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REVIEW AND SYNTHESIS

Mechanisms underlying host persistence following amphibian disease emergence determine appropriate management strategies

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Abstract

Emerging infectious diseases have caused many species declines, changes in communities and even extinctions. There are also many species that persist following devastating declines due to disease. The broad mechanisms that enable host persistence following declines include evolution of resistance or tolerance, changes in immunity and behaviour, compensatory recruitment, pathogen attenuation, environmental refugia, density-dependent transmission and changes in community composition. Here we examine the case of chytridiomycosis, the most important wildlife disease of the past century. We review the full breadth of mechanisms allowing host persistence, and synthesise research on host, pathogen, environmental and community factors driving persistence following chytridiomycosis-related declines and overview the current evidence and the information required to support each mechanism. We found that for most species the mechanisms facilitating persistence have not been identified. We illustrate how the mechanisms that drive long-term host population dynamics determine the most effective conservation management strategies. Therefore, understanding mechanisms of host persistence is important because many species continue to be threatened by disease, some of which will require intervention. The conceptual framework we describe is broadly applicable to other novel disease systems.

Keywords

Chytridiomycosis, compensatory recruitment, density-dependent transmission, environmental refugia, host–pathogen, management, population persistence, population recovery, resistance, tolerance.

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INTRODUCTION

Ecological communities can be devastated by the introduction of novel pathogens, and the role of disease in declines and extinction has probably been underestimated (Preece *et al.*, 2017). Well-known examples include the invasion of the Morbillivirus rinderpest into African ungulate communities (Holdo *et al.*, 2009), the impact of avian malaria (van Riper *et al.*, 1986) and bird pox (Warner, 1968) on the Hawaiian avifauna and white nose syndrome which has had a major impact on bat populations across North America (Langwig *et al.*, 2012). Key drivers of host extinction from disease include (1) stochasticity related to small pre- or post-epidemic populations, (2) non-density-dependent pathogen transmission and (3) the existence of alternate biotic or abiotic reservoirs that maintain a high force of infection even as a species declines (De Castro and Bolker, 2005). In contrast, the mechanisms that enable host persistence or recovery following severe disease-associated declines are often diverse, nuanced and context dependent and therefore less understood (Greenberg *et al.*, 2017), particularly in cases where initial disease-associated declines are severe.

To date, the pathogen emergence posing the greatest threat to biodiversity is the amphibian chytrid fungus, *Batrachochytrium dendrobatidis* (*Bd*), the causative agent of the amphibian disease chytridiomycosis (Box 1) (Berger *et al.*, 1998; Skerratt *et al.*, 2007; Scheele *et al.*, 2019a). The global spread of this pathogen has had catastrophic impacts on biodiversity, causing extinctions and major declines in amphibian populations (Skerratt *et al.*, 2007; Wake and Vredenburg, 2008; Scheele *et al.*, 2019a). Multiple species throughout a range of environments have been affected by *Bd* infection, resulting in a variety of population outcomes.

Despite the devastation of many amphibian communities following the arrival of the fungal pathogen, some amphibian

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Box 1. Biology of the fungal pathogen Batrachochytrium dendrobatidis (Bd), and the amphibian skin disease chytridiomycosis

Batrachochytrium dendrobatidis was first reported as the cause of widespread frog declines in Australia and the Americas in 1998 (Berger *et al.*, 1998). It has now been reported on all continents other than Antarctica and impacts over 500 species (Scheele *et al.*, 2019a). It has a biphasic life cycle consisting of infectious motile aquatic zoospores and sessile zoosporangia that grow within host skin cells and are the reproductive stage of the pathogen. *Batrachochytrium dendrobatidis* can grow and reproduce in culture over a range of temperatures (4–25 °C), with optimal growth between 17 and 25 °C (Stevenson *et al.*, 2013; Voyles *et al.*, 2017). Warmer sites and laboratory environments are often associated with decreased infection loads (Bustamante *et al.*, 2010; Murphy *et al.*, 2011; Roznik *et al.*, 2015b) and one common treatment method in captivity is exposing infected animals to high temperatures (Woodhams *et al.*, 2003; Chatfield and Richards-Zawacki, 2011). *Batrachochytrium dendrobatidis* causes mortality in affected amphibians primarily by interfering with cutaneous osmoregulatory and ion regulation function (Voyles *et al.*, 2007). Pathogenicity varies greatly between amphibian species and increases strongly with zoospore load. In most species that are impacted by *Bd*, tadpoles can become infected but do not experience mortality (Figure S3).

species that initially declined or were thought to have become extinct are persisting at lower densities or are even recovering (Newell *et al.*, 2013; Skerratt *et al.*, 2016; Scheele *et al.*, 2017b). In this paper, we use amphibian chytridiomycosis as a case study to examine the mechanisms of host persistence following declines caused by disease and show how these mechanisms have implications for conservation management. Understanding how these mechanisms of coexistence facilitate persistence of different species will help inform management strategies for species that are currently experiencing declines.

We describe mechanisms enabling persistence following initial declines using the classic disease triangle of the host, the pathogen and their combined environment (Stevens, 1960; Scholthof, 2007), and extend this framework to the population scale by considering populations of hosts and host communities within an ecosystem. We overview the data necessary for attributing host–pathogen coexistence to a particular mechanism or combination of mechanisms. We critically evaluate the extent to which these mechanisms have been explicitly tested and have empirical support. We emphasise that it is important to investigate a wide range of mechanisms for persistence and recovery, including those related to stochasticity, because these mechanisms are not mutually exclusive, and are likely to be context dependent. Finally, we show how the most appropriate management strategies depend on the mechanisms responsible for persistence or recovery and understanding the mechanisms at play will increase the success of management actions.

HOST-ASSOCIATED MECHANISMS FOR COEXISTENCE

Increases in host resistance and/or tolerance to pathogens are key mechanisms that can reduce disease impacts and lead to population persistence or recovery following disease invasion. Resistance can be defined as 'the ability to limit parasite burden' and tolerance as 'the ability to limit the harm caused by a given parasite burden' (Räberg *et al.*, 2009), but these mechanisms are complex phenomena (see Box 2). Resistance or tolerance can occur at the level of the individual, through adaptive immune or learned mechanisms, or at a population level, through natural selection of immunity, behaviour, life history, etc. (Brunner *et al.*, 2005; Tuite and Gros, 2006; Tompkins *et al.*, 2011; Curtis, 2014). Differences in resistance and tolerance among amphibian populations or species can result from variation in immune function, behaviour and/or the environment (Boots *et al.*, 2012).

To determine differences in amphibian resistance and tolerance to *Bd* infection, we conducted a synthesis of experimental infection studies (see Text S1, Figs S1–3). We used pathogen load and survival during the experimental infection to examine variation in resistance and tolerance among species and life stages (Figure 1) and found enormous variation among amphibian species (Figure 1). While host resistance and/or tolerance are important, the wide variation among species and life stages demonstrates that resistance/tolerance alone cannot account for population persistence in all species.

Immune mechanisms of resistance and tolerance

The immune system is the primary host defence against infection, and variation in host immune or physiological function can result in variation in resistance and/or tolerance to pathogens. More broadly, an increase in the number of individuals that are resistant or tolerant due to innate or adaptive immune mechanisms can promote population persistence over time (Anderson and May, 1978; Grogan *et al.*, 2016; Wilber *et al.*, 2017). In order to demonstrate that evolutionary shifts in immune or physiological mechanisms have led to host persistence requires measurement of infection loads, immune/physiological markers and survival during population decline and recovery. For example, a comparison of skin anti-microbial peptide secretions from frogs captured before and after *Bd*-associated declines in Panama indicate an increase in resistance (i.e. the efficacy of *Bd* inhibition; increased ability to limit pathogen growth) post-decline (Voyles *et al.*, 2018).

Where pre- and post-decline data are unavailable, a space-for-time substitution (comparing populations within a species) can provide alternative evidence, particularly when accompanied by evidence for positive selection of genes associated with survival (Savage and Zamudio, 2016). For example, a comparison of alpine tree frogs, *Litoria verreauxii alpina*, raised in the laboratory free from disease, collected as eggs from populations with different histories of pathogen exposure, indicated that animals from a population that persisted with *Bd* for > 20 years survived longer when infected than those from a naïve population (Grogan *et al.*, 2018a). Examination of the major histocompatibility complex (MHC) of animals in this experiment revealed that specific alleles were associated with

Box 2. Resistance and Tolerance

Host defences against pathogen infection can be divided into two distinct but complementary mechanisms, resistance and tolerance. Resistance describes the host's ability to limit the intensity of infection (and resultant pathology and fitness impacts), whereas tolerance describes the host's ability to limit pathology and fitness impacts without altering pathogen load. As a result, increases in host resistance reduce pathogen transmission, whereas increases in tolerance do not.

These traits are most useful in describing relative differences in resistance or tolerance among individuals, populations or species. One way to quantify differences in host defences among populations is to compare pathogen growth rates on individuals (resistance) and host survival as a function of pathogen load (tolerance). If all else is equal (infection dose, temperature, host stage, time since infection, etc.), pathogen growth rates will be lower (shallower slopes and/or lower intercepts) on more resistant hosts throughout the period of infection (i.e. the sampling period), and survival for a given pathogen load will be higher (further to the right) for more tolerant hosts (Figure 4). Pathogen growth rates can vary with time since infection, resulting in increasing, peaking and decreasing loads over time (Figure S1), and this will be evident as time-dependent variation in the slope of the pathogen growth function. More crudely, and when controlling for other factors, more resistant hosts are those with lower average pathogen load, and more tolerant hosts are those with higher survival, when controlling for pathogen load.

There is extensive variation among species and populations in both resistance and tolerance, and this has undoubtedly contributed to the differential impacts of chytridiomycosis (Figure 1). However, there is little direct evidence (for an exception see Voyles *et al*., 2018) that changes in host resistance or tolerance have led to reduced disease impact over time and host persistence. Evidence of changes in resistance would require quantifying pathogen growth rates by measuring pathogen load trajectories in populations in declining and persisting phases. Evidence for changes in tolerance requires quantifying survival as a function of pathogen load in populations over time. Assessing changes in resistance or tolerance as mechanisms of population persistence can be done either in the field by following infection and survival of marked individuals (Phillott *et al*., 2013; Brannelly *et al*., 2018a) or fitting integral projection models to population-level data, or through laboratory experimental infection experiments (Wilber *et al*., 2016, 2017). Finally, we note that differences in resistance and tolerance can result from differences in immune function, host behaviour or environmental variation, as detailed in the main text.

resistance and increased survival, and there was evidence for population-specific positive selection (Bataille *et al*., 2015) (see Box 3). There was also some evidence that higher survival (both in individuals and across different populations) was associated with particular MHC alleles in other species. In the lowland leopard frog, *Rana yavapaiensis*, both MHC allelic diversity and overall genetic diversity were associated with increased survival after exposure to *Bd* (Savage and Zamudio, 2011). However, not all aspects of the immune system have been explored (such as antimicrobial peptides and microbiota) in these species and some associations between population persistence and degree of resistance have been inconsistent in other species, making the importance of MHC allelic diversity or a specific MHC allele unclear (see review by Grogan *et al*., 2018b, 2018c). Furthermore, the importance of immune mechanisms relative to other factors in population persistence has received little attention (Burkart *et al*., 2017).

Hosts' adaptive immune system can eliminate individual infections and can provide protective resistance against reinfection. While there is evidence for the induction of the adaptive immune system in response to chytridiomycosis, the response in most species appears insufficiently protective (likely due to lymphocyte suppression) and the animal still succumbs to disease (Cashins *et al*., 2013; Fites *et al*., 2013), or only elicits a protective immune response after several repeated exposures (McMahon *et al*., 2014). Demonstrating that this mechanism contributes to population persistence would require evidence of increased expression of adaptive immune markers (e.g. antibodies) throughout the course of infection, in combination with lower infection loads and higher survival for individuals in the initial infection and subsequent reinfection experiments.

Behavioural changes leading to resistance and tolerance

Changes in animal behaviour can facilitate host persistence or increase species survival by increasing resistance or tolerance. Behavioural changes can decrease an individual's exposure to the pathogen, slow the pathogen's growth, or reduce the likelihood of onward transmission (Aubert, 1999; Ouedraogo *et al*., 2004; Han *et al*., 2015). In principle, behavioural changes that reduce aggregation within a species, reduce interactions with reservoir species or reduce contact with infected surfaces could decrease exposure and transmission. However, there is little evidence to indicate such behavioural changes occur in multiple species (but see McMahon *et al*., 2014). Behavioural changes that increase exposure to warmer temperatures might reduce fungal growth and promote pathogen clearance. Behavioural fever occurs in ectotherms (Rakus *et al*., 2017), and could be important in host–*Bd* interactions for two main reasons: 1) *Bd* is temperature sensitive (see Box 1) and temperatures above 26°C often reduce pathogen growth (Woodhams *et al*., 2008), and 2) increased temperatures can also increase the immune function of the host (Butler *et al*., 2013).

Behavioural fever or microhabitat preferences for warmer temperatures could reduce pathogen load and/or promote pathogen clearance. Some species become infected in laboratory experiments but are rarely found to be infected in the wild, and basking is one possible explanation for reduced infection risk (Brannelly *et al*., 2012, 2018c; Daversa *et al*., 2018). Similarly, within a species, individuals in warmer microhabitats within a population often have lower infection loads and prevalence (Richards-Zawacki, 2010; Forrest and

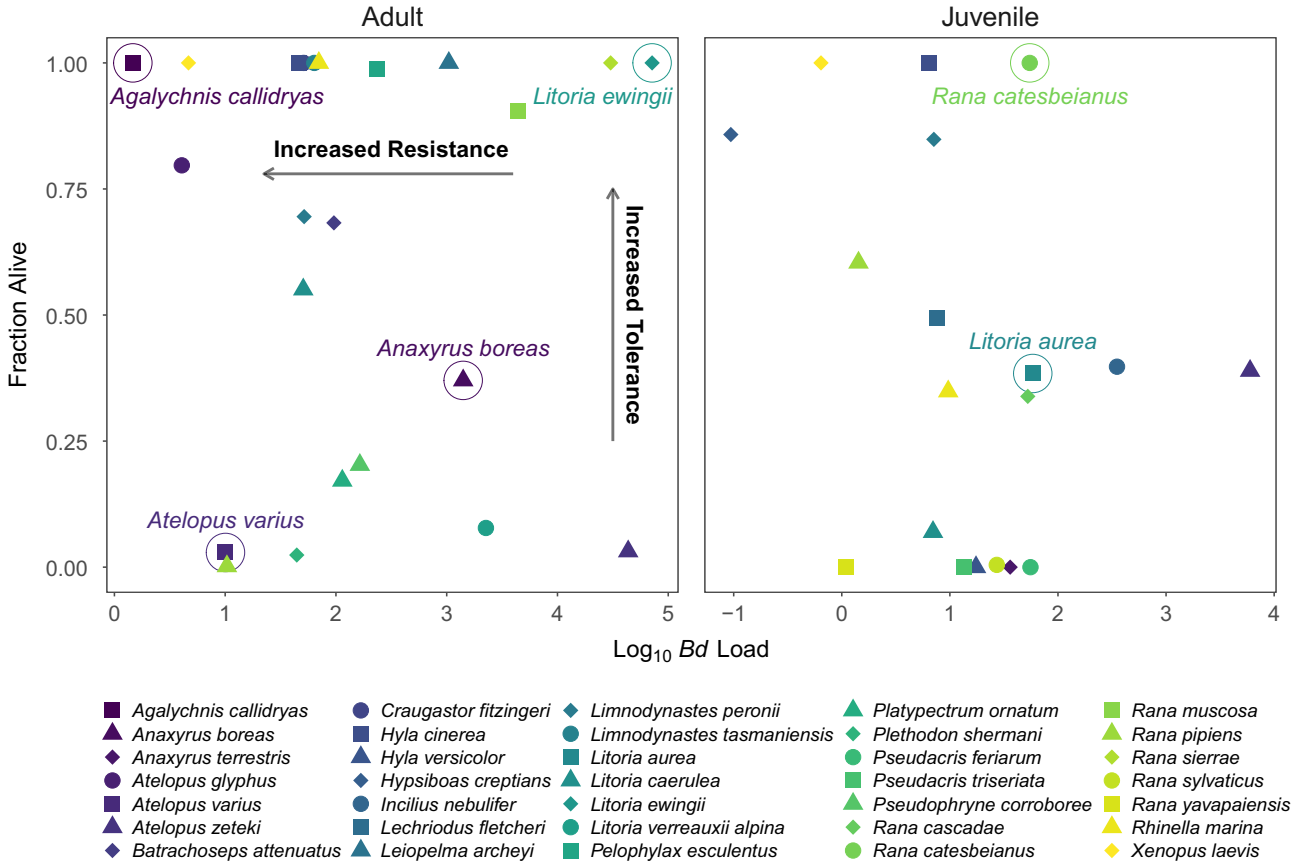

Figure 1 Model-corrected fraction of amphibians alive (± 1 SE) plotted against *Bd* load (in $\log_{10}$ zoospores/swab) across species and life stages (adults and juveniles), corrected for infective dose, days post-infection and temperature. Variation along the x-axis indicates differences in species in resistance, whereas variation along the y-axis for the same load value indicates differences in tolerance (see the labelled arrows). *Bd* load values are estimated from a general linear model that includes species, temperature, total *Bd* dose (because these variables are known to influence disease progression, Sauer *et al.*, 2020) and an interaction between stage and days since infection (including linear and quadratic terms), and represent infected animals; the predicted values shown use mean values across all studies for: temperature (19.1 °C), total *Bd* dose (5.1 $\log_{10}$ zoospores) and days post-infection (DPI, 38.2 for Adults, 39.1 for Subadults; peak loads for these stages occurred between DPI 35 and 40). Points are shown for species which had at least five estimates of *Bd* load. The fraction alive for each species is estimated using a Cox's proportional hazard model with total dose, temperature, stage and species, and predicted values use the same mean values for temperature and total *Bd* dose as given above and DPI = 75 when most mortality has occurred (Figure S2). Arrows indicate relative resistance and tolerance of species based on their position on the figure. The six species identified by large circles represent species identified as tolerant (*R. catesbeiana, L. ewingii*), resistant (*A. callidryas*), and species that are neither tolerant nor resistant (*A. varius, A. boreas, L. aurea*). Model details and data used are described in Text S1.

Schlaepfer, 2011; Rowley and Alford, 2013). However, it is unclear whether frogs infected with *Bd* seek warmer microclimates and whether this results in reduced infection burdens. Only one species, of the six experimentally tested, has demonstrated a behavioural fever response, and there was no indication that the behaviour decreased infection in those animals (Murphy *et al.*, 2011; Sauer *et al.*, 2018). Innate individual temperature preference, rather than behavioural fever responses, might instead affect individual susceptibility to chytridiomycosis (Sauer *et al.*, 2018).

Demonstrating that behaviour contributes to host persistence would require evidence that behaviour results in increased resistance/tolerance for the individual. The behaviour could be plastic (i.e. vary with infection status) or change over time within a population. Several studies have examined the role of behaviour in host–pathogen interactions for *Bd* (Richards-Zawacki, 2010; Sauer *et al.*, 2018), and there is evidence that temperature alters susceptibility to *Bd* (Ribas *et al.*, 2009; Robak and Richards-Zawacki, 2018; Sauer *et al.*, 2020). Nevertheless, there is limited evidence that behavioural fever/microhabitat choice actually influences individual-level resistance or tolerance to *Bd* infection. Furthermore, no studies have explored population-level behavioural variation or changes over time in a population that initially declined and then stabilised.

Compensatory recruitment

In populations experiencing high mortality due to endemic disease, one mechanism of persistence is increasing recruitment (Muths *et al.*, 2011; McDonald *et al.*, 2016). Life-history theory predicts that increased individual reproductive investment is an adaptation to increased mortality (Minchella and Loverde, 1981; Clutton-Brock, 1984; Partridge and Harvey, 1988; Stearns, 1992). There are several cases of endemic

Box 3 Species case studies 3.

We overview the experimental evidence on four species for which multiple mechanisms have been empirically tested. We describe the studies that have been conducted and use the empirical results to determine which mechanisms are important for population persistence, which are summarised in Figure 3.

LITORIA VERREAUXII ALPINA

The alpine tree frog, *Litoria verreauxii alpina*, is endemic to the Australian Alps and experienced dramatic declines. There is an effect of exposure history on resistance/tolerance, where some populations with long exposure history had lower mortality after infection (Grogan *et al*., 2018b). These differences in population-level susceptibility were correlated with variation in MHC alleles (Bataille *et al*., 2015) and higher upregulation of the immune genes early in infection (Grogan *et al*., 2018a). However, adult mortality is still high, with little recovery from infection (Brannelly *et al*., 2015, 2016a; Scheele *et al*., 2015), and thus immunity might not be promoting persistence. Recruitment has been important for this species, where they now exclusively breed in permanent water bodies (Scheele *et al*., 2016), populations with endemic infection are maturing more quickly (Scheele *et al*., 2017c), and infected individuals are investing more in gametes than uninfected individuals (Brannelly *et al*., 2016b). There is some evidence of density-dependent transmission, and a highly tolerant reservoir host *Crinia signifera* maintaining disease within the system (Brannelly *et al*., 2015, 2018d).

RANA MUSCOSA/SIERRAE COMPLEX

The mountain yellow legged frog, *Rana muscosa*/*sierra*, species complex is an endangered species in California. The species is long lived with a multi-year tadpole stage. Nearly all tadpoles are infected with *Bd* at infected sites and there is high mortality due to disease at metamorphosis (Rachowicz *et al*., 2006), indicating that demographic compensation is not supporting population persistence. Density-dependent transmission has been tested in a number of different ways (Rachowicz and Briggs, 2007; Wilber *et al*., 2017) where field and laboratory results indicate a mix between frequency and density-dependent transmission. There is some evidence for immunity playing a role in persistence, where adults at sites with *Bd* are less likely to succumb to *Bd* infection (Knapp *et al*., 2016), but the immune mechanisms are unknown. There is probably also a strong role of stochasticity in whether populations persist after disease epidemic. If some individuals, just by chance, are exposed to a lower force of infection, have time to mount an effective immune response and manage to survive the initial outbreak they can help persist the population. Long-term surveys suggest that occasional pulses of successful adult recruitment might be sufficient for the population to persist, but it will take many years for populations rebound (Knapp *et al*., 2016; Joseph and Knapp, 2018).

LITORIA RHEOCOLA

The common mist frog, *Litoria rheocola* is endemic to North Queensland and has declined from higher elevations sites (Laurance *et al*., 1996), with little upland population recovery (McDonald *et al*., 2005; McKnight *et al*., 2017). Environmental factors such as canopy cover, water temperature, seasonality and stream connectiveness influence *Bd* disease dynamics in the lowland but do not explain upland persistence (Phillott *et al*., 2013; Sapsford *et al*., 2013; Roznik *et al*., 2015b). In the uplands, there is high *Bd* -induced seasonal mortality (Sapsford *et al*., 2015; Grogan *et al*., 2016). Populations might be maintained by high compensatory recruitment (Phillott *et al*., 2013; Roznik *et al*., 2015a), but there is no evidence that recruitment have changed since the introduction of *Bd*. Antimicrobial peptides are ineffective at reducing *Bd* in culture (Woodhams *et al*., 2006). However, microbial symbionts are more effective *in vitro* at higher temperatures (Daskin *et al*., 2014), which could explain the seasonality of infection dynamics but not population persistence. We do not understand the mechanisms of population persistence for *Litoria rheocola*.

RANA YAVAPAIENSIS

The lowland leopard frog, *Rana yavapaiensis* is native to the North American Southwest, and has declined to extinction of some populations (Sredl et al. 1997). Mortality is seasonal (Schlaepfer *et al*., 2007), and while the microbiome is also seasonal, it likely does not impact patterns of population persistence (Longo *et al*., 2015). There are *Bd*-negative populations present around geothermal springs indicating that environmental temperature is a key mechanism of persistence (Schlaepfer *et al*., 2007; Forrest and Schlaepfer, 2011). Host genetics and MHC heterozygosity/alleles appear to influence resistance and tolerance (Savage and Zamudio, 2011; Savage *et al*., 2015), and genetic diversity predicts *Bd* mortality (Savage *et al*., 2015). However, at sites with environmental refugia, local genetic adaptation is absent, indicating that evolution of immunity at those sites is not occurring (Savage *et al*., 2015).

infection where adult mortality is high (Phillott *et al.*, 2013; Lampo *et al.*, 2017) yet populations are rebounding, stabilising or declining more slowly than expected. In these, increased per capita recruitment might be a key mechanism of host persistence or recovery (Muths *et al.*, 2011; Tobler *et al.*, 2012; Newell *et al.*, 2013; Phillott *et al.*, 2013; Lampo *et al.*, 2017).

The best evidence to support compensatory recruitment as a mechanism of host population persistence would measure recruitment rates pre- and post-decline. Although temporal comparisons are few, comparisons among populations following different decline patterns offer some support. Capture–recapture studies at different sites have shown higher recruitment in toad populations with higher adult mortality. In the western toad, *Anaxyus boreas*, Muths *et al.* (2011) compared survival and recruitment rates between a population with endemic disease experiencing a slow decline and a population that was disease-free and stable. The population with endemic disease had 33% lower adult survival, but the per capita recruitment was more than double that of the stable population's recruitment, indicating that high mortality due to disease can be partly compensated for by increased recruitment. In the yellow-bellied toad, *Bombina variegata*, populations were monitored over a 7-year period, and in 1 year of high adult disease mortality, recruitment increased such that population levels remained stable. However, the patterns observed in this study could have also been explained by environmental factors, which demonstrates the complexities of studying compensatory recruitment in wild populations (Spitzen-Van Der Sluijs *et al.*, 2017).

While these examples show increased recruitment in populations with high adult mortality, the exact reproductive mechanisms resulting in increased recruitment are less understood. There is evidence to indicate that high adult mortality at disease endemic sites leads to earlier maturation (Scheele *et al.*, 2017c), which could be a heritable change in populations, a plastic response to lower adult abundance or a response to infection itself. Two examples of responses to infection are increased sexual display of males (calling effort) in infected compared to uninfected males (Roznik *et al.*, 2015a), and both males and females having larger gonads and producing more gametes when infected (Chatfield *et al.*, 2013; Brannelly *et al.*, 2016b). However, infection does not result in increased reproductive effort in all circumstances. In other species, reproductive hormone levels are lower in infected individuals (Kindermann *et al.*, 2017) or testis size is reduced (Campbell *et al.*, 2019). There has been no research directly linking reproductive effort to offspring production or survival in the amphibian disease system, which would be required in order to demonstrate that changes in reproductive behaviour or physiology can lead to compensatory recruitment and result in host persistence.

PATHOGEN ATTENUATION

Coexistence between a pathogen and its hosts can be mediated by spatial and/or temporal variation in virulence, with less virulent strains increasing host survival and resulting in population persistence or recovery. For example, myxoma virus has reduced virulence over time leading to decreased mortality and population impacts on its rabbit hosts (Best and Kerr, 2000; Kerr, 2012). However, in populations where rabbits have developed resistance to myxoma virus, more virulent strains of the virus have become more prevalent, which demonstrates the dynamic coevolution of host–pathogen systems (Kerr *et al.*, 2012).

Recent population genetics studies of *Bd* have shown that *Bd* lineages are genetically diverse (Farrer *et al.*, 2011; Rosenblum *et al.*, 2013). A hypervirulent lineage (Global Panzootic Lineage, *Bd*GPL) has been spread worldwide and seems to be undergoing further diversification by mitotic or sexual recombination (Farrer *et al.*, 2011). Although *Bd*GLP is highly virulent in many species and virulence factors are genetically determined, virulence varies widely among and within host species (O'Hanlon *et al.*, 2018). Several experimental studies have shown *in vitro* differences in phenotype (including virulence) among *Bd* isolates, even over small geographical scales and within strains (Berger *et al.*, 2005; Retallick and Miera, 2007; Fisher *et al.*, 2009; Dang *et al.*, 2017). Differences among *in vitro* growth patterns of isolates have been correlated with genetic differences of *Bd* (Voyles, 2011; Becker *et al.*, 2017) and there is some evidence that *Bd* isolates undergo local genetic diversification and host specialisation (Morgan *et al.*, 2007; Goka *et al.*, 2009; Byrne *et al.*, 2019).

Clearly, virulence could evolve over time and result in pathogen attenuation and population persistence. However, there is little evidence that *Bd* evolution is promoting host–pathogen coexistence in nature. The best evidence indicates that pathogen virulence has remained stable over time in some places (Voyles *et al.*, 2018) and virulence might even be increasing on the invasion front (as predicted by theory; Bolker *et al.*, 2010) or within populations where disease is endemic (Phillips and Puschendorf, 2013; Greenspan *et al.*, 2018). To demonstrate that pathogen attenuation has occurred in the field, experiments would require quantifying pathogen virulence before or during declines and in persisting populations, ideally using live animal infection experiments with local hosts. However, performing laboratory infection experiments with isolates collected years apart or under varying culture regimes can be challenging because the fungus is known to attenuate with passaging in culture (Brem *et al.*, 2013; Langhammer *et al.*, 2013), and the effects of cryoarchiving are not fully understood. In culture, experimental evolution in life-history characteristics has been shown by propagating the fungus under different conditions (Voyles *et al.*, 2012, 2014). In principle, virulence of these strains could be measured using live animal infection experiments with local hosts, but the extent to which this would relate to evolution in the wild is uncertain.

ENVIRONMENTAL FACTORS

Environmental variation can influence prevalence or infection intensity by altering pathogen growth and survival or host resistance/tolerance. At the extreme, environmental refugia where *Bd* is absent could allow species to persist despite long-term presence of the pathogen in the remainder of its range (Puschendorf *et al.*, 2009, 2011). Environmental factors that reduce pathogen presence or load are

commonly proposed as a mechanism for host persistence (Scheele *et al*., 2019b). The data required to support this hypothesis would be populations persisting at a subset of sites while others are extirpated, with consistent environmental differences between the site types. While some evidence supports the existence of refuge habitats, other studies suggest that climatic factors and environmental refuges alone are not sufficient to halt population decline (Bower *et al*., 2017; Reside *et al*., 2019).

Temperature is known to influence the *in vitro* growth of *Bd* and influence susceptibility of species to infection in the laboratory (Box 1) and field studies show decreasing *Bd* infection prevalence with increasing temperature (Puschendorf *et al*., 2011; Zumbado-Ulate *et al*., 2014). Increased temperature and possibly lower humidity might explain lower infection prevalence observed in sites with more open canopies (Van Sluys and Hero, 2009; Hossack *et al*., 2013; Roznik *et al*., 2015b). Similarly, higher temperatures associated with urban areas also have lower infection prevalence (Saenz *et al*., 2015), and populations living in or near thermal hot springs had lower infection than those at nearby unheated ponds (Schlaepfer *et al*., 2007; Forrest and Schlaepfer, 2011). Finally, environmental conditions likely partly explain how amphibians like the spiny common toad, *Bufo spinosus*, clear infection after they leave breeding sites and migrate to warm or dry habitat (Daversa *et al*., 2018). Such seasonal refuges could help host populations persist. It is important to note that higher temperatures do not always confer a benefit against *Bd* infection. Cool adapted and montane animals often have higher mortality due to *Bd* infection at warmer temperatures (Neely *et al*., 2020; Sauer *et al*., 2020).

Salinity can also alter infection patterns and host persistence, with lower infection prevalence and infection intensity occurring at more saline sites in some cases (Stockwell *et al*., 2014; Heard *et al*., 2015), but not others (Heard *et al*., 2018). In a mesocosm study of the green and golden bell frog, *Litoria aurea*, higher salinity reduced transmission between larvae, but did not protect individuals once they were infected (Clulow *et al*., 2018). Higher salinity was also associated with lower *Bd* infection prevalence and higher survival following translocation of *L. aurea* to multiple sites (Stockwell *et al*., 2015). *Bd* prevalence and infection intensity in multiple species is also associated with other water chemistry measures such as dissolved organic carbon, nitrate/nitrites, phosphorus, pesticides, dissolved metals and pH but it is unclear how each of these parameters individually impacts infection dynamics (Threlfall *et al*., 2008; Battaglin *et al*., 2016; Reeves *et al*., 2016).

CHANGES IN HOST COMMUNITY COMPOSITION

Density-dependent transmission

Pathogen transmission often increases with host density, potentially nonlinearly (McCallum *et al*., 2001). If transmission is dependent on host density, there can be a threshold density below which the pathogen cannot persist. However, stochasticity at low population levels can also result in host extinction before the pathogen itself disappears (De Castro and Bolker, 2005; Briggs *et al*., 2010). If transmission does not depend on host density (frequency-dependent transmission), sustained transmission as host populations decline can lead to host extinction.

There are several different ways to test for density-dependent transmission. The disease transmission function can be quantified through experiments in which different densities of susceptible hosts are exposed to different densities of infected hosts. There are, however, very few studies that experimentally quantify *Bd* transmission, because it is difficult to create truly realistic environments in the laboratory (e.g. Rachowicz and Briggs, 2007; Wilber *et al*., 2017). A few studies have varied the density of hosts in their experiments, but they have not interpreted the results in terms of quantifying the transmission function. For example, toads exposed to *Bd* in the presence of another individual had a greater chance of becoming infected with *Bd* than individuals exposed on their own (Bielby *et al*., 2015), and tadpoles placed in infected lakes were found to all become infected, in the absence of direct contact with infected individuals, but direct contact increased the buildup of lethal *Bd* loads (Courtois *et al*., 2017). However, when western toads, *Anaxyus boreas*, were exposed to a constant number of infectious zoospores, the density of the animals did not affect the proportion that became infected, nor the infection intensity (Searle *et al*., 2011). An experimental approach which can bypass some of the issues with the artificial nature of laboratory transmission experiments would be to place uninfected individuals in natural populations with different infection levels and quantify the time that it takes to become infected.

An important consideration for density-dependent transmission is that simple models assume that the pathogen infects just a single host species. However, *Bd* is a generalist pathogen, infecting multiple amphibian (and perhaps non-amphibian; e.g. McMahon *et al*., 2013) host species. If one or more of the co-occurring hosts are able to tolerate infection without succumbing to chytridiomycosis, then the tolerant species might be able to keep the force of infection high enough to drive less tolerant host species extinct. As discussed below, the whole host community needs to be taken into account when considering the impact of host density on transmission, as is clear in other systems (Parker *et al*., 2015).

Shifts in community composition

Community composition affects the dynamics of wildlife disease and the impact on focal species (Parker *et al*., 2015). *Bd* epidemics have caused substantial changes in amphibian community structure, including severe population declines and many extirpations (Lips *et al*., 2006; Scheele *et al*., 2019a). These shifts in community composition cause changes in disease transmission because resistance and tolerance vary widely among species (Figure 1) (Holt and Pickering, 1985). If we can better understand the resistance and/or tolerance of species, we can predict how changes in community composition impact population persistence (Brannelly *et al*., 2015, 2018b; Stockwell *et al*., 2016; Scheele *et al*., 2017a).

Following a disease epidemic that results in a decline of one or more species, the relative abundance of other more tolerant

or resistant species in the community might increase to fill the empty niche (Figure 2). An increase in the relative abundance of tolerant species (often called a reservoir host in the literature; Reeder *et al.*, 2012; Scheele *et al.*, 2017a; Brannelly *et al.*, 2018d) will increase the force of infection on the focal species. In contrast, an increase in the relative abundance of resistant species following a *Bd* epidemic could reduce transmission (Johnson *et al.*, 2008, 2013) by reducing the overall number of zoospores released into the environment (Briggs *et al.*, 2010).

We synthesised experimental infection data to examine variation in resistance and tolerance among species (Figure 1), which can be used to illustrate these potential effects of changes in community composition. For example, the North American bullfrog (*R. catesbeiana*) is a tolerant species for *Bd* (Figure 1), and has been introduced into more than 40 countries around the world where species at risk of *Bd*-related declines occur (Schloegel *et al.*, 2010, 2012). *Rana catesbeiana* co-occurs in Wyoming, USA, with the boreal toad, *Anaxyrus boreas boreas*, a species that suffers substantial mortality from *Bd* infection (Figure 1) (McGee and Keinath, 2004). *Rana catesbeiana* might cause further *Bd*-associated declines in *A. b. boreas* (Figure 1). Similarly, the Southern brown tree frog, *Litoria ewingii*, is relatively tolerant of *Bd* (Figure 1) and widespread across much of southeast Australia, and can co-occur with the vulnerable green and golden bell frog, *L. aurea*, which frequently dies from chytridiomycosis (Figure 1; Pyke *et al.*, 2002). An increase in the abundance of *L. ewingii* might increase infection and mortality in *L. aurea* (Figure 2).

In contrast, the red-eyed tree frog, *Agalychnis callidryas*, which is an abundant species from upland regions of Central America (Ellison *et al.*, 2014), is a relatively resistant species (Figure 1), and can co-occur with the critically endangered variable harlequin toad, *Atelopus varius*, which succumbs to chytriomycosis (Figure 1). If *A. callidryas* increased in density following *Bd* invasion this could reduce infection in *A. varius* and possibly protect *A. varius* from further declines (Figure 2).

These examples explain how changes in community composition due to *Bd* declines might increase or decrease the force of infection depending on the species present (Figure 2). Determining whether changes in amphibian communities have contributed to species persistence would require a multi-community population comparison, with variation in frog communities across locations of the focal species. One would predict, all else being equal, a higher population density of the focal species in those communities containing more resistant species, and a lower population density in communities with a higher density of tolerant species.

MANAGEMENT IMPLICATIONS/SUGGESTIONS

There are many reviews of potential management options for mitigating *Bd* (see Woodhams *et al.*, 2011; Scheele et al. 2014a; Garner *et al.*, 2016), but few peer reviewed studies have tested the efficacy of specific management options in species threatened by chytridiomycosis (Canessa *et al.*, 2019). Many management efforts have had little or no success, with no reduction in disease or a failure of reintroduced animals to establish (Garner *et al.*, 2016). These failures might be due to a disconnect between research and management (Canessa *et al.*, 2019; DiRenzo and Campbell Grant, 2019; Gillespie *et al.*, 2020). For managing species threatened by wildlife disease, understanding pathways of host persistence is essential for identifying effective management options (Table 1). Appropriate management actions differ according to which

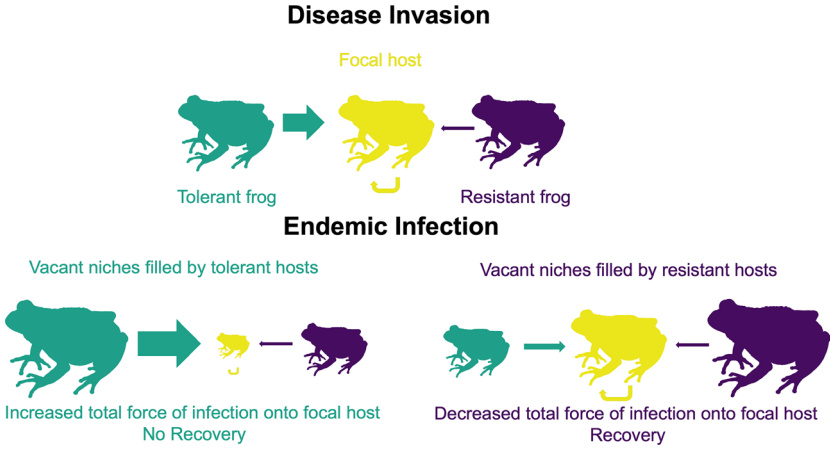

Figure 2 Effect of frog community structure on a focal frog species, as disease moves from invasive to an endemic state. There are three types of frogs in this hypothetical community. Their relative population sizes are indicated by the size of the frog silhouette. The focal host (in yellow) is a species of particular interest for conservation and dies from *Bd* infection. Tolerant hosts (in green) are able to maintain a high disease burden, without major effects on their fitness. Resistant hosts (in purple) do not become infected with high disease burdens. The focal host develop high disease burdens, which has a major effect on their fitness. The force of infection that the populations of each of these host types exert on the focal host is represented by the thickness of the arrows. During the disease invasion, the focal host declines and niches open. Once disease becomes endemic the impact on focal host recovery and persistence depends on whether the niches they vacate are filled predominantly by tolerant or resistant hosts. If the vacated niches are filled by tolerant hosts (left hand side of the diagram), the force of infection on to the focal host is maintained or increased, leading to continued decline in the focal host. If the vacated niches are filled by resistant hosts (right hand side), the overall force of infection on to the focal host is expected to be reduced.

Table 1 Applicability of management strategies based on the mechanisms of recovery and/or persistence

Potential benefits of management intervention

Recovery/ persistence mechanism	Introduction	Supplementation	Host modification	Habitat modification	Culling
Increased host resistance and/or tolerance	Might succeed if introduced frogs are sourced from more resistant/tolerant populations.	Might accelerate recovery if frogs from more resistant populations are translocated to slowly recovering populations.	Might accelerate recovery if frogs released have higher resistance/tolerance than extant animals	None	None
Behavioural changes	As for resistance and tolerance.			Potential benefit from increased availability of favourable microclimate	None
Compensatory recruitment	If the animals are introduced into a habitat that promotes breeding, might accelerate recovery.	Might accelerate recovery if frogs from rapidly recovering populations are translocated to slowly recovering populations.	If the augmentation increases the mechanism promoting persistence, then recovery might be accelerated.	If habitat is modified in a way to promote breeding, then it might accelerate recovery.	None
Pathogen attenuation	Might succeed if frogs are more resistant/tolerant than extant animals to the local pathogen strain	Might succeed if frogs are more resistant/tolerant than extant animals to the local pathogen strain	Might accelerate recovery if frogs released have higher resistance/ tolerance.	None	None
Environmental factors	Might succeed if animals are placed in a habitat that is not optimal for the pathogen.	Might succeed if animals are placed in a habitat that is not optimal for the pathogen.	Might succeed if animals are augmented to have higher fitness in habitats less suitable for *Bd*	Potential benefit from increased availability of environmental refugia.	None
Density-dependent transmission	Might succeed if the number of animals released is low.	None	None	Might decrease aggregation in areas suitable for transmission.	Might succeed if density is made low enough
Shifts in community composition	Might succeed if the other species in the community have high resistance to infection.			Decreasing suitability for reservoir hosts and/or increasing suitability for resistant hosts might be effective.	Might succeed if tolerant hosts are removed

Potential risks of management intervention

Recovery/ persistence mechanism	Introduction	Supplementation	Host modification	Habitat modification	Culling
Increased host resistance and/or tolerance	Likely to fail if frogs originate from less resistant/tolerant populations.	Likely to fail if frogs originate from less resistant/tolerant populations, or frogs are adapted to local pathogen strains.	Likely to fail, and slow evolution if animals released do not have higher resistance/ tolerance than extant animals. Also likely to fail if frogs are augmented in a way that reduces fitness.	Modifications might decrease fitness.	Likely to fail if individuals with high resistance/tolerance are removed from the population.
Behavioural changes	As for resistance and tolerance				
Compensatory recruitment	Likely to fail if frogs originate from less resistant/tolerant populations, and if the habitat at the new site does not promote breeding.	Likely to fail if habitat is unable to support more individuals	The host modification might carry other fitness costs.	Modifications might decrease fitness	Likely to fail if breeding adults are removed prior to breeding
Pathogen attenuation	Likely to fail if an accidental release of a virulent pathogen strain on the released frogs. Also likely to fail if there are local host–pathogen adaptations; that is, if the local pathogen is more virulent than the strain in the population of origin.			Modifications might decrease fitness.	None

(continued)

Table 1 (continued)

Potential risks of management intervention					
Recovery/ persistence mechanism	Introduction	Supplementation	Host modification	Habitat modification	Culling
Environmental factors	Likely to fail if the optimal conditions for the pathogen are suboptimal for the frog, thereby decreasing host fitness.	NA	The host modification might carry other fitness costs.	Modifications might otherwise decrease fitness.	NA
Density-dependent transmission	Might fail if density of the host is too high.	Likely to increase density of the host thereby increasing transmission.	There is a risk that cost of increased transmission from higher density exceeds benefit from modified hosts.	Might increase aggregation in areas suitable for transmission, and therefore fail.	Likely to fail if the density required to decrease transmission is so low that the likelihood of stochastic extinction is increased.
Shifts in community composition	Likely to fail if other species in the community have high tolerance to infection.			Risk of increasing suitability for tolerant hosts and/or decreasing suitability for resistant hosts.	Likely to fail if resistant species are culled rather than tolerant species

Introduction includes both introducing animals to sites where they never were before (i.e. assisted colonisation) and reintroducing animals to sites where they had disappeared. Supplementation means adding animals to sites that currently have existing populations. The animals released in both introductions and supplementations can originate from captive reared colonies or from extant populations in the wild. Host modification means modifying frogs in some way at a site, or added to a site, such as being treated, vaccinated, bioaugmented with bacteria or selectively bred for a particular trait. Habitat modification is any human-caused habitat changes, which includes modifying the habitat to become less suitable for the pathogen (i.e. open up the canopy to increase the temperature or increase salinity), to increase recruitment (i.e. dams), and to exclude tolerant hosts. Culling as used here means frog removal (of one or more species) from the target site.

mechanism or combination of mechanisms is responsible for persistence or recovery. Failure to identify these mechanisms might at best lead to ineffectual actions and at worst be counterproductive.

In Table 1, we summarise the ways in which the benefits and risks of potential management techniques depend on the mechanism(s) of population persistence. We have grouped management options for wildlife disease that have been or could potentially be applied to frogs and *Bd* into the following broad categories (Garner *et al*., 2016; Scheele *et al*., 2019b): introduction, which we define to include both as introducing animals to sites where they never were before (i.e. assisted colonisation) and reintroducing animals to sites where they had disappeared; supplementation, defined as adding additional animals to sites where they still are present; host modification, such as treating animals *in situ*, vaccination, or introducing selectively bred animals; habitat modification, which includes altering habitat to make it less suitable for *Bd* or tolerant reservoirs, or more suitable for frog recruitment; and culling, which can include removing tolerant reservoirs or even removing all frogs entirely before attempting reintroduction (Bosch *et al*., 2015).

Introductions and supplementations act to add animals to a habitat with the aim of either establishing a viable population or of increasing the viability of an existing population (Muths *et al*., 2014). Introductions and supplementations require a large financial investment, long-term monitoring and often multiple introductions to ensure establishment. A basic axiom of conservation biology is that an introduction or supplementation will fail if the threatening process that initially caused decline has not been neutralised (Caughley, 1994). Introductions to sites where *Bd* does not exist or has been eliminated from are a viable management strategy in principle. Unfortunately, few such sites exist that are also suitable for frogs.

There are a number of species for which animal releases have been tested or are currently underway (Stockwell *et al*., 2008; McFadden et al. 2010, 2016; Sredl et al. 2011; Hoskin and Puschendorf, 2014; Randall et al. 2016). For species like the critically endangered Southern corroboree frog, *Pseudophryne corroboree*, in Australia, the only animals present in the wild are the result of the annual introduction of eggs (Hunter et al. 2010). However, simple release of these animals is unsustainable in the long term because *Bd* is still present in the environment and the released animals still have low resistance/tolerance to the pathogen. For introduction and supplementations to be successful they need to be directed, that is, be released into sites less conducive to *Bd,* or originate from populations with higher resistance/tolerance to infection.

Few introductions or supplementations into declining populations have attempted to use frogs from populations persisting with *Bd*. In one such example, alpine tree frogs, *Litoria verreauxii alpina*, released from populations with a long exposure history to *Bd* had higher survival than those released from a population with no *Bd* exposure history (Brannelly *et al*., 2016a). However, the released animals had similar low survival and high infection prevalence/intensity to the local extant populations (Brannelly *et al*., 2016a). If the released animals were to increase the resistance/tolerance of the supplemented population, fitness of the released animals would need to be higher than the extant animals present nearby and at the sites (Brannelly *et al*., 2016a). This introduction and supplementation trial in *L. v. alpina* is an example where

management efforts did not align with the species mechanisms of persistence: *L. v. alpina*'s persistence has since been identified as compensatory recruitment (Box 3), with less evidence for resistance/tolerance. If the mechanism for population recovery is evolution of resistance or tolerance, supplementation with individuals that are less resistant/tolerant can be counterproductive, arresting or even reversing the evolutionary process (Hohenlohe *et al*., 2019).

A range of host modifications has been attempted to reduce *Bd* impacts including vaccination, antifungals and augmenting skin microbiome. Treating animals *in situ* using antifungals has been examined in multiple systems and while effective at reducing infection directly after treatment, it does not provide long-term protection (Hudson *et al*., 2016; Geiger *et al*., 2017). Vaccine development is underway and has not been tested in the field to date. Vaccines can include dead zoospores/metabolites or infection followed by treatment, and these vaccinations have had mixed results in laboratory experiments (Cashins *et al*., 2013; McMahon *et al*., 2014). A less virulent or laboratory attenuated strain (Berger *et al*., 2005; Langhammer *et al*., 2013; Dang *et al*., 2017) could perhaps be used as a transmissible vaccine (Smithson et al 2019). The reduced mortality in rabbits from rabbit haemorrhagic disease in Australia as a result of cross-immunity from related endemic caliciviruses (Cooke *et al*., 2018) shows that this approach is feasible in principle. However, virulence of a *Bd* strain is not always consistent across species, and it is essential that care be taken to ensure that there is no risk of inadvertent introduction of any strain of *Bd* along with introduced animals (Muths and McCallum, 2016). Furthermore, imperfect vaccines could select for increased pathogen virulence (Gandon *et al*., 2001). Host modification of the skin microbiota in a field setting has some promise (Bletz *et al*., 2013). In one field trial, a population of the mountain yellow-legged frogs, *Rana muscosa*, experiencing an active *Bd* epizootic were exposed to a bacterial species with anti-*Bd* properties (*Janthinobacterium lividum*) (Vredenburg et al. 2011). In the short term, there was some indication that this microbial augmentation increased the survival and decreased the fungal loads of the treated individuals. However, the treatment did not protect the population from eventual extirpation. Vaccination and treatments would need to be implemented as part of a long-term management procedure because these strategies do not have long-term effects (Canning *et al*., 2019), although probiotics might persist. Selective breeding and release has been suggested as an option (Scheele *et al*., 2014; Skerratt *et al*., 2016), but has never tested under field or even in laboratory experiments thus far.

Habitat management is a part of many conservation programmes but rarely focuses on reducing *Bd* impacts, and where it has been tested, it has not worked as expected. In the green and golden bell frog, *Litoria aurea*, a species where both recruitment and environmental salinity are assumed to be important factors in population persistence, habitat was created that superficially matched the breeding habitat of the frogs naturally, but the introduced animals did not breed (Valdez *et al*., 2019). In another field experiment, *L. aurea* were released into semi-natural salinity manipulated habitats. More saline habitats had higher survival and lower infection over 18 months of monitoring, but larvae also experienced sublethal effects of developing in high salinity (Stockwell *et al*., 2015). In the phylogenetically related growling grass frog, *Litoria raniformis*, current research has identified that environmental factors like temperature and salinity are important mechanisms for population persistence (Table S1); however, actual field experiments of habitat manipulation have not been undertaken. A modelling approach revealed that creating habitat, even without environmental refugia from *Bd*, might be more effective than manipulating existing habitat, which points to habitat connectivity as more important for population persistence than disease refugia for this species (Heard *et al*., 2018).

Culling as a management option for *Bd* has rarely been tested, and raises both substantial ethical and logistic considerations (Garner *et al*., 2016). Culling, either of the target species or of tolerant sympatric species should only be considered if there is strong evidence for density dependence of disease and/or community composition as mechanisms of persistence. For example, one frog species, the Pacific tree frog, *Pseudacris regilla*, is the predominant maintenance host for *Bd* across 77 amphibian metacommunities in California and models suggested that removing the species would be the most effective strategy for reducing *Bd* across the landscape (Wilber *et al*., 2020). Whether removing this species is practically possible or ethically acceptable is a separate issue. One extreme management option is to combine habitat and *in situ* treatments by eradicating the pathogen from the environment through draining and disinfecting ponds and treating the animals with antifungals. This technique can successfully eliminate infection from the system, but only until there is an introduction event (Bosch *et al*., 2015; Fernandez-Loras *et al*., 2020). However, eradication of disease is unlikely to be successful in the long term for most systems (but see Bosch *et al*., 2015; since tested in 2013 at a site in Mallorca, there has been no reappearance of *Bd*).

COLLATION OF THE LITERATURE ON PERSISTING SPECIES

Through literature review we found that the mechanisms of host persistence are poorly understood for the majority of amphibian species that are persisting after devastating chytridiomycosis-related declines (Table S1). Even in the well-studied species, where multiple mechanisms of host persistence have been explored, the critical mechanism or combination of mechanisms at play can be unclear (see Box 3, Figure 3). Furthermore, species that are in dire need of effective conservation measures are often weakly studied. As overviewed above, the success of management options can heavily rely on understanding the mechanisms of persistence employed by the species. Therefore, we strongly urge future research to prioritise understanding the mechanisms of host persistence following the guidelines for the research required that we have outlined in the sections above.

GENERALISATION TO OTHER SYSTEMS

There are numerous examples of frog species that initially declined following the emergence of *Bd* that have now either recovered or their populations have stabilised (Scheele *et al*.,

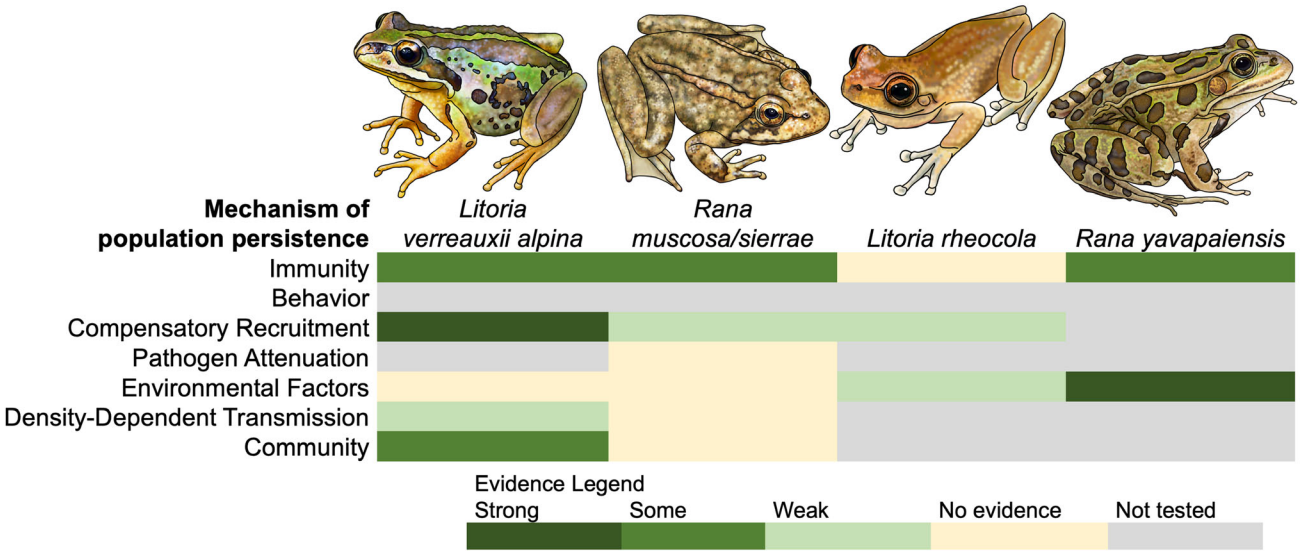

Figure 3 We overview four species for which multiple stated mechanisms of population persistence have been studied. The research conducted on each species is described in Box 3, and here we outline the evidence and support for each mechanism of population persistence and determine whether there is strong evidence, some evidence, weak evidence or no evidence following adequate field or laboratory experiments. See Table S1 for the research conducted on additional species that are persisting or recovering after declining due to *Bd*. Frog figures contributed by L. F. Grogan.

2019a). Similar sharp declines followed by recovery or stabilisation have been observed in other disease systems, some of which have mechanisms of population persistence identified. Tasmanian devils, *Sarcophilus harrisii*, declined dramatically following the emergence of infectious cancer, Tasmanian devil facial tumour disease, in the 1990s, with modelled predictions of complete extinction in the wild (McCallum *et al.*, 2009). However, despite declines, no local population has become extinct and there are signs of local recovery where exposed populations are likely developing resistance (Wright *et al.*, 2017; Jones et al. 2019). Species management involving supplementation of animals from naïve captive populations could likely slow or even reverse this adaptive response (Hohenlohe *et al.*, 2019). The Hawaiian avifauna was dramatically impacted by the introduction of avian malaria and bird pox in the 19th century, but one of the species that initially declined, Hawaii amakihi, *Chlorodrepanis virens*, is slowly recovering in some parts of its range due to a higher proportion of birds being able to limit parasite burden and survive (Woodworth *et al.*, 2005). West Nile virus was introduced into North America in 1999 and spread westward causing substantial mortality and decline in many bird species. Nevertheless, populations of all but two species that initially declined (LaDeau *et al.*, 2007) have stabilised or recovered, possibly due to increased resistance to the virus (Kilpatrick and Wheeler, 2019). Finally, white-nose syndrome, caused by the fungus *Pseudogymnoascus destructans*, caused dramatic declines and extirpations in four North American bat species (Langwig *et al.*, 2012). However, two declining species now have stable and in some places growing populations, likely through both increased resistance and tolerance, as well as possible density dependence (Langwig *et al.*, 2012). Among emerging wildlife pathogens, *Bd* is unique in the wide geographic, taxonomic and habitat range of the species it affects, providing an ideal system to evaluate and compare the various mechanisms of recovery and persistence.

An important insight with applications to many other systems is that persistence or recovery can depend on factors outside a particular host–pathogen pair. While evolutionary forces leading to increased resistance or tolerance in the host or attenuation in the pathogen can be important, the environmental and ecological community context in which the interaction is embedded is also critical. For chytridiomycosis, it is well recognised that the abiotic environment, particularly temperature, is an important factor in population persistence. Similarly, for white-nose syndrome in bats, the temperature in the hibernaculum is a crucial determinant of whether or not bat colonies persist (Langwig *et al.*, 2012). In comparison, the larger biotic community has been poorly investigated as a factor contributing to persistence or extinction of host species across wildlife diseases. Changes in the community composition following pathogen invasion are important when they have been investigated, such as in avian malaria in Hawaii (McClure *et al.*, 2020) and West Nile virus in the United States (Kilpatrick *et al.*, 2006), are likely important in determining whether or not frog species persist or recover following the invasion of *Bd*.

As we have argued, understanding the mechanisms that allow hosts to persist with the pathogen is essential, because management approaches might be ineffective or even counterproductive if they address the wrong mechanism(s) of persistence. Several recent experimental and review papers have investigated factors that might have contributed to recovery or persistence of frogs following *Bd* emergence, but have done so in particular geographic contexts, or with an emphasis on particular mechanisms of recovery (Knapp *et al.*, 2016; Greenberg *et al.*, 2017; Voyles *et al.*, 2018; Scheele *et al.*, 2019b). Previous research that overviews the mechanisms of species

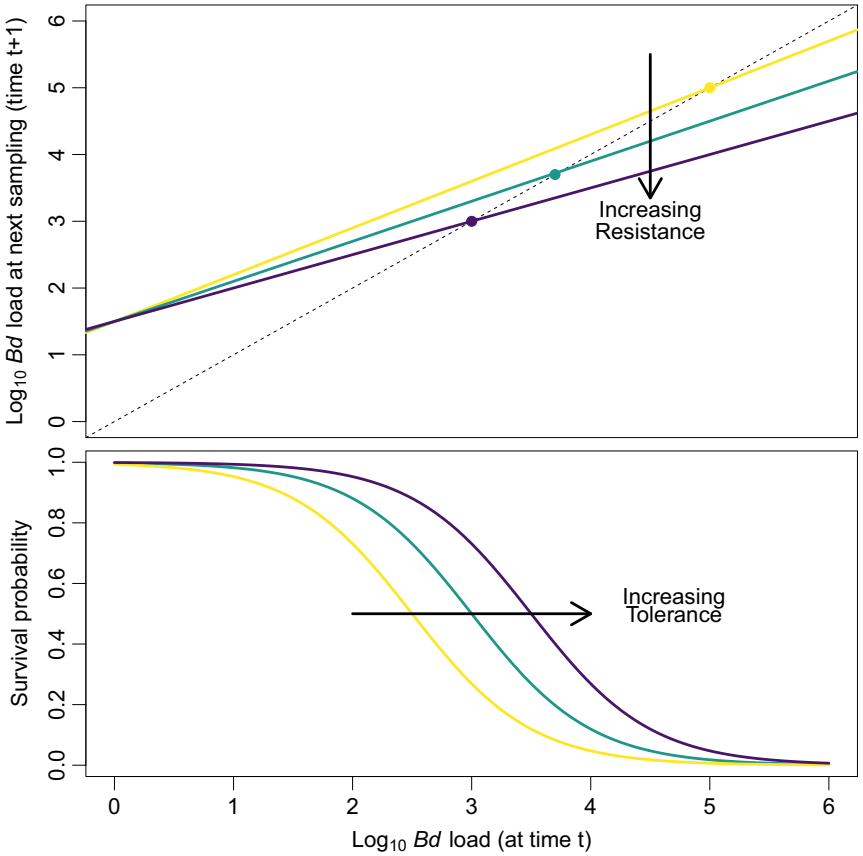

Figure 4 Visual representation of resistance and tolerance (Box 2). Hypothetical relationships for pathogen growth (top panel) and probability of survival (bottom panel) is plotted against pathogen load at time *t*. Top Panel: Lines show pathogen load at time t + 1 (Y-axis) given load at time t (X-axis). Lines with shallower slopes indicate higher resistance and different lines could represent different species, different populations or stages within a species, or changes in pathogen growth in the same individual over time as immune function increased. Dashed line indicates the 1:1 line where pathogen growth is zero; the intersection of any of the solid lines with the dashed line indicates an equilibrium pathogen load for as long as the host survives. The solid lines describe load dynamics where load increases or decrease monotonically to the equilibrium value, whereas as lines that change slope and/or intercept are needed to describe loads that show non-monotonic trends (e.g. an increase followed by a decrease). This simple conceptual model allows one to recreate the full temporal dynamics implied by each line by 'cobwebbing' or tracing a load trajectory over time starting at any infection intensity load determined at time t during the course of infection, moving to a load at the next sampling point (time t + 1) and then resetting time t + 1 to t (i.e. moving to the appropriate location on the x-axis) and repeating. Bottom Panel: Curves show the survival probability as a function of pathogen load with different curves showing variation in tolerance, which again could represent different species, populations, stages or variation over time since infection within an individual. Modelled after Wilber *et al.* (2017).

persistence has been limited to systemic or evolutionary shifts in the interactions between the host, pathogen and environment (McKnight *et al.*, 2017) and has not included some mechanisms such as changes in community composition, density-dependent transmission, immune mechanisms outside microbiota and skin defences and mechanisms related to stochasticity. It is important to investigate a wide range of mechanisms for persistence and recovery because these mechanisms are not mutually exclusive and are likely to be context dependent.

CONCLUSIONS

We have described the potential mechanisms that can promote host persistence for the amphibian disease chytridiomycosis, the data required to determine which mechanisms of coexistence are at play, and the evidence for each mechanism in case studies of persisting species. We draw attention to the overlooked mechanisms of persistence in hosts, particularly density dependence or species community, which are important and known to attribute population persistence, but often difficult to empirically assess. We found that in most cases the mechanism allowing for host persistence is unknown, and this will likely hamper effective conservation into species recovery and halt declines. Even in the well-studied species (see Box 3, Figure 3), or the well-studied mechanisms of persistence (such as immune and environmental factors), there are few clear examples of active mechanisms of host persistence. Understanding mechanisms of host persistence following a devastating decline due to the disease is complicated and multifaceted, and these issues are common to other species threatened by other pathogens. The success of management options can rely heavily on understanding the mechanisms enabling species to persist. We strongly urge future work to prioritise

understanding the mechanisms of host persistence, following the research agenda that we have described.

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AUTHORSHIP

All authors contributed to the idea and design of the project. LAB led the writing. LAB, MPR, MH, TSL, MFL compiled the data for Figure 1 and AMK analysed the data and designed Figures 1, 4 and Box 2. LAB and HIM designed Figure 2, LAB and LFG designed Figure 3. All authors contributed to the writing of the manuscript.

DATA ACCESSIBILITY STATEMENT

No new data were used in this manuscript. Model details and sources of the data used are provided in the electronic supplemental materials.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ele.13621.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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