion might lead to an initial, rapid population decline, but will fail to drive the population to extinction. Amphibians and Bd might then persist in an enzootic state (Box 12.3, Briggs et al. 2010; Fisher et al. 2012; Doddington et al. 2013). In these cases, population-level extinction can still occur, but may be due to sub-lethal effects of Bd on amphibian hosts or the result of small population forces.

#### 12.2.4.1 The extinction of small populations

As population size decreases, the probabilistic nature of births and deaths of individuals in the population known as demographic stochasticity can to lead population-level extinction – this can occur even if the small population is not expected to decline (Lande 1993; Lande et al. 2003). The probability of extinction due to demographic stochasticity is directly related to population size, such that its effects are largest in smaller populations (Lande et al. 2003). In the context of host-pathogen systems, this implies that even if a pathogen does directly drive a host population extinct and the population is able to persist either without the pathogen or in an enzootic state (see Box 12.3), a severe initial epizootic in which the host population is substantially reduced will increase the probability of population extinction. Therefore, understanding the factors determining the size of an initial Bd epizootic are critical for determining extinction risk due to small population forces.

[Figure 12.9 here]

One simple factor that augments the size of a Bd epizootic is the initial density of susceptible hosts. To illustrate this, consider a simple SIS model (Fig. 12.2A) with density-dependent transmission in which amphibians do not recover from infection (i.e. $\gamma = 0$). Given this model, the proportion of hosts that remain uninfected after the epizootic ($s(\infty)$) is given by the root of the equation $\ln(s(\infty)) = R_0(s(\infty) - 1) + \ln(s(0)$, where $s(0)$ is the proportion of susceptible hosts at the start of the epizootic (Diekmann & Heesterbeek 2000). Figure 12.9 shows that populations with larger initial population density actually experience much larger disease-induced population declines and are thus more susceptible to extinction due to demographic stochasticity following an epizootic than populations with small initial densities. This result highlights that even without transmission from an environmental reservoir and/or frequency-dependent transmission, large amphibian populations can still be at substantial risk of extinction. This might be a very real risk for amphibian species where there is little probability of recovery after initial infection and initial population densities are high (Fisher et al. 2012). As mentioned in branch point

2, Bd-load dynamics will also influence the severity of this decline so it will be important for studies to quantify how amphibian mortality rate and recovery rate are affected by the current Bd load of an amphibian host.

#### 12.2.4.2 Sub-lethal effects of Bd on amphibian hosts

While Bd-induced mortality due to chytridiomycosis is the most obvious way that Bd can affect amphibian hosts, there are a number of sub-lethal effects of chytridiomycosis that have important implications for host fitness. For example, Garner et al. (2009) exposed tadpoles of the common midwife toad *Alytes obstetricans* to different doses of Bd and found that, while tadpoles were able to clear Bd infections, tadpole survival probability through metamorphosis and the body size at metamorphosis were significantly reduced with increasing Bd exposure. A number of additional studies have also shown that Bd infection can reduce body mass of tadpoles, metamorphs and adults (Retallick & Miera 2007; Hanlon et al. 2015; Caseltine et al. 2016), in some cases even after Bd infection is cleared (Luquet et al. 2012). Depending on the amphibian species, the mechanisms by which Bd reduces body size can differ. For example, Garner et al. (2009) found that body size reduction in common midwife toad tadpoles was a cost of clearing the Bd infection and Hanlon et al. (2015) found that reduced body size in Bd-infected southern leopard frog *Lithobates sphenocephalus* tadpoles was because Bd-damaged mouthparts reduced foraging efficiency.

The sub-lethal effects of Bd on amphibian body size can have important implications on amphibian reproduction. Increased amphibian body mass at metamorphosis has been shown to increase post-metamorphic survival and decrease the time until reproductive body size is obtained (Smith 1987; Altwegg & Reyer 2003). Similarly, it is speculated that decreased female body condition can lead to reduced egg size (Garner et al. 2009), which results in reduced tadpole growth rate and body size at metamorphosis (Laugen et al. 2002) and, subsequently, reduced tadpole survival (e.g. Semlitsch 1990). If the sub-lethal effects of Bd act to reduce amphibian body size, which in turn impacts reproduction and the survival of the next generation of tadpoles, population-level declines and extinctions can occur even if Bd is no longer present in the population. In terms of the framework presented in this paper, this means that in addition to considering the current *load dynamics* in an amphibian-Bd system, one must sometimes account for the past load dynamics (e.g. the initial Bd exposure) in order to understand the current population-level trajectory.

### 12.2.5 Branch point 5: Does the amphibian population recover from Bd-induced population declines?

The final branch point we consider is if, after persisting in an enzootic state with reduced population density, the amphibian population begins to increase in the presence of Bd (Fig. 12.2). This population-level trajectory has been observed in many *R. sierrae* populations in Yosemite National Park, CA, USA

that are now showing significant increases in population size in the presence of Bd (Knapp et al. 2016). The recovering populations tend to have significantly lower Bd loads than those observed during the initial epizootic in comparable previously naive populations (Knapp et al. 2016). Similarly, populations of the whistling tree frog *Litoria verreauxii verreauxii*, which likely experienced past Bd-induced population declines in south eastern Australia, have recently shown range expansion and population increases in the presence of Bd (Scheele et al. 2014, 2017).

Amphibian population recoveries following Bd-induced declines are only beginning to be documented and the mechanisms affecting this branch point are not yet well understood. In theory, both changes in *transmission dynamics* and *load dynamics* could promote recovery of amphibian populations. If an amphibian-Bd system is largely driven by density-dependent transmission, reduction in host density following an epizootic would decrease the force of infection such that recruitment may be able to compensate for Bd-induced mortality (Tobler et al. 2012; Scheele et al. 2014). However, Bd prevalence can also remain high in some enzootic populations (e.g. $>$ %50; Briggs et al. 2010; Scheele et al. 2014), such that some change to the Bd load dynamics (e.g. resistance or tolerance) or Bd virulence is necessary in order for host recruitment to compensate host mortality. Here we restrict our attention to the load-dependent mechanism of population recovery, recognizing that changing transmission dynamics and/or environmental variables such as temperature may also be playing a role in population recovery.

#### 12.2.5.1 Variation in and evolution of resistance and tolerance in amphibian hosts

For resistance or tolerance to rescue an amphibian population from Bd-induced extinction, the trait conferring resistance or tolerance needs to be heritable and increase in abundance such that population growth rate is greater than 0 before the amphibian population is extinct. This type of rescue is called evolutionary rescue (Gonzalez et al. 2013; Vander Wal et al. 2014). Evolutionary rescue through resistance or tolerance in a closed population can occur through two distinct mechanisms. First, the resistance or tolerance trait may not be present in the population when Bd invades and is introduced into the population via mutation after Bd invasion. The trait must then avoid stochastic extinction and increase in abundance (Orr & Unckless 2014). Second, the resistance or tolerance trait may already be present in the population at low abundance upon Bd invasion. It may then avoid stochastic extinction and increase in abundance (Orr & Unckless 2014). If one of these evolutionary mechanisms rescues the population, then the amphibian population can begin to recover (Orr & Unckless 2014).

Given the drastic decrease in population growth rate in many Bd-infected amphibian populations (e.g. *R. muscosa* median yearly population growth rate $r \approx -4$ following Bd invasion; Vredenburg et al. 2010), the long generation time of many amphibians relative to the speed of Bd-induced declines, and the low single-locus, per generation mutation rate (Schoville et al. 2011; Albert et al. 2015), standing variation in resistance and tolerance seems a more likely mechanism than mutation for rescuing amphib-

ian populations from extinction and promoting recovery. In fact, studies have identified individual-level and population-level variation in genetic traits putatively leading to Bd resistance (Savage & Zamudio 2011; Ellison et al. 2015; Savage & Zamudio 2016). Moreover, studies have also identified signatures of directional selection on these alleles conferring Bd resistance following Bd invasion, tentatively suggesting that selection for these traits is helping rescue some vulnerable amphibian populations (Savage & Zamudio 2016). However, not all amphibian populations that have experienced Bd-induced population declines and are persisting in an enzootic states show evidence for directional selection (Tunstall 2012), emphasizing that other factors, such as environmental variability or the evolution of Bd virulence, may be responsible for preventing Bd-extinction and promoting population recovery. Given that large-scale population recoveries in the presence of Bd are beginning to be documented for multiple amphibian species (Knapp et al. 2016; Scheele et al. 2017), determining the role of resistance and tolerance in whether or not amphibian populations recover from Bd epizootics is an emerging frontier in empirical and theoretical amphibian disease ecology.

#### 12.2.5.2 The evolution of Bd virulence

Evolutionary changes in Bd can also have a significant effect on Bd load dynamics and thus the ability of a host population to recover. Of particular interest for this branch point is the evolution of Bd toward reduced virulence, such that an impacted amphibian population can begin to recover. *In vitro*, Bd has shown a propensity to evolve rapidly over short periods of time (Voyles et al. 2014). Laboratory studies show that simply passaging Bd over multiple generations can lead to decreased virulence (Langhammer et al. 2013). This attenuation in virulence is correlated with reduced chromosomal copy numbers, suggesting a genetic component to virulence attenuation (Refsnider et al. 2015). Complementing these laboratory results, recent field studies have shown reduced Bd virulence eight to ten years following epizootics and amphibian declines in Panama (Voyles et al. 2015). In these same regions, some species of frogs in the genus *Atelopus* that experienced drastic Bd-induced declines are now persisting in an enzootic state with Bd, though there is not yet evidence of population recovery (Perez et al. 2014). More studies are needed to understand the evolution of Bd virulence over the course of an epizootic and how this affects both the ability of amphibian populations to enter an enzootic state (branch point 3) and recover from disease-induced declines (branch point 5). This is will require repeated Bd samples throughout the epizootic, enzootic, and recovery trajectories.

## 12.3 Future directions

Our framework identifies two particular characteristics of amphibian-Bd systems that need immediate attention to improve our understanding of variable population-level outcomes following Bd invasion: the

nature of Bd transmission and the ability of amphibians to regulate their Bd load through resistance or tolerance mechanisms. Regarding transmission, theory shows us that the ability of Bd to invade the system (branch point 1), the propensity of Bd to cause host extinction (branch point 3), and the propensity of populations to recover from Bd-declines (branch point 5) are all largely determined by the characteristics of Bd transmission. However, there are few published studies that have successfully identified the factors leading to Bd transmission. To fill in this important data gap, experiments are needed that simultaneously manipulate amphibian host density and track the number of zoospores in the zoospore pool. These types of experiments will enable researchers to parse apart the relative importance of host to host contact versus environmental contact in transmission (Courtois et al. 2017). If these experiments are not possible, fitting and comparing different transmission models to time series data of infected amphibian populations can provide an alternative way to identify the basic structure of the transmission function (e.g. McCallum et al. 2009; Morris et al. 2015). Without at least a rudimentary understanding of the transmission function in a particular amphibian-Bd system, strategically mitigating Bd-induced population declines is all but impossible.

Regarding resistance and tolerance, it is becoming increasingly evident that the severity of Bd-induced population declines as well as the ability of amphibians to recover from Bd epizootics depends on the ability of amphibians within the population to regulate their Bd load through resistance or tolerance mechanisms (Knapp et al. 2016; Savage & Zamudio 2016). Thus it will be important for future studies to identify the role of heterogeneity in resistance and/or tolerance as well as the mechanisms underlying these traits (Savage & Zamudio 2011; Ellison et al. 2015; Savage & Zamudio 2016). Moreover, it will be critical for future studies to determine the heritability of these resistance and tolerance traits and any trade-off that they have with host fitness (Elderd et al. 2008; Boots et al. 2009). Trade-offs, in particular, are problematic because they are both highly influential on the system dynamics and difficult to quantify empirically (Boots et al. 2009). Ideally, some type of common-garden experiment is needed in which susceptible and non-susceptible amphibian populations are reared in the absence and presence of Bd and reproductive success (or a well-known proxy) is measured.

## 12.4 Conclusions

Determining why amphibian populations, and host populations in general, show variable outcomes in response to pathogen invasion is a major conservation goal (Woodhams et al. 2011; Langwig et al. 2015). Here we identify eight general population-level trajectories in response to Bd infection that have been observed in amphibian populations and five branch points at which amphibian populations can diverge along these different trajectories. By identifying how and when transmission dynamics and load dynamics affect the trajectories of amphibian populations at each branch points, this framework can be used to

inform the most reasonable management strategies conditional on the current and past trajectory of an amphibian-Bd system (e.g. should one manage for transmission dynamics, load dynamics, or both?).

Underlying the framework we have presented here are many ecological, evolutionary, and environmental factors affecting the transmission and load dynamics in amphibian-Bd systems. While we have addressed some of these factors above, there are a number of important ones that we did not directly address. These include, but are not limited to, microbial communities on amphibian hosts which can either alter or be altered by Bd load dynamics (Harris et al. 2009; Jani & Briggs 2014), coinfection of amphibian hosts with other micro or macroparasites (Whitfield et al. 2013), and adaptive immunity (McMahon et al. 2014). These factors can also be considered in terms of how they affect transmission and Bd load dynamics and, depending on the system, will play an important role in determining the trajectory an amphibian population takes at a particular branch point. By integrating epidemiological theory and extensive data from amphibian-Bd systems, we can place seemingly disparate population-level trajectories across amphibian-Bd systems in terms of a number of context-dependent branch points to help better understand and manage amphibian declines and recoveries.

## 12.5 Acknowledgments

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**Box 12.1: Chytrid fungus and amphibian declines**

*Natural history of* Batrachochytrium dendrobatidis

*Batrachochytrium dendrobatidis* (Bd) is an aquatic fungus that is responsible for the declines and extinctions of over 500 species of amphibians across the globe (Fisher et al. 2012). The life cycle of Bd consists of two stages: a free-living, motile zoospore and a reproductive zoosporangium (Longcore et al. 1999). Motile Bd zoospores encysts in the keratinised tissue of amphibian skin and form zoosporangia (Kilpatrick et al. 2010). Additional zoospores then form within this zoosporangium and are released back into the aquatic environment where they can immediately reinfect the same host or become part of the environmental pool of zoospores (Rollins-Smith 2009; Kilpatrick et al. 2010).

Amphibians infected with Bd can suffer from the disease known as chytridiomycosis. The symptoms of chytridiomycosis can include lethargy, increased skin sloughing, lack of appetite, and mortality (Voyles et al. 2007). Chytridiomycosis causes amphibian death by disrupting the ability of amphibian skin to osmoregulate, which leads to sever osmotic imbalance and cardiac arrest (Voyles et al. 2007, 2009). Chytridiomycosis can also have sub-lethal, negative effects on amphibians including reduced foraging in tadpoles (Hanlon et al. 2015), reduction in body size (Hanlon et al. 2015), and, potentially, a decrease in reproduction ability (Bielby et al. 2015).

*Bd and the mountain yellow-legged frog*

Many of our examples throughout the text focus on Bd dynamics in populations of the mountain yellow-legged frog complex (*Rana muscosa* and *Rana sierrae*) (Box 12.1). Mountain yellow-legged frogs live in high elevation lakes and streams in the Sierra Nevada mountains in California, USA. While once abundant throughout the Sierra Nevada, the introduction of trout for recreational fishing between the 1900 and 1960 led to large declines in mountain yellow-legged frog populations (Knapp & Matthews 2000; Knapp et al. 2001, 2016). After the introduction of trout, Bd likely invaded Yosemite National Park in the Sierra Nevada in the 1970's and *R. sierrae* populations suffered severe Bd-induced declines (Knapp et al. 2016). Currently, *R. sierrae* are actually showing a large-scale population recovery in the presence of Bd (Knapp et al. 2016). In contrast, populations of *R. muscosa* in more southern regions of the Sierra Nevada are currently experiencing Bd-induced declines and extinctions (Briggs et al. 2005; Vredenburg et al. 2010; Jani et al. 2017). However, there are some populations of *R. muscosa* where Bd has failed to invade, some that are able to persist with Bd with minimal population-level impacts, and some that seem to be persisting following severe population declines (R.A. Knapp, unpublished). Conservation efforts such as translocations of persistent populations, fungicide treatments, and captive breeding are all currently being implemented to attempt to mitigate these Bd-induced population declines (R.A. Knapp et al., unpublished).

[Fig. 12.1 here]

**Box 12.2: Load-dependent model of amphibian-Bd dynamics and extensions**

*An amphibian-Bd Integral Projection Model*

Understanding the load dynamics of Bd is important for predicting the population-level trajectory of an amphibian-Bd system (Briggs et al. 2010; Jani et al. 2017). To this end, Wilber et al. (2016) developed a discrete-time variant of an SIS model (Fig. 12.2A) in which Bd load was modeled as a continuous host attribute. Bd load is considered continuous because in practice it is measured via molecular analyses from standardised amphibian skin swabs (Boyle et al. 2004).

This discrete-time, continuous-load model takes the form of an Integral Projection Model (IPM) (Easterling et al. 2000) and is useful because it can be directly parameterised from host-level data. Specifically, the number of susceptible hosts in a population at time $t+1$, $S(t+1)$, is given by

$$S(t+1) = S(t)s_0[1-\phi(I(x,t))] + \int_x I(x,t)s(x)l(x)dx \tag{2}$$

where the length of a time step is on the scale of the generation time of Bd (4 – 10 days, Woodhams et al. 2008). The first term in this equation gives the number of susceptible hosts who survive ($s_0$) and remain uninfected ($1-\phi(I(x,t))$) in a time step. $\phi(I(x,t))$ is the transmission function, which is defined below. The second term gives the number of infected hosts who survive with a Bd load $x$ ($s(x)$), lose an infection ($l(x)$) and enter the susceptible class in a time step.

The number of infected hosts with Bd load $x'$ at time $t+1$ ($I(x',t+1)$) is given by

$$I(x',t+1) = \int_x I(x,t)s(x)(1-l(x))G(x',x)dx + S(t)s_0\phi(I(x,t))G_0(x') \tag{3}$$

The first term in this equation gives the number of infected individuals that survive with load $x$ ($s(x)$), do not lose their infection ($1-l(x)$) and transition to load $x'$ in a time step ($G(x',x)$). The second term gives the number of uninfected individuals that transition to an infected individual ($\phi(I(x,t))$) with load $x'$ ($G_0(x')$) in a time step.

Finally, the number of zoospores in the zoospore pool at time $t+1$ ($Z(t+1)$) is given by

$$Z(t+1) = Z(t)\nu + \mu_A \int_x xI_A(x,t)dx - \psi(S_A(t), Z(t)) \tag{4}$$

where $\nu$ is the survival probability of zoospores in a time step, $\mu_A$ is the proportion of total zoospores on adults that are contributed to the zoospore pool in a time step, and $\psi(S_A(t), Z(t))$ is the removal of zoospores from the zoospore pool by frogs transitioning from uninfected to infected.

[Figure 12.4 here]

$\phi(I(x,t))$ describes the transmission function of the amphibian-Bd system under consideration. For example, in the *R. muscosa*-Bd system, a mesocosm experiment demonstrated that the best-fit transmission function had the form

$$\phi(Z(t), I(x,t)) = 1 - \exp\left(-[\beta_0 Z(t) + \beta_1 \int_x I(x,t)dx]\right) \quad (5)$$

where $\beta_0$ and $\beta_1$ are both transmission parameters with units time$^{-1}$. This function shows that transmission depends on both contacts with the zoospore pool and contacts with infected hosts (Wilber et al. 2017).

The above equations are composed of five load-dependent vital rate functions ($s(x)$, $l(x)$, $G(x', x)$, $G_0(x')$, $\phi(I(x,t))$ all of which can be estimated from individual-level trajectories of Bd loads and Bd transmission experiments (Wilber et al. 2016). These estimated functions can then be used to parameterize the load-dependent IPM.

*Including temperature-dependence in the host-parasite IPM*

Temperature-dependence can be included in this IPM framework by allowing the various vital rate functions to depend on temperature. For example, Wilber et al. (2016) used a laboratory experiment in which 15 *Rana muscosa* were exposed to Bd at three different temperatures (five frogs at 4, 12, and 20 °C) and their Bd loads were tracked every three days for 119 days. Using the data from this experiment, they were able to parameterize the IPM such that the loss of infection function ($l(x)$), the Bd growth function ($G(x', x)$), and the initial infection function ($G_0(x')$) all depended on temperature. This was done by using standard regression analyses to fit the various vital rate functions to the experimental data with a continuous covariate of temperature. Armed with this load-dependent and temperature-dependent IPM, as well as an experimentally parameterized transmission function for the *R. muscosa*-Bd system, Wilber et al. (2017) computed the ability of Bd to invade a fully susceptible *R. musocsa* population under different temperatures (Fig. 12.5). They found that while there was a slight protective effect of low temperatures on the ability of Bd to invade a *R. muscosa* population, this protective effect was largely removed when transmission from the zoospore pool was included (Fig. 12.5).

**Box 12.3: Exploring epizootic and enzootic dynamics in amphibian-Bd systems**

Briggs et al. (2010) used a stochastic individual-based model to explore whether the two types of dynamics observed in the mountain yellow-legged frog/Bd system in the California Sierra Nevada (i.e. epizootic and enzootic dynamics) could simply represent different time points in the same stochastic dynamical system. That is, does the observation of epizootic dynamics with a high probability of disease-induced extinction in some lakes, but enzootic dynamics with sublethal Bd infection in other lakes, actually require any differences between the lakes, e.g. in frog susceptibility, Bd virulence, and/or environmental conditions? Or, if (perhaps by random chance alone), some frogs in a lake escape death during the initial epizootic, could the population eventually reach an enzootic state, at a reduced population density, with the frogs carrying only sublethal Bd loads?

[Figure 12.7 here]

To explore this question, Briggs et al. (2010) developed a model (Fig. 12.7) that follows the number of zoosporangia on each frog $i$ at time $t$ ($S_i(t)$, "zoosporangia", i.e. the Bd load on the frog), and the number of zoospores in the lake at time t ($Z(t)$, the "zoospore pool"). The model assumes that uninfected frogs become infected only through encountering zoospores in the zoospore pool (that is, unlike in the Wilber et al. (2017) model in Box 12.2, there is no direct host-to-host transmission). Transmission from the zoospore pool occurs at rate $\beta = \gamma\nu$, where $\gamma$ is the encounter rate, and $\nu$ is the fraction of zoospores that successfully encyst on the frog skin following encounter. Each zoospore that successfully encysts on the frog becomes a zoosporangium. Zoosporangia release zoospores at rate $\eta$. The model assumes that a fraction $f$ of these zoospores immediately re-encounter the same frog, and the remaining $(1 - f)$ enter the zoospore pool. Zoosporangia die at rate $\sigma$, and zoospores in the pool die at rate $\mu$. A frog dies when its Bd load exceeds a lethal threshold, $S_{\max}$. The model assumes that when a frog dies, all of the zoosporangia on a frog also die. If $N(t)$ is the total number of (living) frogs in the population at time $t$, then the deterministic version of this model can be expressed as a system of $N(t) + 1$ ordinary differential equations (however, stochasticity plays an important role in the dynamics, so Briggs et al. (2010) instead used a stochastic version of this model):

$$S_i(t) = \beta Z(t) + \eta\nu f S_i(t) \text{ for } S_i(t) \leq S_{\max}$$
$$Z(t) = \sum_{i=1}^{N(t)} \eta(1-f)S_i(t) - \gamma N(t) Z(t) - \mu Z(t)$$

For a given set of parameters, and at given $N(t)$, this model assumes that the Bd load on a frog will either increase exponentially until it reaches $S_{\max}$ and the frog dies, or decreases exponentially, and the frog loses the infection.

This load-dependent model describes only the short-term dynamics of Bd transmission and disease-

induced mortality. To explore the long-term impact of Bd on the frog population, the demographic processes of birth, death, and maturation must be added to the model. To approximate the highly seasonal system in the California Sierra Nevada, in which the lakes are covered in ice for up to eight months per year, Briggs et al. (2010) assumed that frog reproduction occurred in a discrete pulse as soon as the lake thaws out in the spring, while Bd transmission and disease-induced mortality occurs continuously. Briggs et al. (2010) explored three alternative frog life-histories: (1) an unstructured model approximating an amphibian system with a very short tadpole stage, which assumes that all host individuals are equally susceptible to the pathogen, (2) a stage-structured model with a tadpole and an adult stage, and (3) a model that included the realistic stage-structure of the mountain yellow-legged frog system (including a tadpole stage that lasts up to 3 years, a 2 year sub-adult stage, and a long-lived adult stage). The stage-structured models assumed that maturation between the stages occurred only during the overwinter period (or at the end of the summer). In all of the models, density-dependence was included in the frog population in the recruitment to the adult stage (the model assumed that the lake could sustain a maximum of $K$ adult frogs, and any additional recruits died or dispersed away from the lake).

For the unstructured model, Briggs et al. (2010) found that either extinction of the frogs, or extinction of the pathogen, occurred for most realistic ranges of parameters. Coexistence of the frog and the fungus could occur in only a narrow region of parameter space (Fig. 12.8). However, the presence of a tadpole stage that could become infected and carry high Bd loads, but not die until after metamorphosis, could make coexistence of the frog and fungus possible over a wide range of parameters (Fig. 12.8). Coexistence was especially likely if the adult frogs tended to lose the infection, but get continually re-infected from the pool of zoospores released from the tadpoles. Similarly, and external source of zoospores (as might come from an environmental reservoir for Bd, or the presence a more Bd-tolerant host species in the lakes) can allow for coexistence of the frogs and fungus through continually re-infecting a host that would otherwise lose the infection (Fig. 12.8).

[Figure 12.8 here]

The model with the realistic stage-structure of the mountain yellow-legged frog system illustrated that the same model could produce both the enzootic and epizootic dynamics observed in the field. This suggests that alternative mechanisms, such as selection for reduced frog susceptibility and/or reduced Bd virulence are not necessary to explain the different disease dynamics observed simultaneously in different parts of the California Sierra Nevada.

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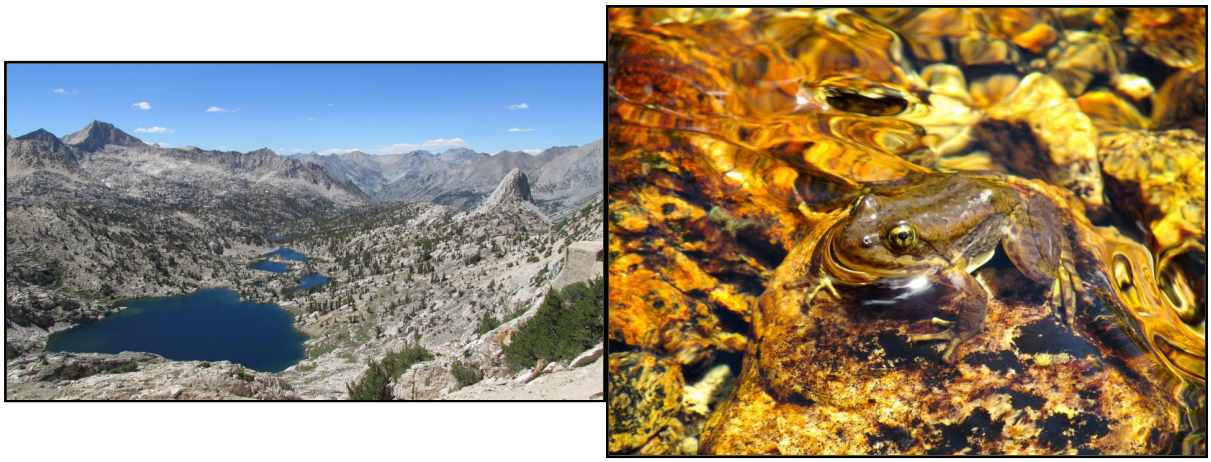

Figure 12.1: *Rana muscosa* and *Rana sierrae* live in high elevation lakes and streams in the Sierra Nevada mountains in California, USA.

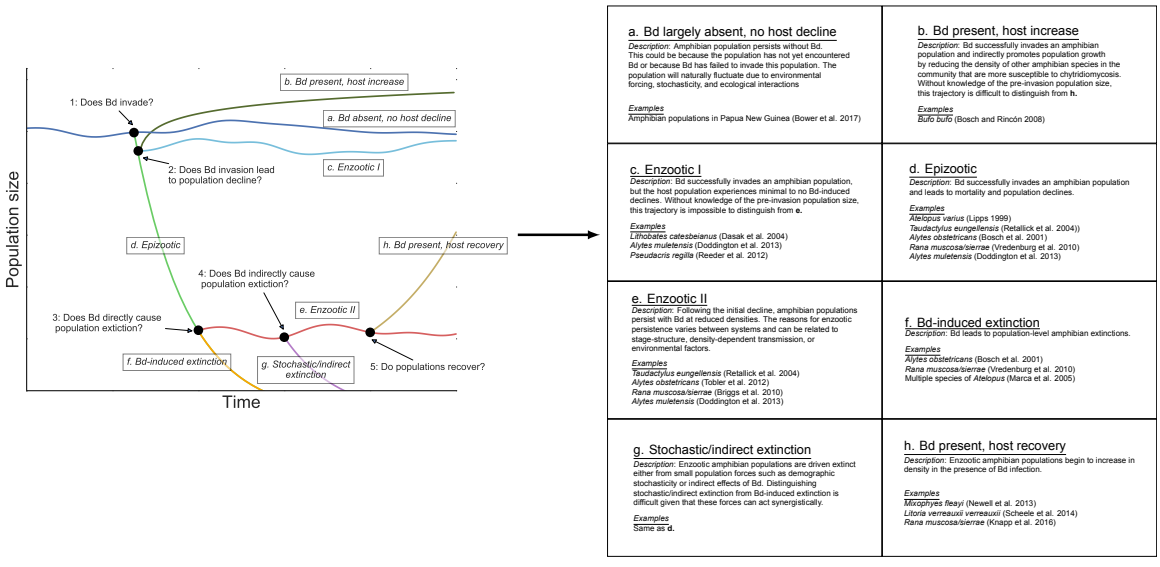


Figure 12.2: Framework for contextualizing different population trajectories in amphibian-Bd systems. The black points give the five branch points at which the trajectories of amphibian-Bd systems can diverge. The boxes refer to the different population-level trajectories observed in amphibian-Bd systems.

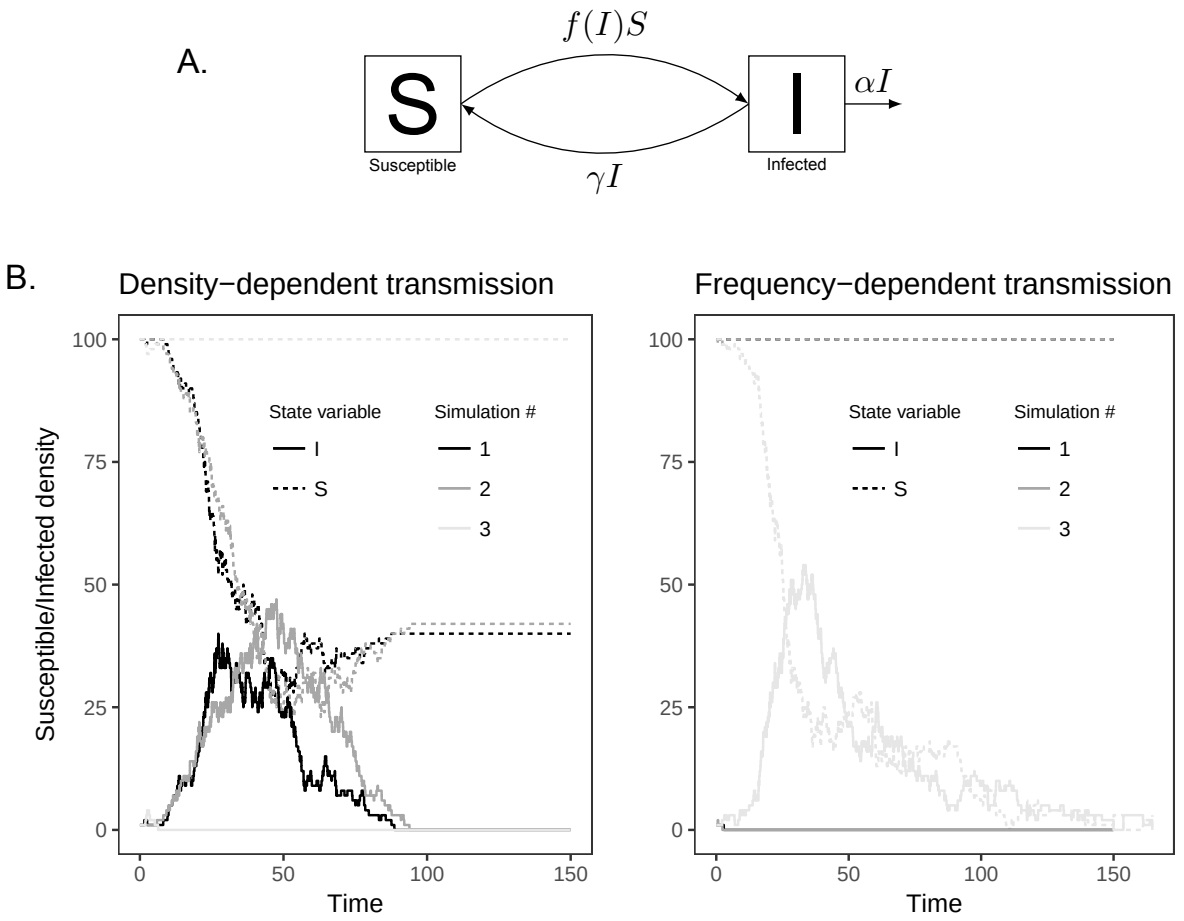


Figure 12.3: A. Susceptible-Infected-Susceptible (SIS) model where $\gamma$ is the rate of host recovery, $\alpha$ is the rate of pathogen-induced host mortality, and $f(I)$ is the force of infection describing the per capita rate at which susceptible individuals transition to infected individuals. Under density-dependent transmission $f(I) = \beta I$ and under frequency-dependent transmission $f(I) = \beta I/H$, where $H$ is the total population size B. Trajectories from three stochastic simulations of the SIS model given density and frequency-dependent transmission. Given that Bd invades, frequency-dependent transmission can directly lead to disease-induced host extinction, while density-dependent transmission cannot. Each model starts with one infected host and 100 susceptible hosts. The parameters values are $\gamma = 0.1$ time$^{-1}$, $\alpha = 0.04$ time$^{-1}$, and $f(I = 1) = 0.003$ time$^{-1}$. $R_0 = 2.14$ for both models. Notice that even though $R_0 = 2.14 > 1$ for both models, the pathogen can still fail to invade (e.g. simulation 3 for density-dependent transmission and simulations 1 and 2 for frequency-dependent transmission).

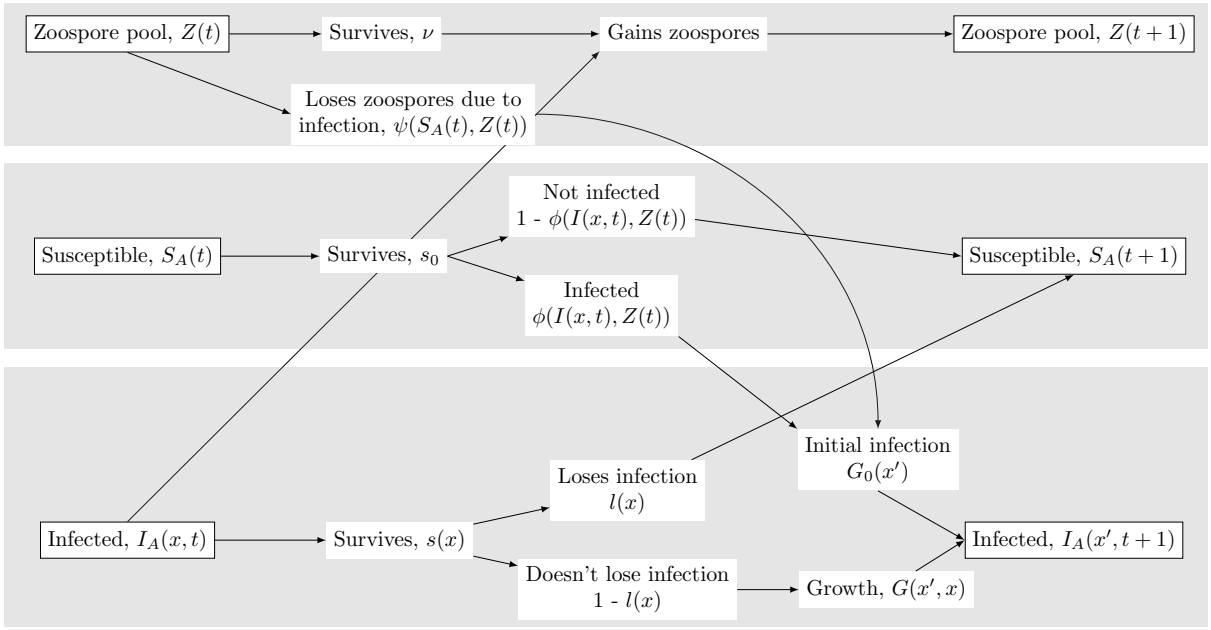


Figure 12.4: Flow chart for the host-parasite IPM model described in Box 12.2. Reproduced from Wilber et al. (2017).

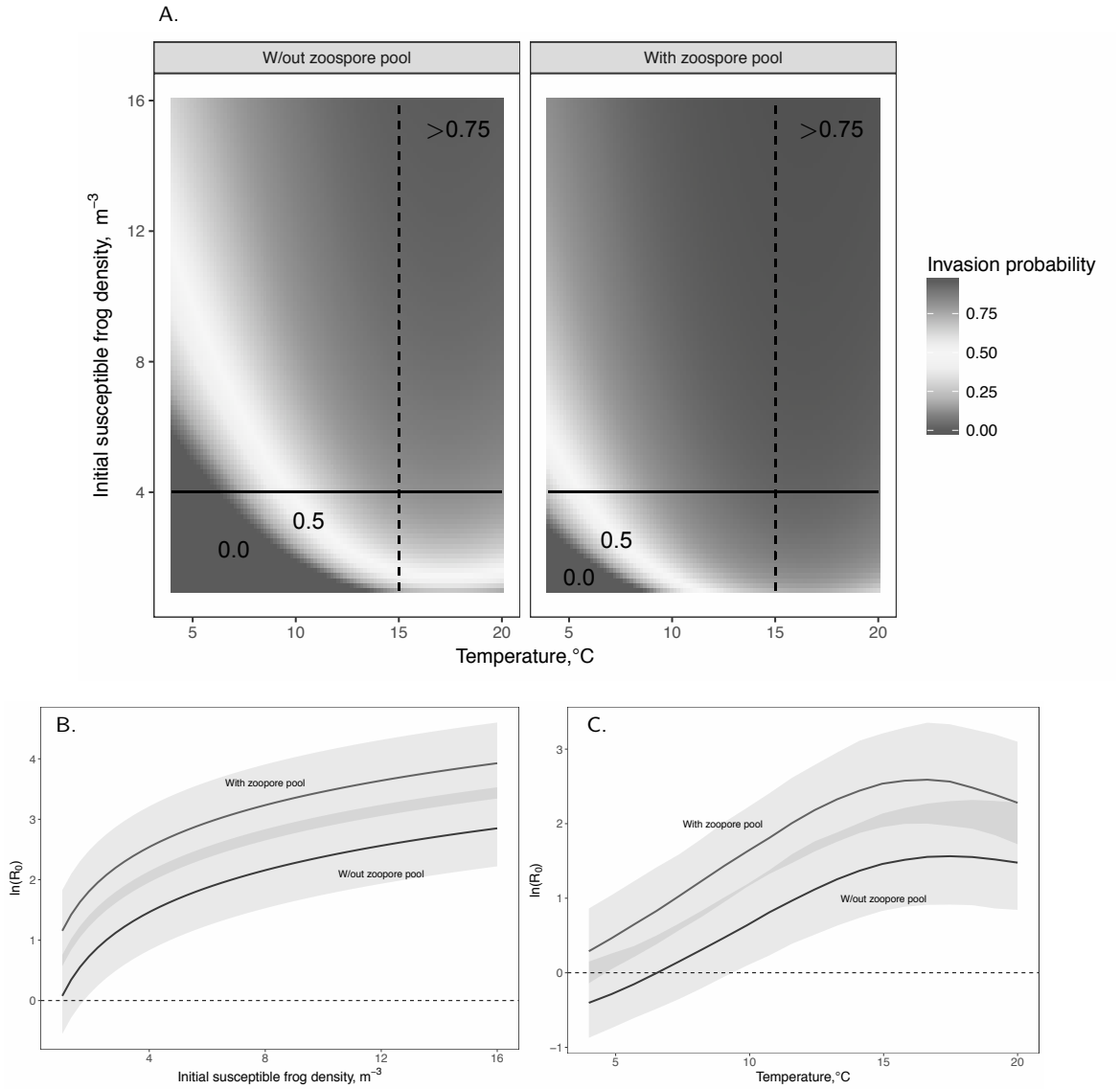


Figure 12.5: **A.** $R_0$ and the invasion probability of Bd $(1-\frac{1}{R_0})$ for different temperatures and host densities with and without an environmental zoospore pool. The numbers in A. give the invasion probability for a given region of the plot. This calculation of $R_0$ uses the experimentally estimated transmission function from Wilber et al. (2017) that includes transmission via density-dependent host contact and contact with zoospores in the zoospore pool. 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 gray 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. Figure reprinted in black and white from Wilber et al. (2017).

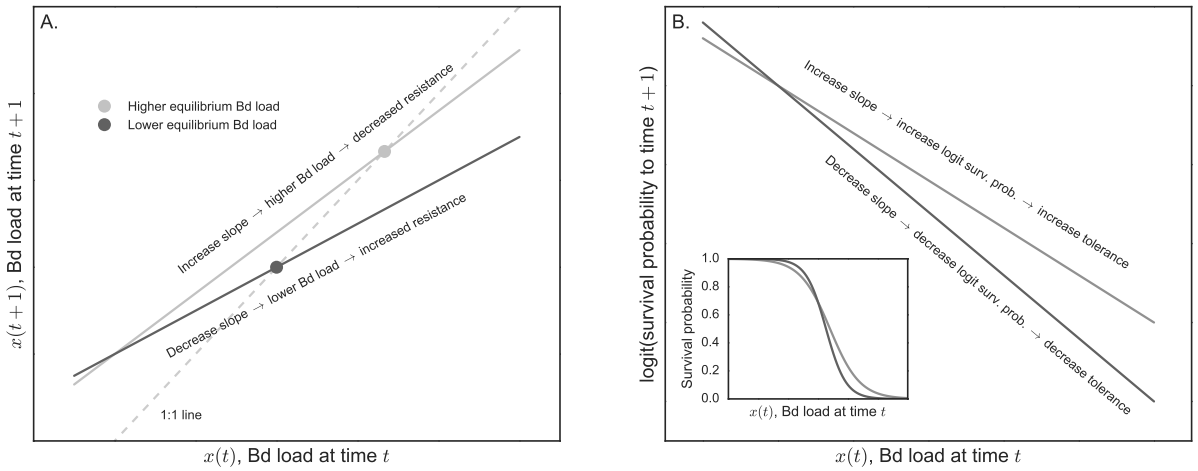


Figure 12.6: **A.** The growth function of Bd on an amphibian host ($G(x', x)$) showing how Bd load $x$ at time $t$ relates to Bd load at time $t+1$ ($x(t+1)$) and its relation to host resistance. **B.** The survival function $s(x)$ and its relation to host tolerance. "logit" indicates a logit transform on survival probability. The inset plot shows how logit host survival probability translates into survival probability.

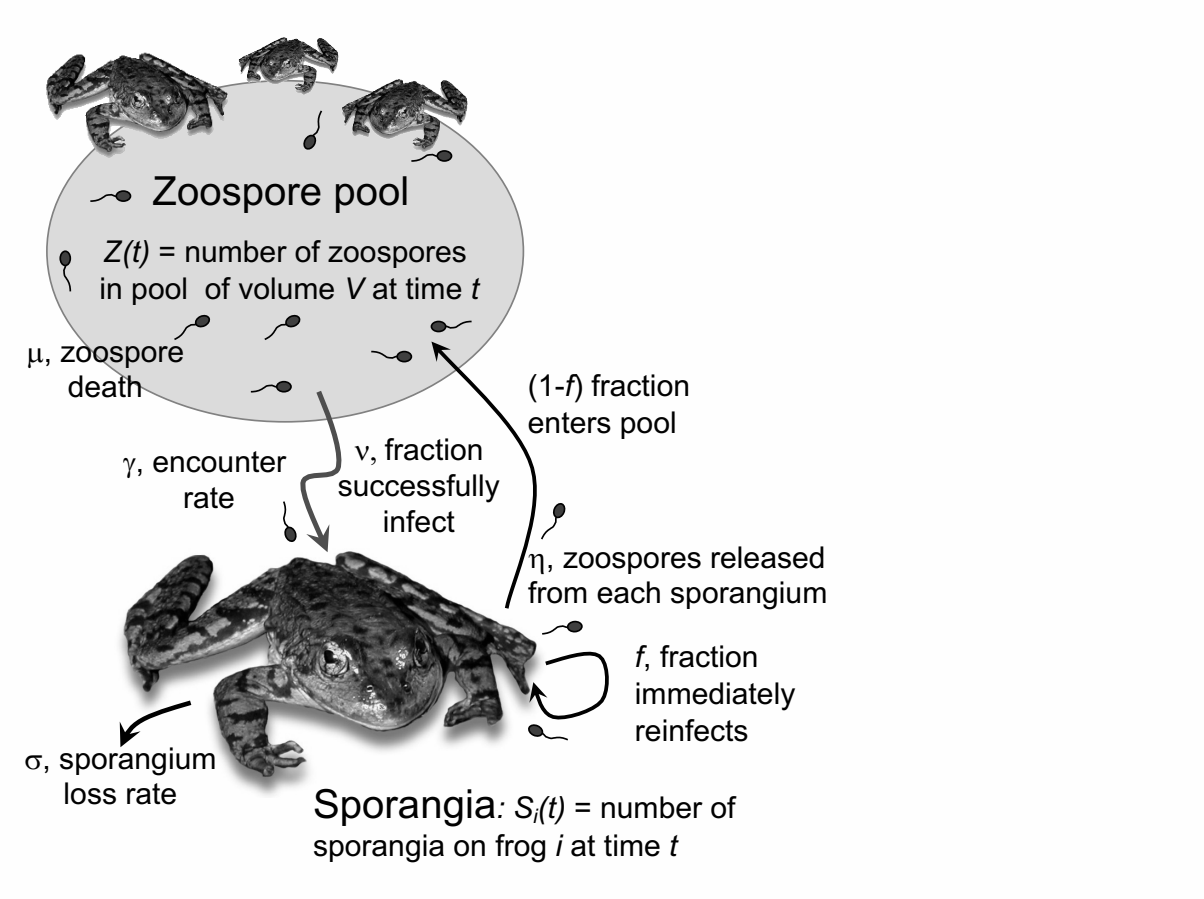


Figure 12.7: Diagram of Bd load dependent model describing Bd transmission and disease-induced mortality. The model follows $S_i(t)$, the number of sporangia on each frog $i$, and $Z(t)$, the number of zoospores in a body of water (the zoospore pool), at time $t$. Figure reprinted from Briggs et al. (2010).

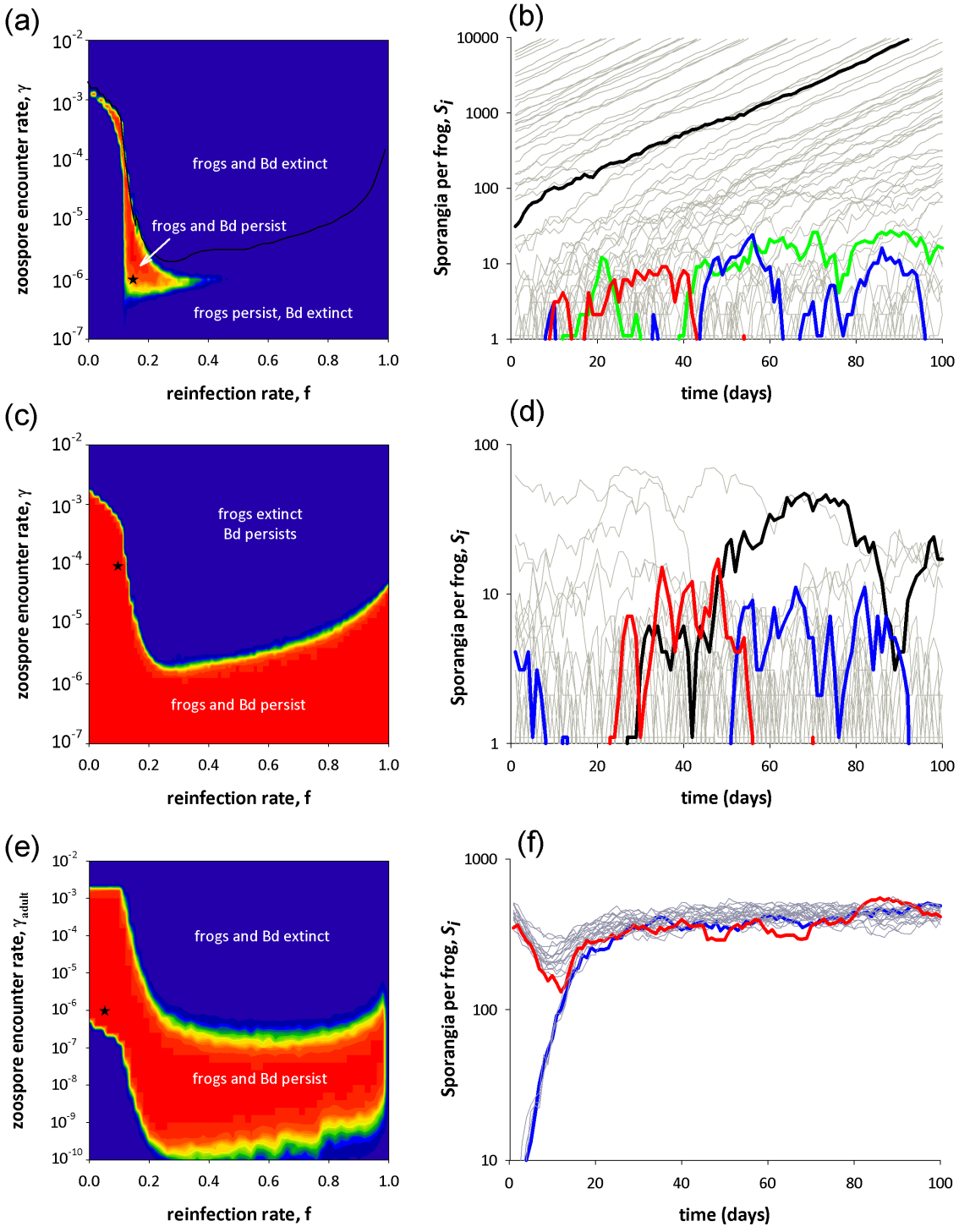


Figure 12.8: Results from the Briggs et al. (2010) model with: (A and B) an unstructured host population in which all individuals are equally susceptible to the pathogen, (C and D) an unstructured host population with the addition of an external source of zoospores, and (E and F). (A, C, and E) show the probability of frogs and Bd persisting for at least 10 years as a function of reinfection rate, $f$, and zoospore encounter rate, $\gamma$. Shown are the fractions of 100 runs for each combination of parameters that persist for at least 10 years (color spectrum red = 100% of runs persist, blue = 0% of runs persist). All runs are initialized with a single infected frog in an otherwise uninfected frog population at its carrying capacity, and no zoospores in the zoospore pool ($Z$=0). (B, D, and F) show examples of the within-season dynamics illustrating the dynamics of the number of sporangia on individual frogs. Colored lines are highlighted examples of trajectories of sporangia on individual frogs. Figure reprinted from Briggs et al. (2010) (the parameter values used are given in Figure 3 of Briggs et al. (2010)).

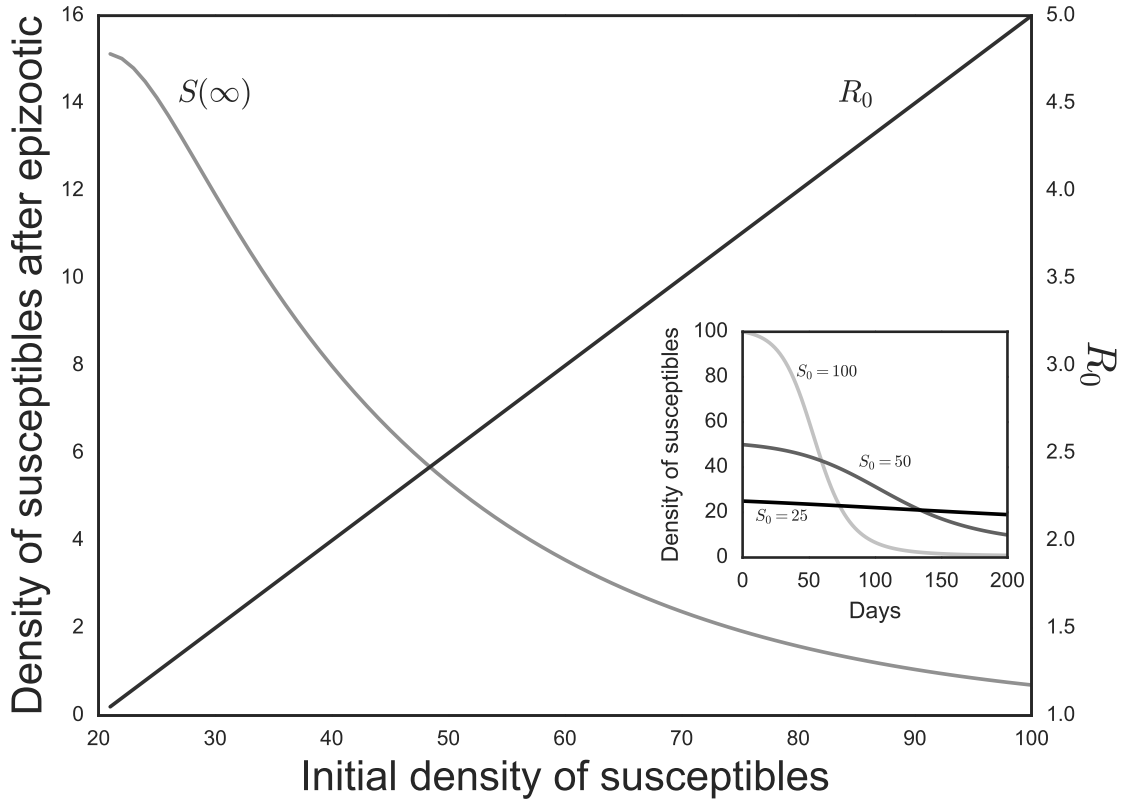


Figure 12.9: The relationship between the final size of an epizootic $S(\infty)$, initial density of susceptibles in a population ($S_0$) and $R_0$. $R_0 = \beta S_0/\alpha$ (for an SIS model with $\gamma = 0$, Fig. 12.2A) where $S_0$ is the initial density of susceptibles, $\beta = 0.001$ day$^{-1}$, and $\alpha = 0.02$ day$^{-1}$. The inset figure shows the epizootic trajectories for the SI model with $S_0 = 100, 50,$ and 25.