



Perspective

Overview of emerging amphibian pathogens and modeling advances for conservation-related decisions

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ARTICLE INFO

Keywords:

Chytrids
 Ranaviruses
 Trematodes
 Perkinsea
 Capture-mark-recapture models
 Site-occupancy models
 Hierarchical models

ABSTRACT

One of the leading causes of global amphibian decline is emerging infectious disease. In this review, we summarize the disease ecology of four major emerging amphibian infectious agents: chytrids, ranaviruses, trematodes, and Perkinsea. We focus on recently developed quantitative advances that build on well-established ecological theories and aid in studying epizootic and enzootic disease dynamics. For example, we identify ecological and evolutionary selective forces that determine disease outcomes and transmission pathways by borrowing ideas from population and community ecology theory. We outline three topics of general interest in disease ecology: (i) the relationship between biodiversity and disease risk, (ii) individual, species, or environmental transmission heterogeneity, and (iii) pathogen coinfections. Finally, we identify specific knowledge gaps impeding the success of conservation-related decisions for disease mitigation and the future of amphibian conservation success.

1. Introduction

Emerging infectious pathogens are among the greatest threats to biodiversity (Daszak et al., 2000; Fisher et al., 2012; Lips et al., 2006; Martel et al., 2014; Tompkins et al., 2015). A few prime examples are West Nile Virus (Kilpatrick, 2011), white nose syndrome (Frick et al., 2010), avian malaria (Freed et al., 2005), and the amphibian-killing fungi *Batrachochytrium dendrobatidis* (Berger et al., 1998) and *Batrachochytrium salamandrivorans* (Martel et al., 2013). Despite the increase in research on emerging infectious agents over the last several decades (e.g., Wake and Vredenburg, 2008; Fisher et al., 2012; Tompkins et al., 2015), ecologists lack the ability to quantify disease dynamics quickly and efficiently (Hudson et al., 2016; Murray et al., 2009; Muths et al., 2011; Scheele et al., 2016; Stegen et al., 2017; Valenzuela-Sánchez et al., 2017; Wilber et al., 2017). Collecting data on individual hosts may be difficult depending on the system because of cryptic behaviors, hiding when sick (Faustino et al., 2004), and financial or logistical constraints for long-term studies (Valenzuela-Sánchez et al., 2017). Pathogens can also be difficult to study when there are no non-lethal diagnostic tools (Karwacki et al., 2018), when individual hosts have low infection intensities (DiRenzo et al., 2018; Lachish et al., 2012; Miller et al., 2012), or when pathogens have not been described. Collectively, these difficulties limit the ability of wildlife managers to characterize and detect wildlife disease outbreaks

proactively, predict future disease dynamics, and evaluate the effectiveness of disease mitigation strategies (Garner et al., 2016).

Theory-driven disease models (e.g., compartmental [SIR and variants] models, agent-based models, or diffusion models) are frequently used to guide management strategies (e.g., vaccination, culling, biological control agents; McCallum, 2016). These models are parameterized using field and/or lab data. In matrix population models, sensitivity and elasticity analyses evaluate the absolute and relative importance of different parameters in determining host population growth rate, which then become the targets of disease mitigation strategies. Conservation-related failure might occur because of logistical difficulties, inadequate data (i.e., quality or quantity of data), and/or the availability of diagnostic tests (e.g., unknown life history and ecology for ex situ projects for amphibian captive breeding; Michaels et al., 2014). One contributor to oversights occurs when field data are used to understand disease dynamics that do not account for uncertainty (e.g., McClintock et al., 2010; Bailey et al., 2014). Uncertainty can manifest in two forms: (i) sampling error of individual host occurrence or abundance (i.e., imperfect individual host detection; Faustino et al., 2004) or (ii) uncertainty of pathogen occurrence or abundance (i.e., imperfect pathogen detection; DiRenzo et al., 2018; Lachish et al., 2012; Miller et al., 2012). Failing to account for sampling errors could result in biased parameter estimates and erroneous future predictions that would propagate the selection of ineffective (at best) or harmful (at worst)

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Received 30 October 2018; Received in revised form 26 February 2019; Accepted 17 May 2019

Available online 13 June 2019

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disease mitigation strategies (Grant et al., 2017; Langwig et al., 2015).

Even the simplest estimators, such as pathogen prevalence, may be biased when imperfect pathogen and individual host detection are not addressed (Jennelle et al., 2007). Using traditional capture-mark-recapture (CMR; Cooch et al., 2012) methods are an improvement over using raw observation data to estimate disease and host species population parameters, but results can be unreliable when too few individuals are recaptured, resulting in large uncertainty of demographic parameter estimates. Thus, a new class of models is needed that explicitly accommodate sampling error to estimate unbiased demographic parameters without unreasonable data needs. Hierarchical unmarked data models (i.e., multi-levels models that take advantage of data where individuals in a population cannot be distinguished) provide a gateway to answering previously intractable questions in a cost-effective manner. In the case of disease ecology, integrated population models (i.e., models that use different kinds of data to improve parameter estimation) have a huge potential to booster our understanding of host-pathogen dynamics (Zipkin and Saunders, 2018). Although there have been repeated calls to improve surveillance programs for detecting disease (e.g., Yasue et al., 2006; Nusser et al., 2008; Plowright et al., 2008; McClintock et al., 2010), few methodological advancements have satisfactorily addressed issues of scale and imperfect individual host and pathogen detections.

Our objectives are two-fold. First, we review four of the most prominent infectious agents leading amphibians species' population declines. Second, we discuss quantitative advancements in studying disease dynamics. We summarize where research has failed to lead to management recommendations, identify knowledge-gaps relevant to making conservation decisions (i.e., biodiversity and disease severity relationship, transmission heterogeneities, and the effects of pathogen coinfection on disease outcome), and discuss the future of amphibian conservation success in relation to disease.

2. Emerging infectious disease agents of amphibians: Pathology, ecology, and individual responses to infection

Scientists have identified four major emerging infectious disease agents that have caused amphibian mortality: chytrids, ranaviruses, trematodes, and Perkinsea (Gray and Chinchar, 2015; Johnson and Lunde, 2005; Lips, 2016; Martel et al., 2013). We review information on the timeline of emergence, host range, life cycle, and pathogen origin for each infectious agent, but note that not all this information is available for each case.

2.1. Chytrids

2.1.1. Timeline of emergence and host range

Batrachochytrium dendrobatidis (hereafter *Bd*) was formally identified in 1999 (Longcore et al., 1999), although amphibian mass mortality worldwide caused by *Bd* was documented before the description of the pathogen (Berger et al., 1998). *Bd* infects over 700 amphibian species (Olson et al., 2013) and causes species extinctions and population declines globally (Catenazzi et al., 2017; Gower et al., 2012; Lips et al., 2003, 2006; Skerratt et al., 2007; Swei et al., 2011; Vredenburg et al., 2010). Amphibian species and populations do not respond equally to *Bd* infection (Crawford et al., 2010; Muths et al., 2011), and often, susceptibility varies by life stage (Briggs et al., 2010). Some species are highly susceptible and entire populations can be locally extirpated while other species decline and persist at low numbers (Brannelly et al., 2018; Crawford et al., 2010; Sapsford et al., 2013; Voyles et al., 2018). At the same time, other species are not affected by *Bd* infection and may act as pathogen reservoirs (Reeder et al., 2012; Vredenburg et al., 2010). Note that mass mortalities and species declines caused by *Bd* are potentially orders of magnitude larger than other pathogens.

2.1.2. Life cycle

Bd has a two-stage life cycle. The first stage is a motile zoospore that encysts on amphibian skin that matures into a zoosporangium. The second stage is the zoosporangium that creates more zoospores and is released onto the surface of the skin of the amphibian (Greenspan et al., 2012). These zoospores can re-infect the same individual or swim into the aqueous environment and infect others (Maguire et al., 2016). However, external zoospore reinfection of an infected individual does not seem to contribute substantially to *Bd* growth (DiRenzo et al., 2018c).

2.1.3. Origin of the pathogen

Bd likely originated in Asia, where the highest genetic diversity has been found along with hybrid strains (O'Hanlon et al., 2018). *Bd* includes lineages from South Africa (*Bd*-CAPE), Brazil and Asia (*Bd*-Brazil/Asia-2, and *Bd*-Asia1), and a hyper-virulent global panzootic lineage (*Bd*-GPL; James et al., 2015; O'Hanlon et al., 2018; Rosenblum et al., 2013; Schloegel et al., 2012). *Bd*-GPL is the primary lineage associated with amphibian mass mortality events and population declines worldwide (Farrer et al., 2011; James et al., 2015; Lips, 2016; Olson et al., 2013), but other lineages (*Bd*-Cape) have been shown to also produce population declines (O'Hanlon et al., 2018). Within the last decade, rapid advances in understanding *Bd* genetic diversity, radiation, and virulence have occurred because of new technology; however, large parts of South America, Asia, and Africa still need to be sampled for a more complete understanding of *Bd* genetic diversity.

In 2013, a second species, a sister lineage of *Batrachochytrium* was described, *Batrachochytrium salamandrivorans* (*Bsal*; Martel et al., 2013). This pathogen is extremely lethal to salamanders in the Family Salamandridae (Martel et al., 2014) and is enzootic in Asia. It is hypothesized that *Bsal* arrived in Europe through salamander trade, and has since appeared in the United Kingdom, Germany, and Belgium (Fitzpatrick et al., 2018). One of the largest differences between *Bsal* and *Bd* is the existence of a resting spore stage in *Bsal* (Stegen et al., 2017), indicating long-term persistence of the pathogen in the environment. *Bsal* has yet to be detected in the Americas (Grant et al., 2016; Parrott et al., 2016), where 14% of the world's 535 salamander species occur (Petranka, 1998). The existence of a resting stage in the *Bsal* life cycle that remains virulent in water and soil makes pathogen management and salamander conservation difficult (Stegen et al., 2017).

2.2. Ranaviruses

2.2.1. Timeline of emergence and host range

Ranaviruses are DNA viruses in the Iridoviridae family, a diverse group of viruses known to infect vertebrate species, including amphibians, fish, and non-avian reptiles (Gray and Chinchar, 2015). Controlled studies have shown that susceptibility to ranavirus infection varies among amphibian species and developmental stages, and is impacted by host-pathogen coevolution, life history strategy (Hoverman et al., 2011), and exogenous environmental factors, such as water quality and aquatic vegetation (Miller et al., 2011).

Ranaviruses infect at least 175 species across 52 families of ectothermic vertebrates, are associated with mass mortality and declines, and are found on all continents but Antarctica (Duffus et al., 2015). Most of what is known about the geography and species host range of ranaviruses come from studies of sporadic surveillance efforts in a small number of amphibian populations, and a few larger-scale surveillance efforts focused on a handful of species of economic importance or conservation interest. Ranaviruses may truncate the age structure of host populations and reduce population viability, increasing their vulnerability to stochastic events affecting recruitment (Campbell et al., 2018). The known geographic distribution and species host range of ranavirus is likely underestimated because gross signs of ranavirus infection are not always obvious and many host species are cryptic.

2.2.2. Replication

Viral DNA replication initially takes place within the nucleus and then moves into the cytoplasm, where a second round of DNA synthesis occurs (Jancovich et al., 2015). Transmission of the virus between individual hosts does not seem to be regulated by contact rates or density-dependence (Brunner et al., 2017). However, ranavirus incidence decreases with increased amounts of emergent vegetation (Greer and Collins, 2008), suggesting that vegetation drives host behavior and disease.

2.3. Trematodes

2.3.1. Timeline of emergence and host range

Since 1992, limb abnormalities, including extra, missing, or malformed limbs, have appeared among amphibian species, in part due to trematodes (Johnson and Lunde, 2005). The trematode parasite *Ribeiroia* targets developing limb tissue of anuran larvae, inducing limb malformations (Johnson, 1999), above and beyond what is expected (0–5%) because of gene mutation, trauma/predation, and/or developmental errors. *Ribeiroia* causes approximately 15–90% of individual mortality and limb malformations among animals exposed during pre-limb and early limb development, but decreases to less than 5% post-limb development (Johnson, 1999). Early stage anuran larvae exposed to trematodes also exhibit a higher frequency of missing limbs into metamorphosis compared to anurans exposed after limb development initiated (Johnson et al., 2011). Individuals infected in later life stages develop normal limbs or exhibit only minor outgrowths and abnormal skin webbings (Johnson et al., 2011). *Ribeiroia* likely impacts amphibian distributions and population dynamics (Johnson and Lunde, 2005).

2.3.2. Life cycle

Ribeiroia has a complex, indirect life cycle that involves three host species (Johnson and Sutherland, 2003). Avian and mammalian predators are the definitive host species of the parasite, where it reproduces sexually (Johnson and Sutherland, 2003). The definitive host species drops feces containing eggs into water (Johnson and Sutherland, 2003). The eggs develop for two to three weeks and hatch into miracidia, a ciliated free-living parasite stage, that then infects snails of the genera *Biomphalaria*, *Helisoma* or *Planorbella*, the intermediate host species (Johnson and Sutherland, 2003). Inside the snail, the parasite colonizes the reproductive tissue and form rediae, a slow-moving worm-like parasite stage (Johnson and Sutherland, 2003). The rediae reproduce asexually. The snails shed *Ribeiroia* cercariae, a second free-swimming stage, that encyst in either larval amphibians or freshwater fish, the secondary host species (Johnson and Sutherland, 2003). These secondary host species are then consumed by the definitive host species (Johnson and Sutherland, 2003).

2.3.3. Origin of the pathogen

Ribeiroia-induced limb malformations have occurred in North America since at least the 1940s (Johnson et al., 2003). An exhaustive literature search yielded less than 15 records of “mass malformation” in the United States, whereas greater than 50 malformation sites associated with *Ribeiroia* were discovered in the late 1990s and early 2000s (Johnson and Sutherland, 2003). As a possible explanation for an apparent increase in malformations, *Ribeiroia* may have emerged as a consequence of changes in host ecology. Malformation hotspots and *Ribeiroia* are associated with highly productive, artificial habitats such as farm ponds used to water crops and cattle. Three mechanisms may drive the role of *Ribeiroia*-amphibian dynamics: (i) these areas are associated with high productivity because of fertilizer and manure runoff, leading to increased algal production and denser populations of snails, (ii) the number of artificial ponds has increased over the mid- to late-1900s as natural wetlands decline, or (iii) all three hosts (snails, amphibians, birds) are frequently found in these systems. However, the

interaction between other stressors, such as increased pesticide use, cannot be ruled out.

2.4. *Perkinsea*

2.4.1. Timeline of emergence and host range

The emerging infectious pathogen *Perkinsea* was described recently (Chambouvet et al., 2015; Davis et al., 2007; Isidoro-Ayza et al., 2017; Isidoro-Ayza et al., 2018; Landsberg et al., 2013). Severe *Perkinsea* infection (SPI) has caused mass mortality in tadpoles across the United States (Isidoro-Ayza et al., 2018). SPI is caused by a protozoan belonging to the phylum Perkinsozoa. *Perkinsea* is genetically similar to *Perkinsus*, the pathogen responsible for the mass mortality of bivalves (Green et al., 2003; Jones et al., 2008); hence the resemblance in the names.

Perkinsea occurs from Alaska to Florida (Green et al., 2003; Landsberg et al., 2013; Isidoro-Ayza et al., 2017; Isidoro-Ayza et al., 2019). It has also been detected in French Guiana, Cameroon, Tanzania, the Island of Sao Tome, and the United Kingdom (Green et al., 2003; Chambouvet et al., 2015). The global extent of its distribution is unknown. *Perkinsea*-associated tadpole mass mortality events usually occur gradually over a breeding season, but the events are generally not large and seldom observed (Atkinson, 2016). Despite signs that suggest an overall small impact of *Perkinsea*, it is a lethal pathogen. Its virulence is affected by water chemistry, such that outbreaks causing mass mortalities can occur in previously unaffected ponds (Cook, 2008; Atkinson, 2016). Additionally, it may act as an insidious mechanism that causes a slow (and perhaps difficult to detect) population decline.

2.4.2. Life cycle

Perkinsea has both spore and zoospore life stages. The spores survive desiccation and tolerate a wide range of temperatures, pH, and salinity. Spores hatch into zoospores when rain starts forming ponds (Cook, 2008). The ponds are used by amphibians to reproduce, and the zoospore stage of *Perkinsea* can penetrate anuran embryos and tadpoles (Davis et al., 2007; Cook, 2008). SPI has not yet been detected in adult amphibians (Isidoro-Ayza et al., 2018). The zoospore then embeds itself in the liver of the amphibian and proliferates throughout internal organs (Green et al., 2003; Davis et al., 2007; Cook, 2008). *Perkinsea* is also associated with muscle inflammation. This symptom makes non-destructive testing possible. Rapid and reliable pathogen identification can be achieved using qPCR (Karwacki et al., 2018) on swabs samples or tissue clippings (Green et al., 2003; Jones et al., 2008).

2.5. The future of amphibian populations faced with emerging infectious diseases

There is an urgent need for larger, longer, spatio-temporal sampling of infectious agents of amphibians to aid in answer questions such as where, when, and how pathogens emerged. For example, understanding where, when, and how *Bd* became virulent has changed several times over the last decade as sampling became more extensive. Originally, *Bd* was hypothesized to have emerged out of Africa due to the increased exportation of *Xenopus laevis* (Vredenburg et al., 2013). More recently, it was determined that *Bd* likely originated in Asia, given the high genetic diversity in this area (O'Hanlon et al., 2018). However, there are still aspects of disease emergence that have not received adequate attention. For example, we know that the spread of *Bd* has caused the restructuring of ecosystems and food webs (Barnum et al., 2013; DiRenzo et al., 2017; Rantala et al., 2015; Regester et al., 2006; Whiles et al., 2006), but bottom-up effects are not well-documented (Buck and Ripple, 2017; Whiles et al., 2006). It is also unclear if ranaviruses, trematodes, or *Perkinsea* have the potential to cause similar large-scale ecosystem restructuring because there are few pathogen/infectious agent datasets prior to invasion for comparisons. There is a shortage of studies documenting widespread mass mortalities, and

large-scale and long-term spatio-temporal studies are often cost-prohibitive or logistically intractable.

There is considerable uncertainty in the extent of the effect of emerging infectious disease on amphibian population dynamics, and in the efficacy of identified conservation mitigation strategies (e.g., Scheele et al., 2019- this issue; Canessa et al., 2019- this issue). For example, there remain large gaps in knowledge with respect to individual pathogen infection and physiology (Russo et al., 2018; Voyles et al., 2009, 2012), differential disease outcomes due to temperature and other abiotic factors (Sonn et al., 2017), the impact of disease on reproductive ecology (Kindermann et al., 2017), the role of super-spreaders (DiRenzo et al., 2014; Lloyd-Smith et al., 2005), understanding causal and directional effects of changes in microbiome (Jani and Briggs, 2014), and the relationship between biodiversity and disease severity (Keesing et al., 2006). Given the recency in the emergence of many amphibian infectious agents, disease ecologists have only begun to understand single-pathogen infection and coinfection (Hoverman et al., 2011, 2013; Johnson and Hoverman, 2012; Stutz et al., 2017; Talbott et al., 2018; Wuerthner et al., 2017), and how multiple infections (coinfection) affects host-pathogen dynamics (Rigaud et al., 2010). To begin to answer these questions, disease ecologists have relied on a number of quantitative methods.

3. Classical estimation and prediction models for disease ecology

Two of the most common quantitative methods used in disease ecology can be classified as either statistical models (i.e., a mathematical model that embodies a set of statistical assumptions concerning the generation of sample data from a larger population) or mechanistic models (i.e., a mathematical model that assumes that a complex system can be understood by examining the workings of its individual parts and the way in which they are coupled; see Valenzuela-Sánchez et al., 2017; Wilber et al., 2017). Statistical models are used to estimate demographic parameters and host-pathogen codependence dynamics from field and lab data; while mechanistic models are used to predict future outbreaks, dynamics, and the risk of species extirpation. Using parameters estimated from statistical models, mechanistic models can be used to make decisions that reduce the severity or spread of a pathogen (Russell et al., 2018).

Estimation of individual host and pathogen parameters using statistical models can incorporate variation in ecological variation (e.g., survival probability, recruitment) and observation error in the form of a probability distribution, though they require replicate observations of detection to estimate ‘false negative’ rates (i.e., probability of species detection, given that the species is present). By repeatedly sampling ‘sites’- which can be defined as an organ, an individual host, or a spatial location- a wide range of disease-related questions can be answered while accounting for imperfect individual host and pathogen detection using methods such as site-occupancy models, N -mixture model, and their variants (Kéry and Royle, 2016). While hierarchical models became popular among ecologists in the early 2000s (MacKenzie et al., 2005; MacKenzie and Bailey, 2004; Royle, 2004), disease ecologists have only recently recognized their utility in estimating the effects of wildlife disease on host species populations (Bailey et al., 2014; Cooch et al., 2012; DiRenzo et al., 2019; McClintock et al., 2010; Mosher et al., 2017a; Mosher et al., 2017b).

While robust study designs and properly executed capture-mark-recapture (CMR) models produce high-quality demographic estimates, these studies can be expensive and logistically infeasible to execute at large spatio-temporal scales or for populations with few individuals (see Conn and Cooch, 2009). A new class of unmarked data models, where individual hosts in a population are not individually marked but a ‘site’ is repeatedly surveyed during a defined period of population closure, are useful tool to estimate similar demographic parameters, while still accounting for imperfect individual detection (Brintz et al., 2018; DiRenzo et al., 2018c; DiRenzo et al., 2019; Zipkin et al., 2014a;

Zipkin et al., 2014b). These models, hereafter referred to as unmarked data models, allow for the estimation of demographic rates or pathogen metrics based on count or detection/non-detection data without needing additional information (e.g., individual identification or distance measurements) and can accommodate heterogeneity in detection probabilities of target species (but see Barker et al., 2018; Link et al., 2018).

The parameters estimated in unmarked data models and CMR models are not identical but similar (e.g., survival probability at the site level versus individual level). The models can be combined to improve inference in so-called ‘integrated population models’ or ‘data fusion models’ (for a recent review see Zipkin and Saunders, 2018). These parameters can be used in mechanistic models to give a greater understanding of the underlying processes, rather than patterns. Other common types of mechanistic models are ordinary differential equations and individual-based models (Briggs et al., 2010; Louca et al., 2014; Mitchell et al., 2008). These models are the theoretical foundation for understanding in disease ecology (Anderson and May, 1978, 1986; Kermack and McKendrick, 1927; May and Anderson, 1979). However, despite the usefulness of predictions from theoretical models, the empirical data often used to parameterize them typically do not account for sampling error (e.g., Barlow, 1995). Such integration would produce a better understanding of the mechanisms underlying population abundance, persistence, and pathogen dynamics, especially in regard to answering topics in disease ecology that have not been resolved because of disparate results.

4. Novel approaches to classic conundrums

Three topics of general interest in disease ecology that have received attention recently because of incongruent results are: (i) the relationship between biodiversity and disease risk, (ii) the heterogeneity in individual, species, and habitat transmission, and (iii) the incidence of pathogen coinfections in the wild. We discuss the debates around each topic, the problems with the using of particular statistical models to investigate these topics, and how hierarchical unmarked data models could help address computational issues.

4.1. Biodiversity and disease severity relationship

There are large debates over when to expect negative or positive relationships in the correlation between biodiversity and disease severity (e.g., Wood and Lafferty, 2013; Johnson et al., 2015). The dilution effect, characterized by a negative correlation between biodiversity and disease severity, is hypothesized to occur when higher species richness leads to reduced encounter rates between susceptible and infectious individuals, reduced transmission rates, reduced population density, increased disease-induced mortality of infected individuals, or accelerated recovery of infected individuals (Keesing et al., 2006). In contrast, the amplification effect, a positive correlation between biodiversity and disease severity, occurs when low species diversity contains incompetent individuals or when adding species to the community increases the number of individuals that easily acquire and transmit the pathogen (Keesing et al., 2006). Support for either hypothesis requires unbiased estimates of local species richness, species-specific densities, and individual survival and transmission rates (Table 1). Although some of these data exist, most studies examining the biodiversity versus disease severity relationship do not account for observation error and may use biased estimates of species richness, species-specific densities, and pathogen prevalence/infection intensity, which could explain the number of inconsistencies among conclusions (Johnson et al., 2015).

The use of hierarchical unmarked or CMR models could improve the estimation of three key parameters used to evaluate the support for the biodiversity and disease relationship. First, unmarked data or CMR models can provide estimates of species richness that account for undetected, rare species by using data augmentation methods (e.g., Kéry

Table 1

Summary of classical conundrums in disease ecology along with a list of parameters of interest, problems that classical approaches have, and new suggested modeling approaches.

Topic	Parameters of interest	Problem	Suggested modeling approach
Biodiversity and disease severity relationship	Species richness Species density Pathogen prevalence	Imperfect host detection Imperfect pathogen detection	Hierarchical unmarked or mark-recapture models
Transmission heterogeneity: individual, species, and habitat superspreaders	Pathogen infection intensity Species or habitat pathogen prevalence Individual, species, or habitat pathogen infection intensity Species abundance or proportion of habitat	Imperfect host detection Imperfect pathogen detection	Hierarchical unmarked or mark-recapture models with or without community structure
Coinfection: infection of a single individual by multiple pathogens	Pathogen prevalence Pathogen infection intensity	Imperfect host detection Imperfect pathogen detection	Hierarchical unmarked or mark-recapture models; two-species site-occupancy model

and Schaub, 2012). This method involves added a large number of zero entries to the data set, representing individuals that might have been in the population but never observed. The model then uses the estimates of imperfect species detection to determine how many species were truly unobserved. Second, unmarked data or CMR models help accommodate differences in individual detection probability between infected and uninfected individuals to improve estimates of true species-specific densities (e.g., Abad-Franch et al., 2010; van Strien et al., 2011). Finally, unmarked data or CMR models account for imperfect pathogen detection caused by sampling and diagnostic methods to provide less biased estimates of pathogen prevalence and true infection intensity (e.g., Lachish et al., 2012; Miller et al., 2012). By accommodating for the unavoidable imperfect detection of species, individuals, and the pathogen, unmarked data or CMR models allow for inference of the true (latent) infection process, thus improving parameter estimation.

4.2. Transmission heterogeneity: individual, species, and habitat superspreaders

While simple models of transmission assume that infection intensity is similar among individuals, species, and habitats, hierarchical unmarked or capture-mark-recapture models accommodate variation in each level to improve parameter precision of key processes, such as transmission (Table 1) and take into account imperfect sampling. Depending on the scale of pathogen aggregation (i.e., individual, species, habitat) and the type of data collected (i.e., single versus multi-species), hierarchical models can accommodate over-dispersion in infection intensity or pathogen prevalence created by superspreaders using a probability distribution. For example, if infection intensities are over-dispersed among individuals, as is common across disease-wildlife systems (Shaw and Dobson, 1995), lognormal (for continuous data, such as that received from a qPCR diagnostic) or negative binomial (for discrete or count data) distributions may characterize the variance of infection intensities.

Variation in individual infection intensity and duration of infectiousness can create large disparities in an individual's ability to maintain and transmit infections. This makes particular individuals, species, or habitats disproportionately more likely to contribute to pathogen transmission either because individual or species level immune response cannot fight the pathogen well (Lloyd-Smith et al., 2005; Hawley and Altizer, 2011; Streicker et al., 2013). As such, these individuals, species, or habitats are frequently referred to as 'superspreaders' (e.g., Paull et al., 2012; Streicker et al., 2013) and are identified as the top 20% of the individuals, species, or habitats responsible for 80% of transmissions (20:80 rule; Woolhouse et al., 1997).

In the tropics, it is hypothesized that the genus *Atelopus* are

superspreaders because they typically carry high infection loads and die within weeks of infection (DiRenzo et al., 2014; Lampo et al., 2011; La Marca et al., 2005; also see Scheele et al., 2017). However, there is a lack of evidence comparing similar community assemblages (one with and one without *Atelopus*) to clearly identify the role of individual species in disease dynamics (for another example see Scheele et al., 2016).

4.3. Coinfection: infection of a single individual by multiple pathogens

Historically, disease ecologists have focused on understanding how a single pathogen infects and causes mortality in multiple host species (Rigaud et al., 2010); however, individuals are regularly infected by multiple pathogens (i.e., coinfection; Rynkiewicz et al., 2015; Seabloom et al., 2015). Coinfections have been implicated as influential to honeybee colony collapse disorder, emerging infections of coral reefs, and human disease outcomes (e.g., Druilhe et al., 2005; Bromenshenk et al., 2010). Collectively, understanding how coinfections drive individual mortality and fitness is a fundamental knowledge gap in disease ecology. By considering an individual analogous to an ecosystem and applying community ecology theory, models from community assembly theory can be used to better understand pathogen coinfection outcomes (Johnson et al., 2015). Community assembly theory posits that the first colonizing species modifies the existing environment and subsequent invaders may be affected by modifications made to the habitat by the primary colonizer (e.g., Flecker et al., 1999). The pathogen interactions (i.e., facilitative, antagonistic, or neutral) between the primary and the secondary infecting pathogen will depend on whether the primary pathogen stimulates or inhibits the individual's immune response and the competition pressure for resources between the individual and the two pathogens.

Coinfection diagnosis can be missed when pathogens are at low levels, especially given that several studies have indicated that there is a positive correlation between the pathogen load and the probability of detecting the pathogen (e.g., Lachish et al., 2012; Miller et al., 2012). Because of this imperfect detection, parameter estimation and the interpretation of within-host pathogen interactions (i.e., neutral, facilitative, antagonistic; MacKenzie et al., 2006) will be biased. For example, if multiple infecting pathogens are each imperfectly detected, we might misjudge the level of competition or facilitation between the two pathogens.

To address this challenge of imperfect detection in a two-pathogen scenario (i.e., coinfection), a specific type of occupancy model, the species co-occurrence model, can separate the ecological process model from the sampling process (Table 1; MacKenzie et al., 2006). This modeling approach differs from the traditional site-occupancy model in that multiple occupancy states are possible rather than the traditional

binary case (i.e., occupied or not occupied). Instead, each site can take on one of four possible mutually exclusive states: (i) occupied by pathogen A and B, (ii) occupied by pathogen A only, (iii) occupied by pathogen B only, and (iiii) not occupied by either pathogen (Mosher et al., 2018). Here, when pathogen A is observed at a site, the true state of that site could either be “occupied by pathogen A only” or “occupied by pathogen A and B.” By extending the number of occupancy states, this modeling approach explicitly aids in testing the following three biological hypotheses: (i) the probability of pathogen co-occurrence, (ii) the independence of detecting each pathogen, and (iii) whether detection of each pathogen depends on the presence of the other pathogen. The development of the multi-state occupancy model is identical to the multi-state CMR model (Kéry and Schaub, 2012). Detection/non-detection data have the advantage of being relatively easy to collect. Therefore, an important assumption in these applications is that the sampled units (i.e., captured individuals) are a random sample of the population (see Bailey et al., 2014 on the applications, flexibility, and requirements of multi-state occupancy models in disease ecology). This model could theoretically be extended to accommodate count data if a multinomial distribution were used rather than a categorical distribution.

5. Identifying conservation-relevant research

To successfully implement a conservation plan, managers need a variety of information, such as a description of host species population dynamics (ecological and evolutionary), pathogen presence and distribution, important heterogeneities (Smalling et al., 2019- this issue), and species genetics. In the past, amphibian conservation planning has focused on ex situ amphibian strategies, making many difficult decisions on which species to target and rear in captivity (Griffiths, 2017); however, more than half of the amphibian species that end up in captive breeding programs do not have a plan for reintroduction (Griffiths and Pavajeau, 2008). More recently, in situ treatment of *Bd* infections have shown promising results (Hudson et al., 2016).

To develop effective and efficient disease mitigation strategies, an understanding of host–pathogen interactions, such as pathogen transmission, influence on demographic rates (e.g., survival, recruitment, population size), and individual hosts interacting with biotic or abiotic pathogen reservoirs, are critical. Despite an understanding of the various factors at play, determining the utility of management actions suggested by a conservation plan is still difficult. This difficulty is primarily because there is almost always uncertainty around how these factors interact when a particular management action is applied (Converse et al., 2017; Gerber et al., 2017). However, managers often are forced to make a decision faced with considerable uncertainty when the ecology of host–pathogen dynamics is not well understood. For example, simple deterministic models with density-dependent transmission predict that a pathogen will be driven to extinction before the individual host, but three conditions can alter their fate (de Castro and Bolker, 2004). First, the existence of pathogen reservoirs (Stegen et al., 2017), either biotic or abiotic, could lead to higher incidence rates independent of population size. Second, small populations could lead to Allee or inbreeding effects or spatio-temporal stochasticity could extirpate a population (Lande, 1993). Lastly, density-independent transmission (i.e., frequency-dependent transmission in vector-borne diseases) or non-homogeneous mixing (e.g., social behavior) could result in host species extinction. These ecological conditions can influence the success of conservation plans if not considered, and complicate the management decision, Canessa et al. (2019- this issue) outline how to approach management decisions using both basic and applied science.

While many studies focus on understanding the ecology of host–pathogen interactions, it is also important to consider the effects of a pathogen on host species population genetic structure. Disease may affect host species population gene flow, alter genetic variability, and ultimately drive selection (McKnight et al., 2017; Savage et al., 2015,

Savage et al., 2016; Savage and Zamudio, 2011; Savage and Zamudio, 2016). Disease often fragments host species populations into small, genetically distinct units with limited gene flow among them; in some cases, isolated host species populations show the signatures of genetic bottlenecks and/or population inbreeding, whereas in other populations, there may be sufficient gene flow or enough survivors to prevent genetic drift and inbreeding. Gene flow can impact the evolution of small host populations in one of two ways (McKnight et al., 2017). First, it can be beneficial if gene flow provides the host population with more genetic variation, reducing the impacts of inbreeding. Alternatively, gene flow can be detrimental to a small population if it is dominated by alleles that are locally maladaptive (McKnight et al., 2017). Differences in gene flow may explain why some species adapt to pathogens and persist while others are driven to local extinction. Genetic information can be used in population viability analyses to predict future host species population and disease dynamics, explicitly accommodating evolution- a critical information needed to develop conservation management plans and disease mitigation strategies.

Active amphibian management (e.g., relocations) generally takes either proactive (pre-emergence of disease) or reactive (post-emergence) approaches to dealing with emerging infectious diseases (Grant et al., 2017). To date, amphibian disease management has occurred reactively (post-emergence), mitigating disease spread and securing captive assurance colonies (Lewis et al., 2019- this issue). There are amphibian conservation projects to mitigate *Bd* impacts that use: habitat management (Scheele et al., 2014), translocations (Bobadilla Suarez et al., 2017; Clulow et al., 2018), reintroductions (Sainsbury et al., 2017), and capture-treat-release (Geiger et al., 2017). Other research has searched for cures for infected individuals using probiotics to alter the microbiome (Bates et al., 2018; Bletz et al., 2013), anti-microbial peptides (Rollins-Smith et al., 2011; Rollins-Smith, 2017; Woodhams et al., 2006), anti-fungal baths and elevated body temperature (Brannelly et al., 2012; Woodhams et al., 2003, 2011). Selective breeding, targeting individuals or populations with characteristics that promote reduced disease severity (e.g., the Mycobome (Kearns et al., 2017), MHC (Ellison et al., 2014a, 2014b; Savage et al., 2015; Savage and Zamudio, 2011)) are also promising avenues for pathogen mitigation and amphibian conservation.

Most reviews of amphibian conservation status echo the need to clearly identify conservation objectives, enumerate the uncertainty of wildlife disease management and associated decisions, quantitatively define metrics of success (i.e., an amphibian population persisting with a pathogen or pathogen elimination), and identify important research directions to support conservation decision-making (Grant et al., 2017). Papers in this special issue (Converse and Grant, 2019- this issue, Canessa et al., 2019- this issue) demonstrate how to proceed in framing and solving decision analyses.

6. Research failures and the future of successful amphibian conservation

With the rise of emerging infectious diseases among amphibians, quantitative methods that identify high-risk areas (e.g., habitats, regions), improve confidence in the selection of mitigation actions, and evaluate the effectiveness of interventions are necessary (Langwig et al., 2015). To achieve this, wildlife managers need unbiased metrics of disease prevalence, infection intensity, and individual host survival probabilities. Unfortunately, a priori, the extent, causes, and cofactors of individual host and pathogen detection heterogeneities are unknown. In addition, failure to accommodate non-detection errors can cause substantial bias in inference and misleading allocation of resources. Given these limitations, we suggest that study objectives focus on testing management actions and discriminating among potential drivers of disease. Studies must be designed to account for imperfect detectability so that data can be more effectively analyzed under a hierarchical modeling approach (DiRenzo et al., 2019). By adopting this

approach, disease ecologists can more rigorously test disease theory with empirical data and obtain more reliable inference about pathogens in natural systems, leading to improved responsiveness, efficiency, and effectiveness of management interventions. Hierarchical unmarked data models provide a useful way to increase our understanding of fundamental ecological and evolutionary processes that can aid in formulating amphibian conservation management plans and disease mitigation strategies.

Acknowledgements

We thank B. Mosher, L. Browne, E. Muths, B. Schmidt, and three anonymous reviewers for improving the quality of this manuscript. GVD was supported by a National Science Foundation Postdoctoral research grant (#1611692). This is contribution #709 of the Amphibian Research and Monitoring Initiative (ARMI) of the US Geological Survey. Any use of trade, firm, or product names is for descriptive purposes only and does not imply endorsement by the U.S. Government.

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