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Review

Effects of Emerging Infectious Diseases on Amphibians: A Review of Experimental Studies

Andrew R. Blaustein [1,*], Jenny Urbina [2], Paul W. Snyder [1], Emily Reynolds [2], Trang Dang [1], Jason T. Hoverman [3], Barbara Han [4], Deanna H. Olson [5], Catherine Searle [6] and Natalie M. Hambalek [1]

1 Department of Integrative Biology, Oregon State University, Corvallis, OR 97331, USA; snyderpa@oregonstate.edu (P.W.S.); trangdn.dang@gmail.com (T.D.); nataliehambalek@gmail.com (N.M.H.)
2 Environmental Sciences Graduate Program, Oregon State University, Corvallis, OR 97331, USA; jenny.gonzalez@oregonstate.edu (J.U.); emilyreneereynolds@gmail.com (E.R.)
3 Department of Forestry and Natural Resources, Purdue University, West Lafayette, IN 47907, USA; jhoverm@purdue.edu
4 Cary Institute of Ecosystem Studies, Millbrook, New York, NY 12545, USA; hanb@caryinstitute.org
5 US Forest Service, Pacific Northwest Research Station, Corvallis, OR 97331, USA; dedeolson@fs.fed.us
6 Department of Biological Sciences, Purdue University, West Lafayette, IN 47907, USA; searlec@purdue.edu
* Correspondence blaustea@science.oregonstate.edu; Tel.: +1-541-737-5356

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Abstract: Numerous factors are contributing to the loss of biodiversity. These include complex effects of multiple abiotic and biotic stressors that may drive population losses. These losses are especially illustrated by amphibians, whose populations are declining worldwide. The causes of amphibian population declines are multifaceted and context-dependent. One major factor affecting amphibian populations is emerging infectious disease. Several pathogens and their associated diseases are especially significant contributors to amphibian population declines. These include the fungi *Batrachochytrium dendrobatidis* and *B. salamandrivorans*, and ranaviruses. In this review, we assess the effects of these three pathogens on amphibian hosts as found through experimental studies. Such studies offer valuable insights to the causal factors underpinning broad patterns reported through observational studies. We summarize key findings from experimental studies in the laboratory, in mesocosms, and from the field. We also summarize experiments that explore the interactive effects of these pathogens with other contributors of amphibian population declines. Though well-designed experimental studies are critical for understanding the impacts of disease, inconsistencies in experimental methodologies limit our ability to form comparisons and conclusions. Studies of the three pathogens we focus on show that host susceptibility varies with such factors as species, host age, life history stage, population and biotic (e.g., presence of competitors, predators) and abiotic conditions (e.g., temperature, presence of contaminants), as well as the strain and dose of the pathogen, to which hosts are exposed. Our findings suggest the importance of implementing standard protocols and reporting for experimental studies of amphibian disease.

Keywords: amphibian population declines; experiments; pathogens; *Batrachochytrium*; ranavirus

1. Introduction

Rapid rates of biodiversity loss have supported the notion that the Earth is heading toward a sixth major extinction event [1–3]. Current species extinction rates are higher than pre-human background rates, suggesting this biodiversity crisis is largely attributed to anthropogenic changes [1–6]. Although numerous species from all taxonomic groups are affected, amphibians are at the forefront of this

crisis [3,7,8]. Their populations are declining more rapidly than those of birds or mammals [8]. Like other groups, amphibians are affected by multiple factors contributing to population declines [9]. These include habitat destruction, contaminants, climate change, over-harvesting, invasive species, predation, and infectious diseases, all of which may work independently or synergistically to affect amphibian populations [9–12] (Figure 1). Some of the research we summarize below focused on how a particular pathogen alone affects a host, whereas some studies addressed how a pathogen may be affected by other variables that may interact with pathogens.

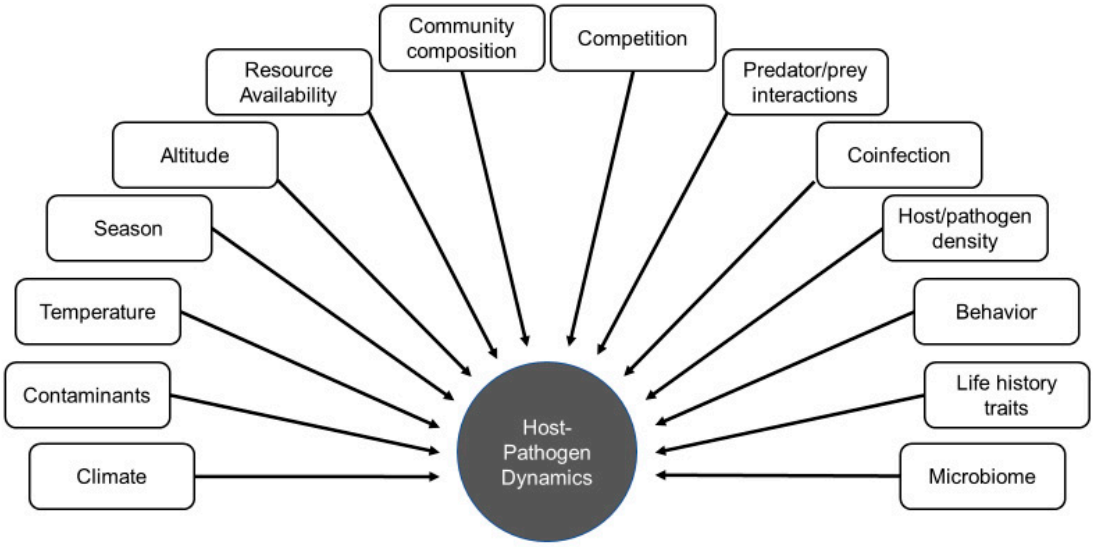

Figure 1. Potential abiotic and biotic factors that may influence host–pathogen dynamics in amphibian disease systems.

Among the major threats to amphibians are emerging infectious diseases (EIDs). Several prominent pathogens and associated EIDs affect amphibian populations worldwide. *Batrachochytrium dendrobatidis* (hereafter referred to as Bd) is a pathogenic fungus that causes amphibian chytridiomycosis [13–15]. This disease can cause population declines, local extinctions and contribute to species extinctions [8,16,17]. A related yet highly divergent fungal pathogen that also causes amphibian chytridiomycosis, *Batrachochytrium salamandrivorans* (hereafter referred to as Bsal), is a newly discovered pathogen primarily infecting salamanders [18]. Iridoviruses of the genus *Ranavirus* (hereafter referred to as Rv) have been implicated in declines and mass mortalities of amphibians [19–23]. Teacher et al. [22] stated that populations can respond differently to the virus and emergence can be transient, catastrophic, or persistent with recurrent mortality events. Although amphibians are hosts to an assortment of pathogens/parasites, including bacteria, viruses, fungi, water molds and helminths [13,24–27], we focus on Bd, Bsal and Rv, given accumulating evidence of their potentially devastating effects on amphibian populations worldwide. In particular, we focus on reviewing the literature that report the results of experiments (manipulation of key variables [28]) conducted with Bd, Bsal, and Rv concentrating on papers that used live amphibian hosts. Given the complexity of these host–pathogen systems, experimental approaches are crucial for disentangling potential mechanisms driving patterns of transmission and examining variation in lethal and sublethal effects due to host species, host life-history traits, pathogen strain, host populations, and environmental conditions.

Prior to 2009, relatively few studies of amphibian diseases employed standard experimental designs [28] (Figure 2). Since 2009, there has been a surge in the use of experiments to determine how diseases affect amphibians. Experimental design, methods, and interpretation vary; thus, it is useful to summarize these aspects to assess generality. One problem with experimental work on amphibian

diseases has been the lack of standardization in experimental methods. Here, we present a synthesis of experimental studies and attempt to address some of the issues regarding the lack of standardization and difficulties in generalizing about the dynamics of the host–pathogen systems we focus on.

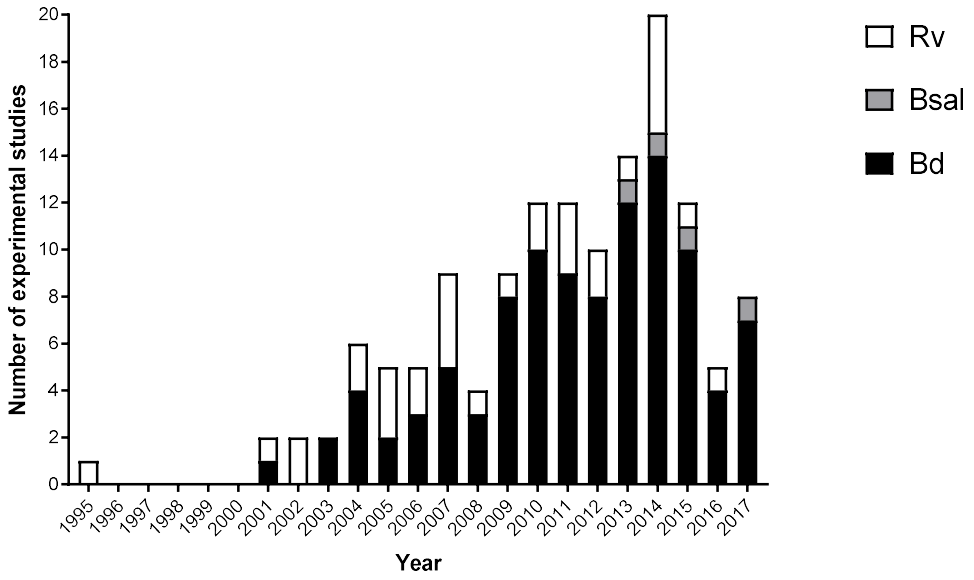

Figure 2. The number of experimental studies of *Batrachochytrium dendrobatidis* (Bd), *B. salamandrivorans* (Bsal) and *Ranavirus* (Rv) by year.

- **Summary of Pathogen Life Histories**
  - ***Batrachochytrium dendrobatidis***

First described by Longcore et al. [29], Bd is a fungal species in the phylum *Chytridiomycota* that has multiple hosts on every continent where amphibians exist [15,16] and has been associated with numerous population declines and some extinctions [30–32]. Recent evidence suggests that that the source of Bd was traced to the Korean peninsula, where one lineage, BdASIA-1, exhibits the genetic hallmarks of an ancestral population that seeded the panzootic emergence [33]. O'Hanlon et al. [33] date the emergence of Bd to the early 20th century, coinciding with the global expansion of commercial trade in amphibians.

Bd has a complex life cycle that consists of a free-living infectious aquatic zoospore stage and a non-motile zoosporangium stage. Motile zoospores are chemically attracted to keratin in amphibian host, such as keratinized larval jaw sheaths or keratinized epidermal layers of adult amphibian skin [34,35]. Infection can lead to hyperkeratosis and hyperplasia of the dermal layer, erosions and ulcerations of the skin, and disruption of the epidermal cell cycle [30,34–37]. The inability to regulate ions through the skin may lead to cardiac arrest [38]. Clinical signs of chytridiomycosis include lethargy, lack of appetite, abnormal posture, loss of righting reflex, cutaneous erythema, and increased skin sloughing [37]. However, not all infected animals are symptomatic when infected. Once within the host, the zoosporangia mature and develop pathogenic zoospores that are released outside the host into the aquatic environment.

  - ***Batrachochytrium salamandrivorans***

The recent isolation and characterization of the fungal pathogen, Bsal may explain some amphibian population declines. For instance, the drastic decline of fire salamanders, *Salamandra salamandra*, in the Netherlands, Germany, and Belgium, has been linked to Bsal [39–41]. A study conducted by Martel et al. [42] proposed Bsal originated in East Asia and coexisted with salamanders there for millions of years. The introduction of Bsal to Europe is hypothesized to have occurred due

to a lack of biosecurity in the international pet trade [42]. Although Bd and Bsal infections result in lethal skin erosion, the pathogenic mechanism of Bsal is not well understood. Bsal produces motile zoospores, contain colonial thalli, and produce germination tubes in vitro [18]. Studies have assessed the presence of Bsal in various amphibian populations in North America (e.g., [43–45]) and China [46] utilizing several methods (phalanges histology, nested PCR, qPCR and duplex qPCR), but its presence has yet to be confirmed in those populations. Given its high lethality, increased field surveillance of these naïve populations will be critical to contain the potential spread of this newly isolated pathogen, particularly in North America, a global biodiversity hotspot for salamanders [47–50].

- **Ranavirus**

Rvs are a group of large double-stranded DNA viruses in the family *Iridoviridae* with fish, reptile, and amphibian hosts [51]. The first Rv were isolated from *Lithobates pipiens* in 1965 [52]. The Global Ranavirus Reporting System (https://mantle.io/grrs/map), created to aid in tracking Rv occurrences and studies, shows Rv to be fairly widespread in Canada and the US west of the Rocky Mountains. This tool is intended to facilitate communication among researchers concerning Rv detection and to accelerate research and management of the disease threat.

The genus Rv is composed of 6 identified viral species, three of which infect amphibians (*Ambystoma tigrinum* virus (ATV), Bohle iridovirus (BIV), and Frog Virus 3 (FV3)) [51]. Although the effects of Rv are well documented, little is known about the genetic basis for virulence across isolates [53]. FV3 and ATV infect many amphibian species, but these isolates are most virulent within the anurans and urodelans, respectively, from which they were isolated [54]. Laboratory experiments have shown that introduced Rv isolates may be significantly more virulent than endemic strains [55].

Amphibians become infected with Rv by physical contact, dermal exposure to contaminated water, or direct ingestion of virions [56,57]. Infection can occur in as short as a one second of direct contact with an infected individual of the same species [56] or 3 h of contact with contaminated water [58]. Empirical studies confirming its potential effects in amphibians are limited [56,59–61]. Fish can also be infected with Rv, but susceptibility to Rv in fishes appears to be low, though there is potential for fish to transfer Rv to amphibians in habitats where they overlap [62,63].

Rvs infections can cause cell apoptosis and tissue necrosis within a few hours [51,64]. Common indicators of Rv infection include erratic swimming, lethargy, erythema, skin sloughing, loss of pigmentation, lordosis (excessive inward curvature of the spine), and ulcerations [65,66]. Lesions and hemorrhages associated with fatal cases of Rv occur in internal organs, particularly the liver, kidney, intestine, spleen, and reproductive organs [25,67,68]. However, the precise mechanisms of Rv dissemination within the host are relatively unclear, especially at the earliest stages of infection. A recent study demonstrated that FV3 infection is capable of altering the blood brain barrier in *Xenopus laevis* tadpoles eventually, leading to Rv dissemination into the central nervous system [69]. Death can occur without external signs of infection [70].

2. Methods

The effects of Bd, Bsal, and Rv found in experimental studies are summarized in Table 1. Our search was conducted via the Web of Science and supplemented with a Google Scholar search using the keywords "*Batrachochytrium dendrobatidis* + amphibians", "*Batrachochytrium salamandrivorans* + amphibians", and "*Ranavirus* + amphibians", respectively. Duplicates and non-experimental studies were removed and the remaining studies were documented. Studies that examined interactive effects (i.e., pesticide + pathogen) were included, but only the effect of the pathogen independently was reported. The Bd search (1999–2017) resulted in 1207 hits, of which 110 were experimental studies. The Bsal search resulted in 41 hits, of which 5 were experimental studies. The Rv search (1992–2017) yielded 269 hits, of which 33 were experimental studies. If one publication examined multiple species or host life stages, each species and life stage was reported separately (Figure 3).

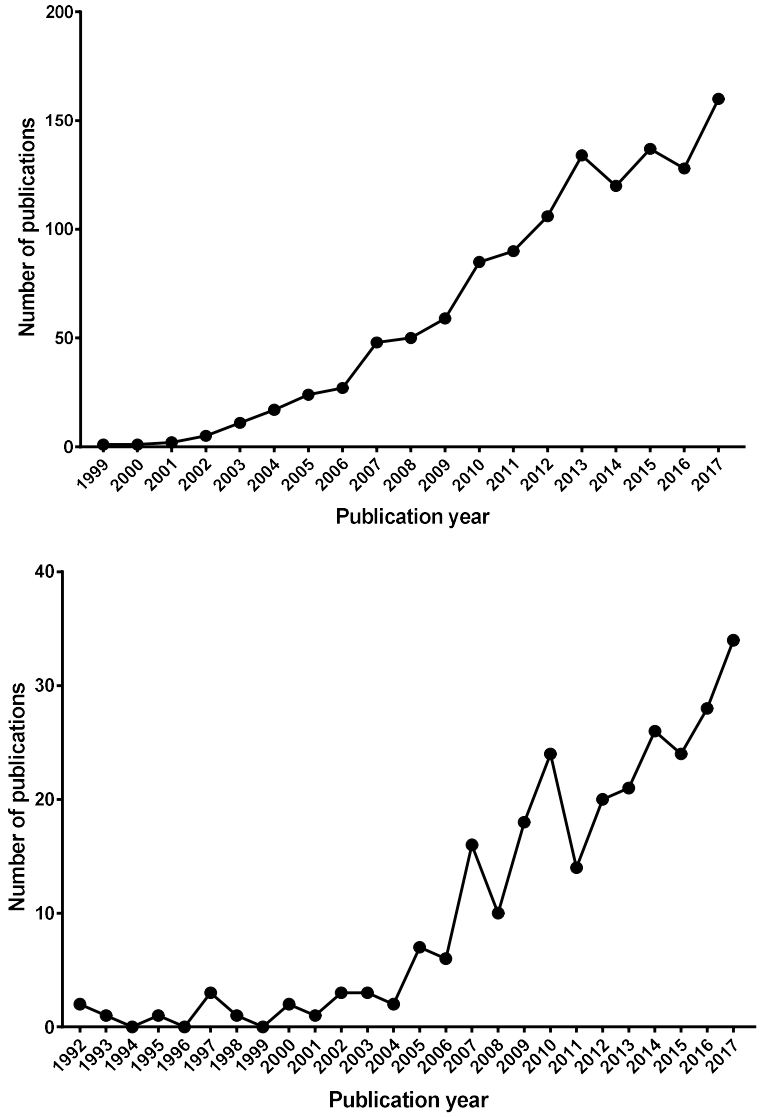

Figure 3. Trends in all articles published on Bd (**top**) and Rv (**bottom**) in the literature over time. Publications were compiled using the search strings "*Batrachochytrium dendrobatidis* + amphibians" and "*ranavirus* and amphibians" in the Web of Science database, from which duplicates and articles that were unrelated were removed. The Bd search yielded a total of 1207 hits and the Rv search yielded 269 hits.

3. Results

Results from experimental studies are summarized below. We presented general trends across studies according to the response variable (e.g., physiology, behavior) and/or source of response variation (e.g., life stage, virus strain). We then focused on interactive effects and summarize the experimental work with each pathogen in combination with natural or anthropogenic environmental stressors. Below, we provide a summary of patterns and gaps in the accumulated experimental work on host–pathogen dynamics of Bd, Bsal, and Rv and their amphibian hosts. Specific results of experimental studies are detailed in Table 1 and data summarizing the number of papers published, survivorship and life stages are summarized in Figures 4–6.

The number of experimental studies conducted on hosts at different life stages varied, with most studies of Bd conducted in hosts after metamorphosis and most studies of Rv conducted with larvae (Figure 4). The only experimental studies we found on Bsal were conducted with post-metamorphic

hosts (Figure 4). Experimental studies and survival showed clear differences with host life stage (Figures 5 and 6). Moreover, the dose of pathogen administered during susceptibility experiments is also important in interpreting results (Figure 7).

3.1. Batrachochytrium dendrobatidis

Host–pathogen dynamics are influenced by many factors (Figure 1). For example, biotic variables, such as the presence of predators, density of hosts and competition among pathogens, may affect host susceptibility, mortality and pathogen loads [71–74]. Laboratory and field experiments have shown that abiotic factors influencing Bd–host dynamics include climate, season, altitude, resource availability, and temperature [75–77]. Experimental studies found dose-dependent differences in development, infection load, and mortality, indicating increased infection virulence associated with inoculum dose [74,78–80] (Figure 7). Experiments have confirmed temperature as a critical mediating factor in Bd dynamics. For example, Andre et al. [75] found that host frogs housed in warmer temperatures (22 °C) exhibited significantly lower mortality than those housed in cooler temperatures (17 °C). Infection in post-metamorphic amphibians can be cleared when temperatures are elevated above the noted Bd thermal optimum range [77,81–84].

Some experimental studies illustrate strain-dependent infection outcomes [15,34,80,85–88], while other studies have revealed no effect associated with strain differences [89,90]. Whether or not strain differences are detected can depend on the amphibian host species used in experiments [91]. Comparative strain experiments along with observational amphibian surveys are useful in investigating the relationships between host population trends and Bd virulence variation. For example, Piovia-Scott et al. [92] linked an observed *Rana cascadae* population decline to a known, highly infectious, and lethal Bd strain through multiple lines of analyses. In one experiment, adult *Rana cascadae*, exposed to the Bd strain cultured from a site undergoing a host population decline, had significantly lower survival rates, compared to those exposed to a strain from a site with a stable host population [92]. This Bd strain also displayed greater immunotoxicity in experimental assays [92]. Exposure to endemic vs. novel strains can also affect host survival. Doddington et al. [93] found survival differences in captive-bred *Alytes muletensis* experimentally exposed to two Bd strains, a local Mallorcan strain (TF5a1) or a hypervirulent Bd-GPL strain (UKTvB). Toads exposed to the Bd-GPL strain had higher mortality than individuals exposed to the Mallorcan strain or control group [93].

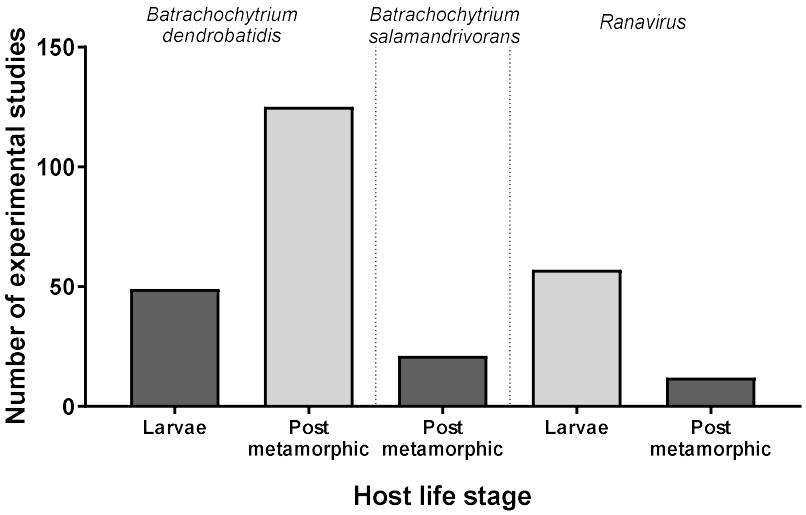

Figure 4. The number of experimental studies conducted at a single life stage. Obtained from direct counts from Table 1.

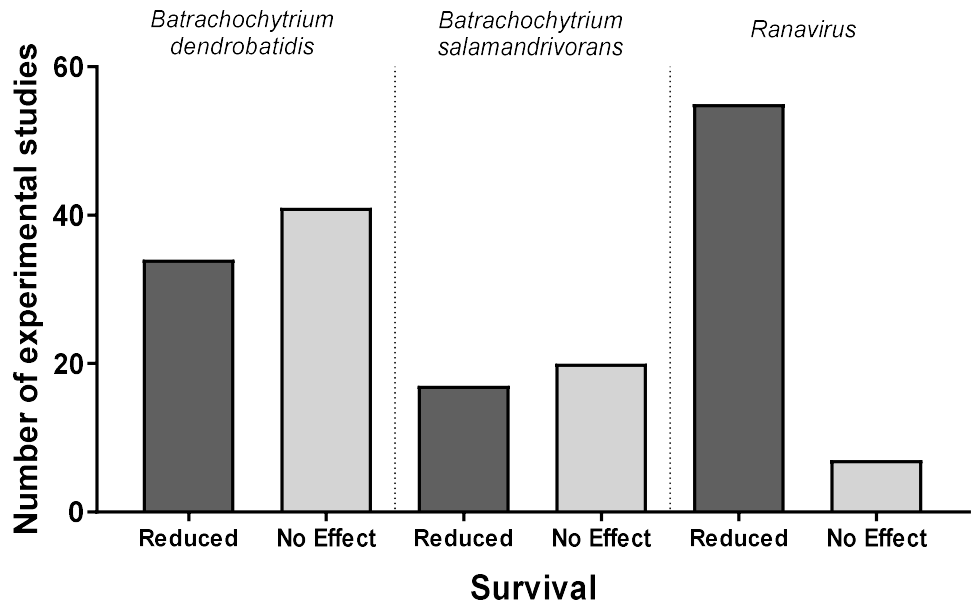

Figure 5. Effects on survival in experimental studies. These data are direct counts from Table 1.

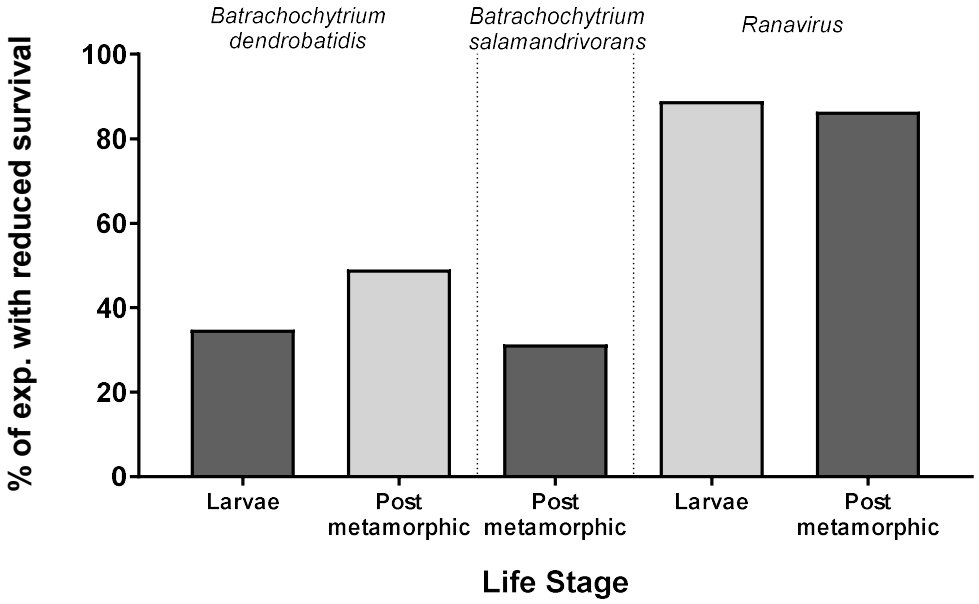

Figure 6. Percentages of experiments showing reduced survival at a single life stage. These data are percentages from Table 1 (Experiments showing reduced survival/total # of experiments with survival as an endpoint).

Differences in methodology can complicate our interpretation of the results from comparative strain experiments. For example, Bd dosage, site of strain isolation, and strain passaging history can influence outcomes of strain experiments [15,86–88,94–96].

Accumulating evidence suggests that some host species vary in their susceptibility to Bd. Some species can persist with infection [97] and others experience mortality rapidly after Bd exposure [86,97–100]. Variation in skin composition, including keratin abundance, distribution, and thickness, may affect the depth, of the zoospore-produced germination tube which can affect the severity of infection among amphibian hosts [35,101]. Differences in the ability of amphibian species to mount sufficient endocrinological responses, particularly stress responses, may also play a role [102–105]. Furthermore,

habitat preference may influence host susceptibility to infection [106,107]. Future research should consider amphibian life-history traits, particularly of species that do not seem to be susceptible to Bd infection, to better understand differences in host susceptibility and will be useful to target species, which may act as reservoirs for the pathogen.

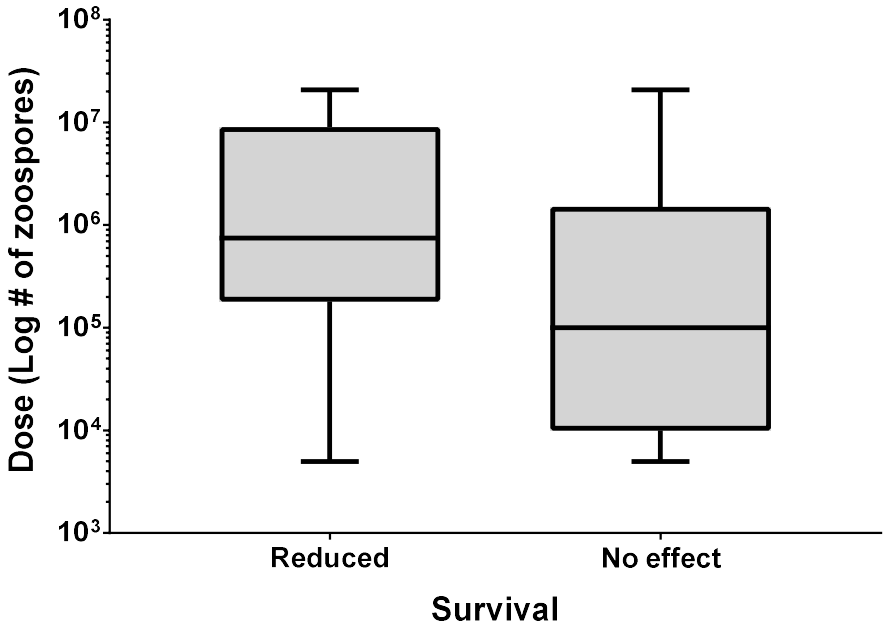

Figure 7. The effect of Bd dose (in log zoospores) on survival. These data are direct counts from Table 1. Experiments that use multiple dose levels or multiple strains were excluded. Reduced survival means mortality of hosts exposed to *Batrachochytrium* was significantly higher than control mortality. Here, we display the minimum, first quartile, median, third quartile, and maximum zoospore dose regarding host survival.

An important driver of host–pathogen interactions is host behavior [72,108,109]. Basking, for example, may be an indication of disease infection in amphibians [110–112]. Altered thermoregulatory behavior (i.e., behavioral fever) may aid in clearing Bd infection. However, fever behavior depends on species and life stage [108,113]. Additionally, it has been suggested that aggregation behaviors can increase Bd prevalence. Thus, schooling species may be more at risk than amphibian species with solitary life styles [109]. This prediction depends strongly on the assumption that infected hosts shed infectious zoospores. Recent work shows that spillover infection does not occur in all hosts, suggesting that aspects of life history (e.g., body size) and behavioral interactions (e.g., interspecific competition) between hosts may drive infection severity in host communities [114]. Infected tadpoles have demonstrated altered activity levels, which may be an important indicator of anti-predator behavior [72,115]. While reduced activity can make tadpoles less visible and thus less at risk for predation, sluggish behavior can hinder an individual's ability to escape a predation event. Han et al. [115] observed Bd-infected toad tadpoles seeking refuge more often than other species tested. Parris et al. [72] demonstrated that when tadpoles were exposed to only visual predation cues, uninfected individuals positioned themselves farther from the predator than infected animals. Carey et al. [99] observed that post-metamorphic toads exposed to Bd were holding their bodies out of water more than unexposed individuals. In one study, frogs that had never been exposed to Bd displayed no significant avoidance or attraction to the pathogen, whereas previously infected frogs associated with pathogen-free frogs a majority of the time [83]. This indication of potentially learned behavioral avoidance to Bd and perhaps other pathogens warrants further exploration.

Differences in Bd susceptibility are dependent on amphibian life stage, with juveniles and adults usually being more susceptible than embryos and larvae, most likely due to increased keratin distribution and abundance after the larval stage [80,116]. Bd infection in tadpoles rarely results in mortality (see [15,86,98], but has generally been related to reduced foraging efficiency and food intake in larvae [117–120]. In post-metamorphic amphibians, Bd infection is manifested in the keratinized epidermis; thus, the effects of foraging efficiency are dependent on the locality of infection. For example, in adult salamanders (*Plethodon cinereus*), Bd-infected individuals displayed increased feeding behaviors in comparison with uninfected individuals, a behavioral modification that has been suggested as a strategy to offset the costs associated with immune activation [121].

Body size may also be a factor in host susceptibility to pathogens [122]. Experiments have shown that individual size may be an influential factor in Bd susceptibility [116]. Garner et al. [79] showed that smaller toads (*Anaxyrus boreas*) were more prone to Bd-induced mortality compared with larger individuals.

Experiments on host–Bd interactions have addressed physiological stress responses. In both field and laboratory investigations, Bd significantly elevated physiological stress hormone (corticosterone) levels in amphibian hosts of multiple species [102–104,123], though there is no evidence that exposure to endogenous corticosterone alters amphibian susceptibility to Bd [104]. Different strains of Bd elicit significantly distinctive hormonal stress responses from their hosts, with more virulent strains resulting in higher corticosterone levels [123]. New methodologies, such as a non-invasive stress hormone assay [102], enhance the value of field studies coupled with experimental laboratory investigations on physiological stress response. The dynamics between stress response and chronic disease manifestation warrant further exploration.

3.2. *Batrachochytrium salamandrivorans*

Due to its recent discovery, there are few experimental studies documenting the effects of Bsal on amphibian hosts (Table 1b). Bsal primarily affects newts and salamanders rather than anurans. The common midwife toad (*Alytes obstetricans*), a species susceptible to Bd, did not experience any clinical signs of Bsal infection [18]. Further, Martel et al. [42] showed that ten anurans tested were resistant to skin invasion, infection, and disease signs when exposed to a dose of 5000 zoospores of Bsal. Studies conducted with Bsal on potential urodelan hosts demonstrated that responses varied across species and within the same genus. Bsal induced lethal effects on *Lissotriton italicus*, the Italian newt, whereas no infection or disease signs were documented in *L. helveticus* [42]. The results of Bsal–host experiments show that Bd and Bsal differ in how they show the effects of exposure to these pathogens [18,42]. Experimentally infected fire salamanders, *Salamandra salamandra*, experienced ataxia, a rarely reported sign in experimental studies with Bd. The study also identified three potential reservoir species, the Japanese fire belly newt (*Cynops pyrrhogaster*), the *Chuxiong* fire-bellied newt (*Hypselotriton cyanurus*), and the Tam Dao salamander (*Paramesotriton deloustali*), as individuals of these species were able to persist with or clear infection in some capacity [42].

Bsal transmission dynamics are not yet well documented. In a study examining transmission between infected and naïve hosts, Martel et al. [18] found that two days of shared housing in salamanders resulted in infection and mortality of formerly naïve hosts within one month. All experimental work done regarding Bsal has used only one pathogen isolate, a small range of doses, and few source populations for each species tested (Table 1b). Because experiments conducted on Bd–host dynamics show that responses are heavily dependent on species, population, pathogen isolate, temperature, and exposure dose, future research should consider how these factors influence infection dynamics in the Bsal system.

3.3. *Ranavirus*

Experimental studies have shed light onto the comprehensive effects of Rv on amphibians worldwide (Figure 3; Table 1c). Experimental Rv mortality is influenced by a variety of factors most

notably, exposure method. Ingestion of Rv infected carcasses result in infection transmission and reduced survival [57,124]. Exposure to Rv via water induced variable rates of mortality, with most studies showing slower rates of mortality when transmission occurred via water, compared to when it occurred via ingestion [70,125]. Hoverman et al. [126] found that infection and mortality rates were greater for tadpoles that were orally inoculated with Rv compared to those exposed via water bath. Aggressive interactions may serve as an efficient transmission route of Rv [56]. Cannibalistic behavior may be harmful to the individual exemplifying the behavior because of disease transmission, but an experimental study showed cannibalism can result in decreased contact rates between naive and infected individuals in the population [56]. Additionally, experiments have suggested that necrophagy may serve as a common route of Rv transmission, shifting transmission from density-dependent to frequency-dependent [56,57,124,127,128].

Temperature influences Rv infectivity and survival rates in hosts [129,130]. When exposed to the Rv, ATV, larval *Ambystoma tigrinum* salamanders experienced higher survival rates when exposed at 26 °C than those exposed at 18 °C and 10 °C with virus titer being higher in cooler temperatures, and viral replication rates were higher at higher temperatures [130]. Similarly, Echaubard et al. [129] found that the probability of Rv infection increased at lower temperatures (14 °C), but that the effects were isolate and species-dependent.

It is critical to take a comparative approach to experimentally investigate species variation in susceptibility with regards to Rv. Understanding the relative susceptibility of hosts to a pathogen is important for predicting host–pathogen dynamics. Coevolution between Rvs and their hosts has been hypothesized to be a driving force behind host variation of susceptibility [131]. Hoverman et al. [132] discovered a wide range of lethal effects among 19 larval amphibian species, which resulted in mortality rates spanning from 0 to 100%. Their study showed that anurans in the family Ranidae were typically more susceptible to Rv than the other five families tested.

Previous experimental work has demonstrated infection and virulence variation among isolates and Rv species [54,125,132,133] though phenotypic variation among Rv isolates is not well understood. Schock et al. [54] determined that FV3 and ATV Rv species vary in their ecology and restriction endonuclease profiles, even though they have identical major capsid protein (MCP) gene sequences. Their results further emphasize the importance of characterizing isolates beyond MCP sequence analysis. Cunningham et al. [125] detected differences in tissue trophism and pathology between two strains of FV3-like Rvs in common frogs (*Rana temporaria*). Schock et al. [133] revealed that ATV strains differed in virulence, but this was dependent upon the origin of the salamander host. Similarly, Hoverman et al. [132] showed that mortality rates were ~50% greater with a Rv isolate obtained from an American bullfrog (*Lithobates catesbeianus*) culture facility compared to FV3. These results highlight the importance of controlled experimental studies to elucidate patterns of differential host susceptibility with regards to Rv isolates and species.

Experimental and observational field studies have shown that late-stage larvae that are nearing metamorphosis are the most susceptible to lethal effects of Rv infection [60,61,105,134,135]. When exposed to ATV, metamorphosed *Ambystoma tigrinum* larvae were five times less likely to be infected than those that remained at the larval stage [70]. Experimental studies suggest that the effects of Rv are more lethal to larvae than any other host life stage. In an experimental study examining seven amphibian species at various developmental stages, Haislip et al. [136] observed that mortality and infection prevalence were greatest at the hatchling and larval stages in four of the species tested compared with frogs undergoing metamorphosis, and that the embryo was the least susceptible stage, possibly due to the eggs protective membranous properties. Similarly to what has been observed with Bd infections, life-stage variation in susceptibility has been attributed to changes that occur in the hypothalamic–pituitary–interrenal axis (the central stress response system) around the time of metamorphosis, which helps to mediate the immune system [137]. Host gene expression variation may contribute to life-stage differences in susceptibility. Andino et al. [134] found that larvae experienced greater infection rates and possessed lower and delayed expression of inflammation associated antiviral

genes. It has been suggested that impacts of epizootic events may be underestimated due to increased difficulty of detecting mass mortality of hatchings and larvae in the field [136].

Though few studies have examined host physiological responses to Rv, these studies are important in assessing species-specific impacts of infection. Warne et al. [105] demonstrated tadpoles infected with an FV3-like isolate had higher corticosterone relative to controls. In a study examining immune function, Maniero et al. [138] demonstrated that *Xenopus laevis* frogs develop an effective and persistent humoral immunity after exposure to FV3.

- ***Interactive Effects of Disease, Anthropogenic, and Natural Stressors***

Anthropogenic and natural environmental stressors can exacerbate the effects of emerging wildlife diseases [14]. Though the impact of one factor may be particularly devastating to amphibians in certain regions, considering simultaneous effects of several factors may be more realistic because amphibians, like other organisms, are exposed to many abiotic and biotic factors simultaneously [9,139]. Host–pathogen relationships in amphibians are mediated by, for example, climate, contaminants, disease, predation, and competition [9,15,79,140] (Figure 1). These factors display a high degree of spatial and temporal variation and can result in complex local interactions that are often poorly understood [9]. Realistic insight can be gained by taking a population-specific approach in assessing the variables involved and overall status of a population using long-term field data [141]. Experimental approaches can be particularly helpful in disentangling the mechanisms of interacting variables. Gaining a comprehensive understanding of how environmental factors may influence infection and pathology is critical to amphibian conservation.

- ***Pathogens Climate and Atmospheric Change***

Climate change and associated atmospheric changes may alter disease dynamics by fostering conditions more or less hospitable for pathogens and their hosts. For example, different outcomes have been reported regarding the interaction of ultraviolet-B (UV-B) radiation and pathogens. A modeling approach by Williamson [142] suggests that the selective absorption of ultraviolet radiation by dissolved organic matter (DOM) decreases the valuable ecosystem service wherein sunlight inactivates waterborne pathogens. In controlled experiments, Overholt et al. [143] showed that low levels of UVR (as well as longer-wavelength light) sharply reduced the infectivity of parasitic fungal spores, but did not affect host (*Daphnia*) susceptibility to infection. However, a field experiment showed that fluctuations in water depth were associated with increased UV-B radiation, which resulted in greater sensitivity to the pathogenic water mold, *Saprolegnia* [139]. Experimental studies regarding the effects of UV-B radiation and Rv are absent from the literature. However, decreased pond depth has been associated with increased Rv prevalence [63], which suggests the possibility that water depth and UV-B penetration may affect Rv–host dynamics, as Kiesecker et al. [139] showed for *Saprolegnia*–amphibian interactions. In a laboratory experiment, no interaction was found with increased UV-B radiation and Bd [144,145]. However, Ortiz-Santaliestra et al. [146] showed that Bd loads were significantly lower in tadpoles exposed to environmental UV-B intensities than in tadpoles not exposed to the radiation. Another field experiment showed that ultraviolet radiation (UVR) killed the free-living infectious stage of Bd. However, permanent ponds with more UVR exposure had higher infection prevalence [147]. The authors suggested that UVR reduced the density of Bd predators and that permanent sites fostered multi-season host larvae that fueled parasite production.

Global climate change appears to increase temperature variability, which can mediate disease dynamics. Bosch et al. [148] documented rising temperatures are linked to the occurrence of chytridiomycosis. Fluctuating temperature regimes have had negative effects on survival and development of amphibians in the presence of Bd [149–151], while higher temperatures often resulted in higher host survival rates [78,152]. Raffel et al. [150] demonstrated that Bd growth and infection-induced mortality on newts, *Notophthalmus viridescens*, was greater following a shift to a new cooler temperature, but this was dependent on increased soil moisture. Host thermal acclimation

is context-dependent and can serve as a key mediator of climate–disease dynamics. Recent models based on the Intergovernmental Panel on Climate Change (IPCC) suggest that Bd will shift into higher latitudes and altitudes due to increased environmental suitability in regions under predicted climate change [153]. Specifically, these models predicted a broad expansion of areas suitable for establishment of Bd on amphibian hosts in temperate zones of the Northern Hemisphere. Thus, novel amphibian hosts may be susceptible to predictable shifts in Bd.

- ***Pathogens and Contaminants***

Many contaminants break down quickly in the environment, yet exposure can have major carry over effects, and the effects of interactions between multiple contaminants and between contaminants and disease cannot be well understood without experimentation [154,155]. Contaminant exposure may contribute to amphibian population declines directly or indirectly [9,156–158]. However, research on the interactive effects of contaminants and pathogens remains inconclusive. Some studies examining this interaction investigate if pesticides and contaminants play a role in decreasing amphibian immune response, rendering amphibians more susceptible to infectious disease [159–161]. However, few experimental studies support this hypothesis [118,162–172]. Rohr et al. [173] found that early-life exposure to atrazine decreased survival post-metamorphosis when combined with Bd in *Osteopilus septentrionalis*. Likewise, Buck et al. [163] demonstrated that exposure to pesticides in tadpoles resulted in higher Bd loads and increased mortality in post-metamorphic individuals from three species, but not for two other species. A possible reason for findings with little or no interactive effects may be that certain compounds can inhibit or diminish the growth or integrity of Bd, as was demonstrated outside of the host species [162,167,170]. Thus, contaminants may have direct negative effects on both amphibian hosts and Bd, which can lead to no differences in infection across a range of contamination.

The use of pesticides has been associated with increased Rv prevalence in the field [63]. Forson and Storfer [174] revealed that ecologically relevant levels of the pesticide atrazine and the fertilizer sodium nitrate significantly decreased *Ambystoma tigrinum* larvae peripheral leukocyte levels and that larvae exposed to atrazine significantly increased susceptibility to ATV. Furthermore, Kerby and Storfer [175] showed that atrazine and Rv exposure marginally decreased survival in larvae of the same species. Conversely, Forson and Storfer [174] revealed *Ambystoma macrodactylum* larvae exposed to atrazine and ATV had lower mortality levels and ATV infectivity compared to larvae exposed to ATV alone, suggesting atrazine may compromise virus integrity. Additional research is needed to assess the impacts of pesticides and fertilizers and their metabolites on Rv viability and amphibian physiology. Contaminants are becoming increasingly widespread with over 50% of detected insecticide concentrations exceeding regulatory thresholds [176]. Thus, the importance of researching the interrelationships between contaminants and disease in amphibian disease should not be overlooked. Experiments designed to identify mechanisms that are generalizable across classes of pesticides will also enable better management and conservation planning, as known contaminants are phased out and new ones are introduced to market.

- ***Pathogens and Community Composition***

Higher biodiversity may influence disease risk through a variety of mechanisms. The dilution effect hypothesizes that greater biodiversity in an assemblage decreases disease risk, but this is somewhat controversial [177–179]. Olson et al. [16] reported a negative association between Bd occurrence and species richness. Some experimental evidence supports the dilution effect in the Bd–host system. Greater species diversity of larvae resulted in lower Bd zoospore abundance [100,180–182]. Searle et al. [100] demonstrated that the experimental addition of *Rana cascadae* tadpoles to tanks with larval toads (*Anaxyrus boreas*) decreased the infection risk for toad larvae, which may be due to differing feeding strategies and life-history traits between species.

Venesky et al. [183] showed that some tadpoles can filter feed Bd zoospores. Moreover, experiments have shown that zooplankton, such as *Daphnia*, can consume Bd zoospores, significantly

reducing infection probabilities in tadpoles [184–186]. Additionally, species "reservoirs" may be important for community-level Bd dynamics. For example, evidence suggests the Pacific treefrog, *Pseudacris regilla*, may act as a Bd reservoir; *P. regilla* thrive and occupy 100% of study sites where a sympatric species has been extirpated by Bd [101].

Predation can interact with infection in varying ways. The healthy herd hypothesis states that predators may decrease infection prevalence by decreasing overall population size of potential hosts and through selective predation upon infected individuals [187–189]. Several hypotheses regarding predator/prey dynamics and disease remain untested regarding disease and amphibians. For example, is selective predation occurring, or alternatively, are predators capable of avoiding infected prey? Han et al. [115] experimentally demonstrated the potential of non-selective predation occurring in the predator/prey interactions in the Bd system. Salamander predators consumed Bd-infected and uninfected tadpoles at the same frequency and predation risk among prey was not altered by Bd infection. This area warrants further exploration as predation behavior may have significant impact on outcomes in amphibian disease systems. The presence of a predator resulted in decreased infection loads in wood frog (*Lithobates sylvaticus*) larvae [190] and has resulted in increased developmental rates [162,191]. Effects of predation in combination with Rv remain inconclusive. Dragonfly predator cues have resulted in decreased survival in combination with Rv exposure [192]. However, Haislip et al. [193] found no evidence that Rv exposure in combination with predator cues increased mortality across four species of larval anurans.

In addition to predator presence, other aspects of community composition can play an influential role in disease dynamics. When reared in higher densities, amphibians metamorphose at smaller body masses than when reared individually [194,195]. Furthermore, when these higher densities were combined with the presence of Bd, larvae also experienced a delayed time of metamorphosis [194,195]. Increased densities have also been associated with the increased likelihood of Bd infection [196], but other experimental studies have not observed this association [100]. These results are in direct contrast with the effects of density with regards to Rv. At higher densities of larvae and in the presence of Rv, the rate of metamorphosis was documented to be three times faster and the probability of mortality was five times lower than in the controls [197]. However, even though higher densities lead to higher contact rates, transmission of Rv rapidly saturates as density increases [198].

- ***Coinfection Dynamics***

Infection by multiple pathogens is common for most wild animals [199], though experimental evidence of coinfection patterns in amphibians remain sparse. Several studies have investigated coinfection dynamics in amphibian hosts in the field and have found that coinfections in amphibians is common [132,200–202]. However, there are few experimental studies of coinfection dynamics in amphibians. Romansic et al. [74] experimentally investigated the effects of three pathogens: Bd, the trematode *Ribeiroia* sp., and the water mold, *Achyla flagellata*, which resulted in little evidence for interactive effects. Wuerthner et al. [203] found that prior infection with trematode parasites (*Echinoparyphium* sp.) reduced ranavirus loads and increased survival of Rv-infected frogs. Thus, the interrelationships of coinfection could be explored further via experiments.

- **Host, Isolate, and Geographic Biases**

Uneven sampling of host species is considered to be a source of bias when interpreting the dynamics of host–parasite systems [204]. There are 7728 amphibian species described [205], yet our analysis of experimental studies documenting the effects of these pathogens have only reported effects for <1% of species across these pathogens (0.01% of species with regard to Bd, 0.005% of species for Bsal, and 0.005% of species with regard to Rv). Of the species studied in these disease systems, there is a high degree of interspecific variation in disease susceptibility [80,86,97,98,100,132]. Furthermore, responses can vary based on strain, population, and host life-stage [54,56,70,88,98,124,133,206–208]. Additionally, a distinct disparity exists in species-studied and geographic regions (Figure 8). Much of

the research has focused primarily on host species located in Europe, North America, and Australia. However, Bd and Rv have global distribution and effects, yet far less is known about infection in hosts from Africa, Asia, and South America. For Bsal, experiments have only been conducted with an isolate from Europe, and most studies have used a dose of 5000 zoospores, a low dose in comparison to studies on Bd [80]. Similarly, the bulk of the studies examining Rv pathogen–host dynamics are largely biased toward those in North America, with a minority of studies coming out of Europe, Africa, and Australia (Table 1). These biases are likely due to the number of researchers in these regions, institution locality, and access to collaborators, species, isolates, feasibility and cost.

- **Non-Standard Methods and Reporting**

Experimentation is advantageous because it is repeatable, and well-designed studies can provide unequivocal results [209,210]. However, there are limitations on experimental work, as is illustrated in amphibian disease ecology. One problem with experimental work on amphibian diseases has been the lack of standardization in experimental methods. Kilpatrick et al. [87] highlighted the importance of standardizing and reporting all relevant infection protocols within and between species when conducting laboratory studies regarding Bd and its host species. This includes how individuals are collected for experiments, how they are reared, the developmental stage in which they are tested, the population origin, inoculation and exposure protocols, and strains of pathogen being used. For instance, reporting and standardizing the zoospore exposure concentration (total number of zoospores per mL of water in total volume of water) in experimental procedures would make relative species comparisons among experiments more useful. Developmental stage should always be reported as this can also confound the interpretation of results. Additionally, whether hosts are reared from eggs or caught as larvae, juveniles, or adults, or even bought from supply houses can dramatically alter the results of experiments and their interpretation. Our analysis shows that, 27%, 12%, and 23% of experiments examining Bd, Bsal, and Rv, respectively, were using animals not reared from eggs, even though rearing amphibians from eggs ensures that individuals have not previously been infected with Bd or Bsal. Even when tested for current infection prior to an experiment, wild-caught individuals have different ecological histories and may have a more or less robust immune system depending upon whether they were previously exposed to a particular pathogen [86]. Field surveillance shows that amphibian parasites, such as echinostomes, are widespread [211,212] and essentially many, if not all individuals, collected from the wild will inevitably possess trematodes. The potential influence of these parasites on amphibian immunological response poses a serious problem for experiments that use individuals, not reared as eggs.

We emphasized the importance of utilizing subjects raised from the embryo stage in experimental investigations. Because of lack of standardization, each experiment must be taken independently and applied to those specific individuals at the reported experimental conditions. When protocols are standardized, we can more easily generalize effects of Bd and Rv on hosts, as has been accomplished in several studies [80,97,98,100,132]. However, even in experimental studies that have standardized methods, interpretation of results must be in context with, for example, the knowledge that the results of susceptibility to a particular pathogen may vary with host age, life history stage, population, the presence of abiotic factors (e.g., contaminants), biotic factors (e.g., competitors, predators), pathogen strain etc.

Experimental studies using different methods for the same host species illustrate the difficulties in making generalizations of how specific pathogens affect a host. For example, western toads (*Anaxyrus boreas*) have been investigated in a number of experimental studies (Table 1a). These studies used different Bd strains, different Bd doses and different life stages and the results of how the host was affected differed among the studies. For example, some studies showed reduced survival after exposure to Bd, whereas others did not. Even experiments by the same investigators [108,115] on western toads showed certain differences in how toads responded to Bd. In these studies, western

toads were examined at the same life stage, but each study used different Bd strains and different Bd doses.

Small differences in experimental methods and design can lead to different results, highlighting the importance of standardized experimental protocols. Importantly, under controlled environmental conditions, observed effects after pathogen exposure can be attributed to intrinsic biological factors of the host, rather than environmental differences [206].

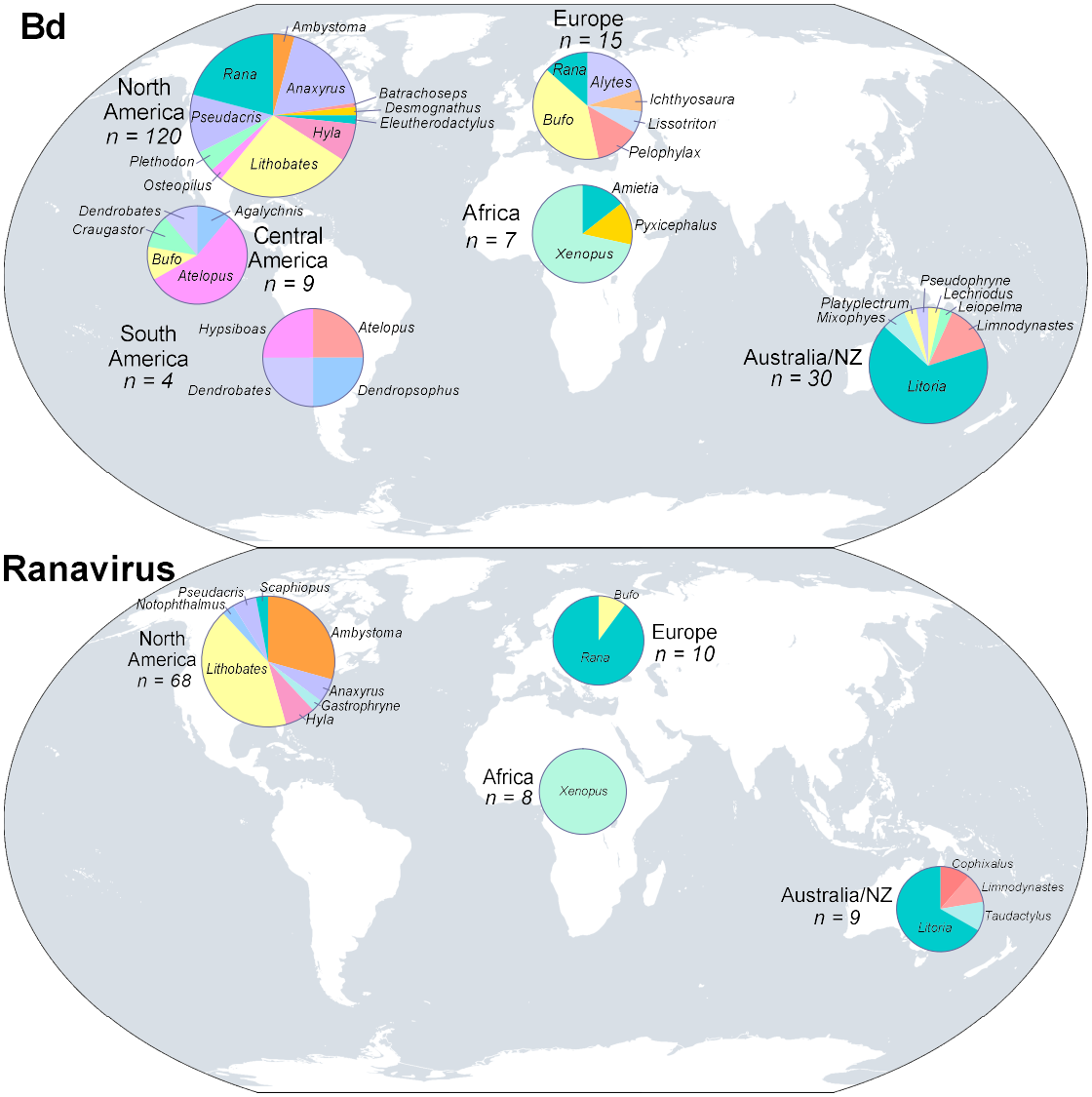

Figure 8. Experimental studies published on Bd and Rv with respect to amphibian host genus and geographic range. Methods to generate the number of studies were produced in the same fashion as explained in Table 1. N indicates the number of studies for a particular region.

4. Conclusions

The initial sounding of the alarm for amphibian population declines in the 1990s [213] prompted a multitude of interdisciplinary investigations focused on understanding the causes of the declines. As part of this interdisciplinary approach, field observations along with well-designed experiments have helped us more fully understand the dynamics of amphibian population declines [214]. Because disease is one of the key factors contributing to amphibian population declines, experiments have been especially useful in aiding our understanding of amphibian host–pathogen dynamics.

Well-designed experiments are useful tools that can provide unambiguous answers to specific questions about host–pathogen interactions. Several types of experiments have been employed. Field experiments are useful in mimicking natural conditions, but are not always feasible when investigating disease. Laboratory and mesocosm experiments have been used successfully to examine a variety of ecological processes [209,210], including various aspects of amphibian population declines [214] and amphibian–pathogen dynamics (Table 1).

Studies of the three pathogens we focused on show that (1) host susceptibility varies with such factors as species, host age, life history stage, population and various ecological conditions including biotic (e.g., presence of competitors, predators) and abiotic conditions (e.g., temperature, presence of contaminants); (2) host susceptibility also depends upon the strain of the pathogen, to which they are exposed. The number of experimental studies of the three pathogens conducted on hosts at different life stages varied (Figure 4). Experimental studies and host survival showed clear differences with host life stage (Figures 5 and 6). Moreover, the dose of pathogen administered during susceptibility experiments is also important in interpreting results (Figure 7).

The issues we discussed in this paper illustrate some of the difficulties of standardizing experimental methods and interpreting and comparing results from studies that use different methods. As a baseline for standardization of experiments and to help interpret and compare the results of different experimental studies we recommend several protocols: (1) Collecting newly laid eggs and rearing them from larva through metamorphosis for experimentation lowers the likelihood that animals used in experiments were exposed to pathogens in the field; (2) the developmental stage, age, snout-vent length and mass of experimental animals should be reported; (3) abiotic conditions (e.g., temperature, humidity) during experimentation in the laboratory or field (mesocosm) should be recorded; (4) the duration of the study should be reported; (5) in susceptibility experiments, the method of exposure of hosts to the pathogen should be detailed. Important information would include dose parameters such as units used (e.g., #zoospores per unit volume); (6) explanation of the procedures used to quantify pathogen load should be reported in detail (e.g., qPCR); (7) the strain and if possible the origin of the strain of pathogen should be reported. Moreover, the age of the strain should be reported if possible because strain virulence may change while in culture; (8) treatments should be described fully and the number of individuals exposed to each treatment, including controls, should be reported. Many but not all studies include the parameters we listed above. Moreover, our list was not an exhaustive one but we feel that experiments reporting those parameters would aid researchers in interpreting and comparing results of different experimental studies.

We suggest future studies examine differences in susceptibility at the species and population levels as well as those that investigate strain variability, using controlled experiments. Controlled experimental studies examining differences in susceptibility to pathogens can aid in our understanding of the dynamics of epizootic outbreaks. Standardizing experimental methods is an essential component of investigating the role of pathogens in amphibian population declines. Moreover, studies that focus on a single cause contributing to amphibian population declines may underestimate the roles of multiple factors working simultaneously to cause both direct and indirect effects. Developing a mechanistic understanding of how biotic and abiotic factors can drive disease dynamics will allow us to better predict outbreaks and better manage and alleviate consequences associated with emerging infectious diseases [215].

Table 1. An overview of the effects of Bd (**a**), Bsal (**b**), and Rv (**c**) on amphibian species based on experimental studies. Publications were compiled using the search strings "*Batrachochytrium dendrobatidis* and *amphibians*", "*ranavirus* and *amphibians*" and "*Batrachochytrium salamandrivorans* and *amphibians*" in the Web of Science database from which duplicates and articles that were unrelated were removed. If one publication examined multiple species or host life stages, each species and life stage was reported separately. We have included each species International Union for Conservation of Nature (IUCN) Red List Status (http://www.iucnredlist.org), a widely recognized mechanism for assessing conservation status. Species of Least Concern (LC), Near Threatened (NT), Vulnerable (VU), Endangered (EN), and Critically Endangered (CE). na = not available. Reduced survival means mortality of hosts exposed to a pathogen was significantly higher than hosts in controls that were not exposed to a pathogen. * animals were not reared from eggs. ** animals were not reared from eggs but were verified as Bd or Rv negative before the start of the experiment. *** collection information unavailable.

a. Effects of *Batrachochytrium dendrobatidis* on amphibian hosts						
Species	**IUCN status**	**Bd Strain**	**Dose (Total zoospores)**	**Life Stage**	**Effect on host**	**Reference**
Agalychnis callidryas	LC	JEL 423	5×10^5 zoospores	na	Increased expression of genes of proteolitic enzymes	[216]
Alytes muletensis	VU	UKTvB, TF5al	23,000 zoospores over two weeks	Through metamorphosis	Strain differences in infection	[93]
Alytes obstetricans	LC	na	na	Through metamorphosis	Population differences in survival	[217] **
	LC	na	Dose reported in the field	Larvae different cohorts	Mitigation of Bd with fungicide was transient not able to prevent spread of Bd	[218]
Ambystoma californiense	VU	JEL 270	1000 and 100,000 zoospores	Juveniles	No significant differences in survival or mass	[219] **
Ambystoma laterale	LC	JEL 423, JEL 404	10^5–10^6 zoosporangia	Juveniles	No significant differences in survival	[86]
Ambystoma opacum	LC	277	250,000 zoospores	Larvae	No infection detected, no significant differences in survival	[119]
Ambystoma tigrinum	LC	A-277, R-230	9,000,000 and 6,000,000 zoospores	Juveniles	No significant differences in survival	[220]
		Bd-GPL isolate	10,000 and 200,000 zoospores	Juveniles	No differences in zoospore outputs	[221] **
Amietia delalandii	LC	South Africa 1a and 1b, South Africa 2 and 3, UK 1 and 2, Spain and Sardinia	1×10^6 zoospores	Adults (mucosome)	Skin mucosomes inhibited Bd growth	[222]
Anaxyrus americanus	LC	JEL 197	500,000 zoospores	Juveniles	Age dependent effect of Bd susceptibility	[116]
		JEL 423, JEL 404	10^6–10^7 zoospores and 10^5–10^6 zoosporangia	Larvae	Reduced survival	[86]
		JEL 213	2.10×10^6 zoospores	Juveniles	Reduced survival	[172]
		JEL 660	1×10^5 zoospores	Juveniles	Elevated body temperatures	[223]
Anaxyrus boreas	NT	JEL 215	12,600 zoospores	Larvae	Reduced survival	[98]
		JEL 274	170,000 zoospores	Larvae	Higher stress hormones and increased length	[104]

Table 1. *Cont.*

a. Effects of *Batrachochytrium dendrobatidis* on amphibian hosts						
Species	**IUCN status**	**Bd Strain**	**Dose (Total zoospores)**	**Life Stage**	**Effect on host**	**Reference**
		JEL 274	2 culture dishes inoculated in batches with 20 tadpoles	Larvae	Did not avoid infected conspecifics, increased activity, no differences in temperature selection	[108]
		JEL 274	100,000, 50,000, or 1000 zoospores	Larvae	No significant differences in survival	[80]
		JEL 274	100,000, 50,000, or 1000 zoospores	Juveniles	No significant differences in survival	[80]
		JEL 215	2.08×10^7/plate	Juveniles	Reduced survival	[144] *
		JEL 275	10^6 zoospores/toadlet daily	Juveniles	Mass dependent survival time, exposed toadlets held bodies out of water as much as possible	[99]
		JEL 275	5.8×10^5 zp/mL	Adults	Reduced survival	[152]
		JEL 275	1.13×10^6 zoospores	Adults	High infection intensity, loss in body weight, mild hyperkeratosis and perturbations in gene expression	[224]
		JEL 425, JEL 630, JEL 646, JEL 627	1×10^5 zoospores	Larvae	Increased mortality dependent on isolate	[91]
		JEL 423	2.0×10^6 zoospores	na	Bufadienolides extracted inhibited Bd growth	[225]
Anaxyrus boreas boreas	LC	JEL 275	100,000 zoospores	Adults	Electrolyte alterations, lymphocytic infiltration	[226] **
Anaxyrus fowleri	LC	na	na	Larvae	Reduced foraging efficiency	[119]
		FMB 001	6,000,000 zoospores	Larvae	Negatively impacts growth	[109]
		USA isolate 284	6,000,000 zoospores	Larvae	Reduced foraging efficiency	[120]
Anaxyrus terrestris	LC	JEL 274	2.6×10^5 zoospores	Juveniles	Reduced survival, decreased feeding	[100]
Anaxyrus woodhousii	LC	Bd-GPL isolate	10,000 and 200,000 zoospores	Juveniles	No significant differences in zoospore outputs	[221] **
Atelopus glyphus	CR	JEL 423	3×10^5	na	Genes with elevated expression in infected individuals were enriched for GO terms, including cell adhesion, immune response and regulation of cell proliferation.	[216]
Atelopus varius	CR	JEL 410, JEL 412, JEL 413, and 3 contemporary isolates	50×10^2	Adults	No differences in infection intensity or survival by Bd strain	[227]
Atelopus zeteki	CR	JEL 423	30,000 zoospores	Adults	Infection intensity and zoospore output were positively correlated.	[228]
		JEL 423	30,000 zoospores	Adults	Significant differences in expression of numerous genes involved in innate and inflamatory responses	[229] **

Table 1. *Cont.*

a. Effects of *Batrachochytrium dendrobatidis* on amphibian hosts						
Species	**IUCN status**	**Bd Strain**	**Dose (Total zoospores)**	**Life Stage**	**Effect on host**	**Reference**
		JEL 408	100 zoospores, 10^4, 10^6	Adults	Dose and temperature dependent effects	[78]
		JEL 310	3000 zoospores	Juveniles	Probiotics use did not prevent or delay mortality by Bd.	[230]
		JEL 423	3×10^3 zoospores	na	Genes with increased expression were enriched for GO terms, including response to wounding, inflammatory response and apoptosis	[216]
Batrachoseps attenuatus	LC	na	3×10^9 zoospore equivalents	Adults	Cleared infection, wild caught infected individuals experienced 100% mortality in the laboratory	[84] **
Bufo bufo	LC	IA042, IA043, 0711 (Pyrenees, BdGPL), VAo2, VAo4, VAo5 (Valencia, BdGPL lineage), CCB1, TF5a1 and TF1.1 (Mallorca, BdCAPE lineage)	3000–17,000 active zoospores	Larvae	Strain differences in mortality and infection dynamics	[85]
		UK Bd UKTvB, Mallorca Bd TF5a1, Pyrenneen Bd IA042	19,000 zoospores, 190 zoospores	Larvae	Reduced survival, differences in mass, strain differences in virulence and infection	[15]
		Bd-GPL IA-42	160, 16,000 zoospores	Juveniles	Reduced survival, mass-dependent effects	[196]
		IA2004 043	30 to 70, 3000 to 15,000 zoospores	Through metamorphosis	Dose-, size-, and age-dependent effects	[79]
		na	120–300 zoospores, 12,000–30,000 zoospores	Juveniles	Warmer overwintering regime increases the probability of infection. Proliferation of Bd in the host was better in toadlets that experienced a colder winter	[81]
Bufo marinus	LC	JEL 275	2.04×10^6 zoospores	Adults	Minimal hyperkeratosis, no differences in survival neither in body weight	[224]
Bufo quercicus (Anaxyrus quercicus)	LC	SRS 812	60,000 zoospores	Adults	Learned behavioral resistance to Bd	[83]
Craugastor fitzingeri	LC	JEL 423	5×10^5 zoospores	na	Genes with increased expression were enriched for GO terms, including response to wounding, inflammatory response and apoptosis.	[216]
Dendropsophus meridensis	EN	BdLEcat10CG-1	9×10^6 zoospores	Juveniles	Reduced survival	[231] **
Dendrobates auratus	LC	na	na	Juveniles	Reduced survival	[36]

Table 1. *Cont.*

a. Effects of *Batrachochytrium dendrobatidis* on amphibian hosts						
Species	**IUCN status**	**Bd Strain**	**Dose (Total zoospores)**	**Life Stage**	**Effect on host**	**Reference**
Dendrobates tinctorius	LC	na	na	Juveniles	Reduced survival, skin lesions	[36]
Desmognathus monticola	LC	JEL 197	1.068×10^7 zoospores	Adults	Reduced survival	[232] **
Desmognathus orestes	LC	BD 197	1,000,000 zoospores	Adults	No clinical signs of infection	[233] **
Eleutherodactylus coqui	LC	JEL 427	50,000 or 100,000 zoospores	Juveniles	Reduced survival, population differences	[94] **
		JEL 427	10^6 and 10^5 zp/mL in 10 mL	Adults	No significant differences in survival, cleared or reduced infection	[94]**
Hyla chrysoscelis	LC	na	7000 zoospores/mL	Through metamorphosis	No significant differences in survival, reduced metamorphic body mass, delayed time to metamorphosis	[234]
		JEL 646, JEL 423, JEL 213, JEL 660, FMB 003, JEL 404	8×10^3 zoospores	Through metamorphosis	No significant differences in survival, growth, or time to metamorphosis	[235]
		na	7000 zp/mL	Larvae	No significant differences in survival or larval period length, reduced body mass at metamorphosis	[118]
		na	125,000 zoospores	Larvae	Reduced foraging efficiency	[119]
		na	6,000,000 zoospores	Larvae	Reduced foraging efficiency	[120]
Hyla cinerea	LC	JEL 423, SRS810	76.7×10^6, 4.7×10^6 zoospores	Juveniles and Adults	No clinical signs of infection. Infection did not negitively affect body condition or growth rate for either strain or lifestage	[89] **
Hyla versicolor	LC	JEL 274	2.6×10^5	Juveniles	Reduced survival	[100]
		FMB 003	75,000	Larvae	Reduced survival, age-dependent effects	[167]
		FMB 001	6,000,000 zoospores	Larvae	Negatively impacts growth	[109]
Hypsiboas crepitans	LC	Bd1006	9,000,000 zoospores	Juveniles	Cleared infection	[82]
Ichthyosaura alpestris	LC	na	na	Adults	Reduced survival	[236]
Lechriodus fletcheri	LC	EPS4	750,000 zoospores	Sub-adults	Significant differences in survival, increased sloughing rates	[237]
Leiopelma archeyi	CR	JEL 197	250,000 zoospores	Adults	Cleared infection	[238] **
Limnodynastes peronii	LC	Gibbo River-Llesueuri-00-LB-1	20×10^6 zoospores	Larvae and Juveniles	Reduced survival, infection loads increased over time	[239]
		EPS4	750,000 zoospores	Adults	Low mortality rates, increase in sloughing rates	[237]

Table 1. *Cont.*

a. Effects of *Batrachochytrium dendrobatidis* on amphibian hosts						
Species	**IUCN status**	**Bd Strain**	**Dose (Total zoospores)**	**Life Stage**	**Effect on host**	**Reference**
Limnodynastes tasmaniensis	LC	GibboRiver-Llesueuri-00-LB-1	5000 zoospores + 2 mL water	Juveniles	No significant differences in survival	[240]
		EPS4	750,000 zoospores	Adults	No significant differences in survival, sloughing rate increased at lower Bd loads	[237]
Lissotriton helveticus	LC	na	~2000 zoospores	Adults	Decreased mass, no evidence of hastened secondary sexual trait regression, exposure associated with a 50% earlier initiation of the terrestrial phase	[241] **
Lithobates catesbeianus	LC	JEL 274	48,000 zoospores	Larvae	Higher stress hormones and increased length	[104]
		JEL 215	8400 zoospores	Larvae	No significant differences in survival	[98]
		JEL 274, JEL 630	1.7×10^4 zoospores/mL in 15 mL	Juveniles	Strain differences in infection	[80]
		JEL 423	8×10^7 to 2×10^8 zoospores	Juveniles	Disruption of the epidermal cell maturation cycle	[35] **
		JEL 423, JEL 404	10^6–10^7 zoospores and 10^5–10^6 zoosporangia	Juveniles	No significant differences in survival	[86]
		Bd-GPL isolate	10,000 or 200,000 zoospores	Juveniles	Produces more infective zoospore stage than other species tested	[221] **
		Crater Meadow isolate, Finley Lake isolate	10^6 and 2×10^6 zoospores	Juveniles	No significant differences in survival, low infection prevalence, relatively low infection loads and lack of clinical disease for Finley Lake strain	[86] **
		JEL 310	7×10^6 zoospores and 4.8×10^7 zoospores	Juveniles	Manipulation of frogs microbiota did not affect Bd infection intensity.	[242]
		Isolate from dead *Alytes obstetricans*	150,000 zoospores	Larvae	No significant differences in survival	[236]
Lithobates clamitans	LC	JEL 423, JEL 404	10^6–10^7 zoospores and 10^5–10^6 zoosporangia	Juveniles	Strain differences in infection	[86]
Lithobates pipiens	LC	JEL 423, JEL 404	10^6–10^7 zoospores and 10^5–10^6 zoosporangia	Juveniles	No significant differences in survival	[86]
		JEL 423	3.98×10^6 zoospores	Juveniles	Increased skin shedding, no significant differences in survival or splenosomatic or hepatosomatic	[171] **
		JEL 424	3.98×10^6 zoospores	Juveniles	indices, the densities and sizes of hepatic and splenic melanomacrophage aggregates, the density and size	[171] **

Table 1. *Cont.*

a. Effects of *Batrachochytrium dendrobatidis* on amphibian hosts						
Species	**IUCN status**	**Bd Strain**	**Dose (Total zoospores)**	**Life Stage**	**Effect on host**	**Reference**
		JEL 425	3.98×10^6 zoospores	Juveniles	of hepaticgranulomas, proportions of circulating leucocytes, the ratio of neutrophils to lymphocytes,	[171] **
		JEL 426	3.98×10^6 zoospores	Juveniles	or the ratio of leucocytes to erythrocytes	[171] **
		JEL 197	500,000 zoospores	Juveniles	No significant differences in survival regardless of age	[116]
		JEL 423	1.69×10^7–7.43×10^8 zoospores	Adults	Lower peak jumping velocity in infected subjects, testes width significantly greater in infected individuals	[243] **
Lithobates sphenocephalus	LC	na	2.88×10^6 zoospores	Larvae	No significant differences in survival, reduced foraging efficiency	[117]
		na	400,000 zoospores	Larvae	Low protein diets resulted in smaller and less developed tadpoles and reduced immune responses, high protein diets significantly increased resistance to Bd	[244]
		JEL 197	10^6 zoospores	Juveniles	Increased pathogen skin burden within two weeks of exposure, higher pathogen burden in deceased frogs, decrease in pathogen loads over time	[245]
Lithobates sylvaticus	LC	JEL 404, JEL 423	10^6–10^7 zoospores and 10^5–10^6 zoosporangia	Larvae	Reduced survival, no differences in growth or time to metamorphosis	[86]
		JEL 404, JEL 423	10^6–10^7 zoospores and 10^5–10^6 zoosporangia	Larvae	Reduced survival	[86]
		JEL 197	10^4 zoospores	Juveniles	No significant differences in survival regardless of age	[116]
		JEL 274	2.6×10^5 zoospores	Juveniles	Reduced survival	[100]
		JEL 274	1.55×10^5	Juveniles	Population differences in survival	[206]
		JEL 423	1×10^7 to 2×10^7 zoospores	Juveniles	Disruption of the epidermal cell maturation cycle	[35] **
Lithobates yavapaiensis	LC	Arizona Bd strain PsTr2004	1×10^5 zoospores	Juveniles	MHC heterozygosity as a predictor of survival	[246]
Litoria aurea	VU	Gibbo River-Llesueuri-00-LB-1	20×10^6 zoospores	Larvae and Juveniles	No significant differences in survival, decrease in pathogen loads over time	[239]
Litoria booroolongensis	VU	AbercrombieNP-L. booroolongensis-09-LB-P7)	750,000 zp in 5 mL	Juveniles	No evidence that prior Bd infection increases protective immunity	[247]

Table 1. *Cont.*

a. Effects of *Batrachochytrium dendrobatidis* on amphibian hosts						
Species	**IUCN status**	**Bd Strain**	**Dose (Total zoospores)**	**Life Stage**	**Effect on host**	**Reference**
Litoria caerulea	LC	GibboRiver-Llesueuri-00-LB-1	5000 zoospores + 2 mL water	Juveniles	Reduced survival	[240]
		Strain 98 1469/10, Strain 99 1385/12, Strain 00 545	50,000 zoospores	Juveniles	Differences in survival rates among infected groups	[34]
		na	na	Adults	Decreased blood pH, low plasma osmolality and reduced concentrations of sodium, potassium, chloride and magnesium	[38]
		EPS4	250,000 zoospores	Adults	Increased skin sloughing rate with increased infection intensity	[248] **
		Gibboriver-Llesueuri-00-LB-1P50 and P10 (passages)	93×10^4/mL-1	Adults	No significant differences in survival or mass	[96]**
		na	250,000 zoospores	Adults	Impaired immune response	[249] **
		na	na	Adults	Impaired stress and immune response, increased skin shedding	[103] *
		Paluma-Lseratta-2012RW-1	6×10^5 zoospores	Juveniles	Immunological profiles changed according to acclimated regime	[250]
		EPS4 and Waste point-Lverreauxii-2013-LB	1.25×10^6 zoospores	Adults	Low mortality rates, increase in sloughing rates	[237]
		JEL 423 and Rio Maria isolate	1.5×10^6 zoospores	Adults	No differences in infection intensity or survival by Bd strain	[227]
		JEL 423 and Rio Maria isolate	indirect	Adults	No differences in infection intensity or survival by Bd strain	[227]
Litoria chloris	LC	GibboRiver-Llesueuri-00-LB-1	5000 zoospores + 2 mL water	Juveniles	Reduced survival	[240]
		GibboRiver-Llesueuri-00-LB-1	15,000 zoospores + 2 mL water	Juveniles	Temperature did not influence leukocyte populations	[240]
		na	15,000 zoospores	Juveniles	Temperature dependent effects on survival	[77] ***
Litoria infrafrenata	LC	na	250,000 zoospores	Adults	Reduction in white blood cells and serum globulin concentrations	[249] **
Litoria raniformis	EN	na	100,000 zoospores	Adults	Compromised ability to osmoregulate and rehydrate, no significant difference in metabolic or breathing rates	[251] **
Litoria verreauxii alpina	LC	AbercrombieNP-L.booroolongensis-09-LB-P7)	750,000 zoospores	Adults	No effect of MHC heterozygosity or allelic divergence on survival	[252]
		AbercrombieR-L.booroologensis-2009-LB1 and WastePoint-L.v.alpina-2013-LB2	1×10^6 zoospores in 3 mL and 5×10^5 zoospores in 10 mL	Adults	Oogenesis and spermatogenesis increased in infected animals	[253]

Table 1. *Cont.*

a. Effects of *Batrachochytrium dendrobatidis* on amphibian hosts						
Species	**IUCN status**	**Bd Strain**	**Dose (Total zoospores)**	**Life Stage**	**Effect on host**	**Reference**
Mixophyes fasciolatus	LC	GibboRiver-Llesueuri-00-LB-1	5000 zoospores + 2 mL water	Juveniles	Reduced survival	[240]
		No. 00/545	1000 zoospores	Adults	Lower temperatures enhanced pathogenicity	[76] *
Osteopilus septentrionalis	LC	SRS 812	3×10^4 zp/mL in 2 mL	Larvae	The loss of keratin in the mouthparts associated with a loss of Bd	[254]
		SRS 812	3 mL of 6×10^4 (after each water change)	Larvae	Reduced survival	[170]
		SRS 812	3×10^6 zp/mL	Juveniles	Pathogen loads decreased over time; increased lymphocyte proliferation with increased exposures; previous exposure increased chances of survival	[83]
Pelophylax esculentus	LC	TG 739	$1.5–2 \times 10^5$ zoospores	Adults	Reduction in skin peptide and microbiota immune defenses caused less weight gain and increased infection rates.	[255] **
Pelophylax lessonae	LC	TG 739	$1.5–2 \times 10^5$ zoospores	Adults	Reduction in skin peptide and microbiota immune defenses caused less weight gain and increased infection rates.	[255] **
Platyplectrum ornatum	LC	EPS4	750,000 zoospores	Adults	Significant differences in survival	[237]
Plethodon cinereus	LC	JEL 660/JS OH-1	7×10^5 in 5 mL	Adults	Increased feeding activity	[121] *
Plethodon glutinosus	LC	BD 197	1,000,000 zoospores	Adults	Clinical symptoms of infection	[233] **
		BD 197	10,000 or 100,000 zoospores	Adults	No significant differences in survival	[233] **
Plethodon metcalfi	LC	JEL 197	1.068×10^7 zoospores	Adults	Reduced survival	[232] **
Plethodon shermani		JEL 197	1×10^7 zoospores	Adults	Decreased body mass, reduction in locomotory activity	[256]
Pseudacris crucifer	LC	JEL 423, JEL 404	$10^6–10^7$ zoospores and $10^5–10^6$ zoosporangia	Adults	No significant differences in survival	[86]
Pseudacris feriarum	LC	JEL 274	2.6×10^5 zoospores	Juveniles	Reduced survival	[100]
Pseudacris regilla	LC	JEL 215	12,600 zoospores	Larvae	No significant differences in survival	[98]
		JEL 626	27,800 zoospores	Larvae	Reduced survival and activity, delayed time to metamorphosis	[169]
		JEL 215	2 culture dishes inoculated in batches with 20 tadpoles	Larvae	No differences in temperature selection	[108]

Table 1. *Cont.*

a. Effects of *Batrachochytrium dendrobatidis* on amphibian hosts						
Species	**IUCN status**	**Bd Strain**	**Dose (Total zoospores)**	**Life Stage**	**Effect on host**	**Reference**
		JEL 216	6.18×10^6/mL	Larvae	No significant differences in activity or refuge use	[115]
		JEL 274	100,000, 50,000, or 1000 zoospores	Larvae	No significant differences in survival, dose-dependent infection loads	[80]
		JEL 274	100,000, 50,000, or 1000 zoospores	Juveniles	Reduced survival, dose-dependent infection loads	[80]
		JEL 215	2.08×10^7 zoospores	Juveniles	No significant differences in survival	[144] *
		JEL 274	50,000 zoospores	Juveniles	Reduced survival, Infection load increased over time, lower lymphocyte levels	[257]
		JEL 274	2.6×10^7 and 1.1×10^6 zoospores/L	Through metamorphosis	Dose-dependent effects	[74]
		JEL 425, JEL 630, JEL 646	1×10^5 zoospores	Larvae	No significant differences in survival	[91]
Pseudacris triseriata	LC	27-mile lake isolate, Lost lake isolate	8×10^4 zoospores	na "frogs"	Strain differences in infection	[88]
	LC	Bd-GPL isolate	10,000 and 200,000 zoospores	Juveniles	No significant differences in zoospore outputs	[221]
Pseudophryne corroboree	CR	AbercrombieR-L.booroologensis-2009-LB1	1×10^6 zoospores in 3 mL	Adults	Oogenesis and spermatogenesis increased in infected animals	[253]
Pyxicephalus adspersus	LC	South Africa 1a and 1b, South Africa 2 and 3, UK 1 and 2, Spain and Sardinia	1×10^6 zoospores	Adults (mucosome)	Skin mucosomes inhibited Bd growth	[222]
Rana aurora	LC	JEL 215	2 culture dishes inoculated in batches with 20 tadpoles	Larvae	No differences in temperature selection	[108]
		na	2×10^5 zp added every other day for 8 days	Larvae	High temperature variability in the presence of Bd had decreased growth	[149]
		JEL 216	6.18×10^6/mL	Larvae	No significant differences in activity or refuge use	[115]
Rana blairi/Rana sphenocephala (Lithobates blairi/Lithobates sphenocephala)	na	na	7000 zp/mL	Larvae	No significant differences in survival, reduced metamorphic body mass	[118]
Rana boylii	NT	LJR 119	9.4×10^6 zoospores in 50 mL	Juveniles	No significant differences in survival, reduced growth, increased skin peptide concentrations	[165] *
		A-227, R-230	1,275,000; 127,500 zoospores	Juveniles	No significant differences in survival	[220]

Table 1. *Cont.*

a. Effects of *Batrachochytrium dendrobatidis* on amphibian hosts						
Species	**IUCN status**	**Bd Strain**	**Dose (Total zoospores)**	**Life Stage**	**Effect on host**	**Reference**
Rana cascadae	LC	JEL 215	12,600 zoospores	Larvae	No significant differences in survival, increased incidence of mouthpart abnormalities	[98]
		JEL 274	48,000 zoospores	Larvae	Higher stress hormones and increased length and mass	[104]
		JEL 274	50,000 zoospores	Larvae	No significant differences in mortality, Infection load decreased over time, stronger bacterial killing response over time, elevated neutrophil levels	[257]
		JEL 274	4 culture dishes inoculated in batches with 90 tadpoles	Larvae	Non-infected individuals were observed more frequently on Bd+ side of test chamber	[108]
		JEL 216	6.18×10^6/mL	Larvae	No significant differences in activity or refuge use	[115]
		JEL 274	100,000, 50,000, or 1000 zoospores	Larvae	No significant differences in survival	[80]
		JEL 274	100,000, 50,000, or 1000 zoospores	Juveniles	Reduced survival	[80]
		JEL 215	2 culture dishes inoculated in batches with 20 tadpoles	Juveniles	No differences in temperature selection	[108]
		JEL 274	8.5×10^4 zp	Juveniles	Lower stress hormone levels	[104]
		Section line lake and Carter Meadow	2.2×10^5 zoospores	Juveniles	Strain differences in mortality and infection dynamic, no differences in survivorship between populations BUT Bd prevalence and infection intensity differed between populations	[92]
		JEL 215	2.08×10^7 zoospores	Juveniles	Reduced survival	[144] *
		JEL 425, JEL 630, JEL 646	1×10^5 zoospores	Larvae	No significant differences in survival	[91]
Rana draytonii	VU	JEL 270	1000 and 100,000 zoospores	Juveniles	No significant differences in survival or mass	[219] **
Rana muscosa	EN	JEL 217	3.6×10^9 zoospores	Larvae	Infected but appear healthy, loss of mouth pigmentation	[208] **
		JEL 217	na	Larvae	Transmitted infection to each other and to post-metamorphic individuals	[208] **
		LJR089	1×10^7 zoospores	Larvae	Proportion of hosts that became infected increased with the number of previously infected *R. muscosa* tadpoles to which they were exposed	[73]
		na	>100,000 in 1 mL	Adults	Disruption of skin integrity, ion imbalance	[258]

Table 1. *Cont.*

a. Effects of *Batrachochytrium dendrobatidis* on amphibian hosts						
Species	**IUCN status**	**Bd Strain**	**Dose (Total zoospores)**	**Life Stage**	**Effect on host**	**Reference**
		LJR089	1×10^7 zoospores	Juveniles	Temperature dependent effects on survival, increased skin shedding	[75]
Rana Once (Lithobates Onca)	EN	CJB7 from Rana muscosa and SLL from *Rana cascadae*	3×10^6	Juveniles	No significant differences in survival, cleared infection	[259]
Rana pipiens (Lithobates pipiens)	LC	na	2,800,000 zoospores	Larvae	Reduced activity	[72]
		JEL 275	10^4 zoospores	Juveniles	Reduced survival	[260] **
		JEL 274	2.6×10^5 zoospores	Juveniles	Reduced survival	[115]
Rana sierrae	EN	TST75,CJB4, CJB5, CJB7	200,000 zoospores	Juveniles	Altered microbiome	[261] **
Rana temporaria	LC	BdGPL IA-42	160 and 16,000 zoospores	Juveniles	No significant differences in survival, high dose resulted in less weight gain or weight loss	[196]
		Isolate IA 042	100,000 zoospores	Juveniles	Significant transcriptional response to Bd	[262]
Rana yavapaiensis (Lithobates yavapainensis)	LC	A-277, R-230	8.5×10^3 zoopores/mL	Juveniles	No significant differences in survival	[220]
Silurana tropicalis (Xenopus tropicalis)	LC	IA042	10^6 zoospores	Adults	Temperature dependent effects on immune response	[263] **
		na	na	Adults	Altered gene expression to physiological and immunological genes	[264] **
Xenopus laevis	LC	JEL 197 and JEL 275	na	Adults	Impaired lymphocyte proliferation and induced splenocyte apoptosis	[265]
		JEL 197 and JEL 275	10^6 zoospores	Adults	Peptide-depleted frogs became more susceptible to Bd infection with higher burdens and weight loss	[266] **
		JEL 197	10^7 zoospores	Adults	Inhibition of local lymphocyte responses in host to promote infection	[267]
b. Effects of *Batrachochytrium salamandrivorans* on amphibian hosts						
Species	IUCN Status	Bsal Strain	Bsal Dose (Total zoospores)	Life Stage	Effect on Host	Reference
Alytes obstetricans	LC	AMFP13/1	5000 in 1 mL	<1 year	No infection or disease detected	[42]
		AMFP13/1	5000 in 1 mL	Adults	No significant effect	[18]
		AMFP13/1, AMFP14/1, AMFP14/2, AMFP15/1	10^5	Juvenile	No signs of disease but able to transmit infection after 14 days	[18]
Ambystoma maculatum	LC	AMFP13/1	5000 in 1 mL	<1 year	No infection or disease detected	[42]

Table 1. *Cont.*

b. Effects of *Batrachochytrium salamandrivorans* on amphibian hosts						
Species	IUCN Status	Bsal Strain	Bsal Dose (Total zoospores)	Life Stage	Effect on Host	Reference
Ambystoma opacum	LC	AMFP13/1	5000 in 1 mL	<1 year	No infection or disease detected	[42] **
Bombina variegata	LC	AMFP13/1	5000 in 1 mL	Adults	No infection or disease detected	[42]
Cynops pyrrhogaster	LC	AMFP13/1	5000 in 1 mL	<1 year	Susceptible to infection and disease	[42]
Discoglossus scovazzi	LC	AMFP13/1	5000 in 1 mL	<1 year	No infection or disease detected	[42]
Epidalea calamita	LC	AMFP13/1	5000 in 1 mL	<1 year	No infection or disease detected	[42]
Euproctus platycephalus	EN	AMFP13/1	5000 in 1 mL	Adults	Reduced survival, confirmed invasion of the skin	[42]
Gyrinophilus porphyriticus	LC	AMFP13/1	5000 in 1 mL	Adults	No infection or disease detected	[42]
Hyla arborea	LC	AMFP13/1	5000 in 1 mL	<1 year	No infection or disease detected	[42]
Hynobius retardatus	LC	AMFP13/1	5000 in 1 mL	Adults	No infection or disease detected	[42]
Hypselotriton cyanurus	LC	AMFP13/1	5000 in 1 mL	Adults	Susceptible to infection and disease	[42] **
Ichthyosaura alpestris	LC	AMFP13/1	5000 in 1 mL	<1 year	Reduced survival, confirmed invasion of the skin	[42]
		AMFP13/1	10^4, 10^3, 10^2, 10	Juvenile	High doses resulted in mortality, previous infection offered no protection on reinfection	[268]
Lissotriton helveticus	LC	AMFP13/1	5000 in 1 mL	<1 year	No infection or disease detected	[42]
Lissotriton italicus	LC	AMFP13/1	5000 in 1 mL	<1 year	Reduced survival	[42]
Lithobates catesbeianus	LC	AMFP13/1	5000 in 1 mL	Adults	No infection or disease detected	[42]
Neurergus crocatus	VU	AMFP13/1	5000 in 1 mL	Adults	Reduced survival, confirmed invasion of the skin	[42]
Notophthalmus viridescens	LC	AMFP13/1	5000 in 1 mL	Adults	Reduced survival, confirmed invasion of the skin	[42]**
Pachyhynobius shangchengensis	VU	AMFP13/1	5000 in 1 mL	Adults	No infection or disease detected	[42]
Paramesotriton deloustali	VU	AMFP13/1	5000 in 1 mL	Adults	Susceptible to infection and disease	[42]
Pelobates fascus	LC	AMFP13/1	5000 in 1 mL	<1 year	No infection or disease detected	[42]
Plethodon glutinosus	LC	AMFP13/1	5000 in 1 mL	Adults	Confirmed infection of the skin, no disease detected	[42] **
Pleurodeles waltl	NT	AMFP13/1	5000 in 1 mL	<1 year	Reduced survival, confirmed invasion of the skin	[42]

Table 1. *Cont.*

b. Effects of *Batrachochytrium salamandrivorans* on amphibian hosts						
Species	IUCN Status	Bsal Strain	Bsal Dose (Total zoospores)	Life Stage	Effect on Host	Reference
Rana temporaria	LC	AMFP13/1	5000 in 1 mL	<1 year	No infection or disease detected	[42]
Salamandra salamandra	LC	AMFP13/1	5000 in 1 mL	Adults	Reduced survival, ataxia. Cohousing effectively transmits infection	[18]
		AMFP13/1	5000 in 1 mL	Adults	Warmer temperatures can clear infection	[269]
		AMFP13/1	10^5 in 1 mL	Adults	Topical treatments can reduce fungal loads and in combination with warmer temperature can clear infection	[269]
		AMFP13/1	5000 in 1 mL	<1 year	Reduced survival, confirmed invasion of the skin	[42]
		AMFP13/1, AMFP14/1, AMFP14/2, AMFP15/1	100 spores (low), 10^4 (high)	Juvenile	Mortality was delayed in low dose treatment	[268]
		na	2.6×10^4, 1.3×10^4	na	Mortality was delayed in low temp treatment	[268]
		AMFP13/1	10^3	na	Reinfection did not change disease dynamics	[268]
Salamandrella keyserlingii	LC	AMFP13/1	5000 in 1 mL	Adults	Confirmed infection but no effects of disease or on survival	[42]
Salamandrina perspicillata)	LC	AMFP13/1	5000 in 1 mL	<1 year	Reduced survival	[42]
Silurana tropicalis	LC	AMFP13/1	5000 in 1 mL	<1 year	No infection or disease detected	[42]
Siren intermedia	LC	AMFP13/1	5000 in 1 mL	Adults	Confirmed infection but no effects of disease or on survival	[42]
Speleomantes strinatii	NT	AMFP13/1	5000 in 1 mL	Adults	Reduced survival	[42] **
Taricha granulosa	LC	AMFP13/1	5000 in 1 mL	<1 year	Reduced survival	[42]
Triturus cristatus	LC	AMFP13/1	5000 in 1 mL	<1 year	Reduced survival, confirmed invasion of the skin	[42]
Tylototriton wenxianensis	VU	AMFP13/1	5000 in 1 mL	<1 year	Reduced survival	[42]
Typhlonectes compressicauda	LC	AMFP13/1	5000 in 1 mL	Adults	No infection or disease detected	[42]

Table 1. *Cont.*

c. Effects of ranavirus on amphibian hosts							
Species	IUCN Status	Rv Strain	Dose	Type of Exposure	Life-Stage	Effect on Host	Reference
Ambystoma californiense	VU	ATV	200 uL of inoculum w/1000 virions of ATV in APBS solution	Injection	Adults	Reduced survival	[270] **
Ambystoma gracile	LC	ATV	na	Water bath	Larvae	Reduced survival	[128] *
Ambystoma maculatum	LC	FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival, strain differences in infection	[132]
Ambystoma mavortium	na	ATV	$1 \times 10^{3.3}$ and 7.1×10^3 TCID50/mL (1.4 million virions per animal)	Water bath	Larvae	Population differences in infection	[133]
Ambystoma opacum	LC	FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival, strain differences in infection	[132]
Ambystoma talpoideum	LC	FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	No difference in survival, no difference in infection	[132]
Ambystoma tigrinum	LC	ATV (ATV-DO211)	10^2, $10^{2.5}$, 10^3, $10^{3.5}$, 10^4, 10^5 PFU from original plaque assay of 4.5×10^7	Water bath	Larvae	Dose dependent infection and survival rates	[70]
		ATV	2×10^6 from 200 mL of 10^4 PFU/mL in aged tap water	Water bath	Larvae	No differences between transmission rates	[56]
		ATV	2×10^7 of ATV for a final concentration of 6.67×10^4 PFU/mL	Water bath with pond sediment	Larvae	No infection when exposed to virus in dried substrate, but when substrate was kept moist they became infected and experienced reduced survival	[56]
		ATV	500 PFU in 200 uL	Injection	Larvae	1s ventral surface to ventral surface contact results in infection	[56]
		ATV	4×10^6 PFU from 400 mL of 10^4 PFU/mL in aged tap water	Water bath	Larvae	Infection rate increases with time and increased SVL	[56]
		ATV	10^3 PFU/mL, 10^4 PFU/mL	Water bath	Larvae	Temperature influences infectivity, survival, and time to death. Sublethal infections result in viral carrier status.	[130]
		ATV	10^2, $10^{2.5}$, 10^3, $10^{3.5}$, 10^4, 10^5 PFU from original plaque assay of 4.5×10^7	Water bath	Larvae	Dose and developmental stage dependent infection rates	[70]

Table 1. *Cont.*

c. Effects of ranavirus on amphibian hosts							
Species	IUCN Status	Rv Strain	Dose	Type of Exposure	Life-Stage	Effect on Host	Reference
		FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival	[132]
		ATV	10^3 PFU/mL	Water bath	Larvae	No differences in survival rates between larvae and juveniles	[56]
		ATV	10^3 PFU/mL	Water bath	Juveniles	Reduced survival	[56]
Ambystoma mavortum	na	ATV	200 uL of inoculum w/1000 virions of ATV in APBS solution	Injection	Adults	Reduced survival	[270] *
Ambystoma tigrinum nebulosum	na	ATV	200 uL of inoculum w/1000 virions of ATV in APBS solution	Injection	Adults	Reduced survival	[270]
Ambystoma tigrinum stebbinsi	na	ATV	200 uL of inoculum w/1000 virions of ATV in APBS solution	Injection	Adults	Reduced survival	[270] *
Anaxyrus americanus	LC	FV3-like isolate	10^3 PFU/mL	Water bath	Embryo through metamorphosis	Developmental stage dependent infection and survival rates	[136]
		FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival	[132]
Anaxyrus boreas	LC	FV3-like isolate	10^3 PFU	Water bath	Larvae	100% mortality	[55]
		FV3-like isolate	10^3 PFU	Water bath	Juveniles	100% mortality	[271]
Bufo bufo	LC	RUK 11, RUK 13, BUK 2, BUK 3	10^6 pfu, 10^4 pfu [all exposures standardized to 30 mL]	Water bath	Larvae	Reduced survival, dose dependent infection and survival, strain differences in infection	[272]
Cophixalus ornatus	LC	BIV	10^3 TCID50/mL	Water bath, Injection, contact	Adults	Reduced survival	[273] *
Gastrophryne carolinensis	LC	FV3 and FV3-like isolate	10^6 PFUs in 10 uL of Eagle's MEM	oral dose, Water bath	Larvae	No differences in survival and no strain differences in viral load	[126]
Hyla chrysoscelis	LC	FV3-like isolate	10^3 PFU/mL	Water bath	Embryo through metamorphosis	Reduced survival	[136]
		FV3 and FV3-like isolate	10^6 PFUs in 10 uL of Eagle's MEM	Oral dose, Water bath	Larvae	Reduced survival, exposure type dependent effects on survival and infection	[126]
		FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival	[132]
		FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival	[132]

Table 1. *Cont.*

c. Effects of ranavirus on amphibian hosts							
Species	IUCN Status	Rv Strain	Dose	Type of Exposure	Life-Stage	Effect on Host	Reference
		FV-3	10^3 PFU/mL	Water bath	Larvae	Transmission can occur between vertebrate classes. Amphibian larvae more susceptible to ranavirus than other vertebrate classes.	[62]
Limnodynastes terraereginae	LC	BIV	10^0, 10^1, $10^{2.5}$, and 10^4 TCID50/mL (bath); 0.1 mL of 10^3 TCID50/mL (injection)	Water bath, Injection	Larvae	Reduced survival, renal, hepatic, splenic, and pulmonary necrosis	[274] *
		BIV	10^0, 10^1, $10^{2.5}$, and 10^4 TCID50/mL (bath); 0.1 mL of 10^3 TCID50/mL (injection)	Water bath, Injection	Juveniles	Reduced survival, renal, hepatic, splenic, and pulmonary necrosis	[274] *
Lithobates catesbeianus	LC	ATV	Tadpoles were fed infected salamander	feeding	Larvae	Reduced survival	[128] *
		FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	No differences in survival	[132]
		ATV	200 uL ATV/EPC which had 4×10^5 PFU/mL for adults injection.	Injection	Adults	Reduced survival	[128] *
Lithobates clamitans	LC	FV3-like isolate	10^3 PFU/mL	Water bath	Embryo through metamorphosis	Reduced survival	[136]
Lithobates palustris	LC	FV3 and FV3-like isolate	10^6 PFUs in 10 uL of Eagle's MEM	oral dose, Water bath	Larvae	Reduced survival, exposure type dependent effects on survival and infection	[126]
Lithobates pipiens	LC	FV3-like isolate	10^3 PFU/mL	Water bath	Embryo through metamorphosis	Reduced survival	[136]
		FV3 strains (SSME, wt-FV3, aza-C)	50 mL of water with 10,000 PFU/mL	Water bath	Larvae	Strain dependent effects on survival	[275] *
		FV3 isolate (wt-FV3), azacR, SsMeV	50 mL of water with 10,000 PFU/mL	Water bath	Larvae	Infection dependent on temperature and strain	[129]
		ATV	100 uL of ATV/EPC which had 4×10^5 PFU/mL in EPC cells	Injection	Adults	Reduced survival	[128] *
Lithobates sevosus	CR	FV3-like isolate	400 mL of water with 10^3 PFU/mL	Water bath, Injection, oral dose	Adults	Reduced survival, exposure type dependent effects on survival	[276]
		FV3-like isolate	10^3 PFU	Water bath	Eggs	Reduced survival	[271]
		FV3-like isolate	10^3 PFU	Water bath	Hatchling	100% mortality	[271]

Table 1. *Cont.*

c. Effects of ranavirus on amphibian hosts							
Species	IUCN Status	Rv Strain	Dose	Type of Exposure	Life-Stage	Effect on Host	Reference
		FV3-like isolate	10^3 PFU	Water bath	Larvae	100% mortality	[271]
		FV3-like isolate	10^3 PFU	Water bath	Juveniles	100% mortality	[271]
		FV3-like isolate	10^3 PFU	Water bath	Juveniles	Reduced survival	[271]
		FV3-like isolate	10^3 PFU	Water bath	Adults	Reduced survival	[271]
Lithobates sylvaticus	LC	FV3-like isolate	10^3 PFU/mL	Water bath	Embryo through metamorphosis	Reduced survival	[136]
		FV3 isolate (wt-FV3), azacR, SsMeV	50 mL of water with 10,000 PFU/mL	Water bath	Larvae	Infection dependent on temperature and strain	[129]
		na	na	contact and feeding on infected individuals	Larvae	Reduced survival	[57] *
		na	na	Exposure to contaminated sediment and Water	Larvae	Reduced survival	[57]
Litoria caerulea	LC	BIV	10^3 TCID50/mL; $10^{4.5}$ TCID50/mL	Water bath, Injection	Juvenile	Reduced survival, exposure type dependent effects on survival	[273] *
		BIV	10^3 TCID50/mL	Water bath, Injection, contact	Adults	No differences in survival	[273] *
Litoria inermis	LC	BIV	10^3 TCID50/mL	Injection	Adults	Tested negative for infection	[273] *
Litoria latopalmata	LC	BIV	10^3 TCID50/mL	Injection	Larvae	Reduced survival, renal, hepatic, splenic, and pulmonary necroses	[274] *
	LC	BIV	10^3 TCID50 mL	Injection	Juveniles	Reduced survival, renal, hepatic, splenic, and pulmonary necrosis	[274] *
Litoria rubella	LC	BIV	$10^{4.5}$ TCID50/mL	Injection	Adults	No differences in survival	[273] *
Notophtalmus viridescens	LC	ATV	na	contaminated Water	Larvae	Reduced survival	[128] *
	LC	FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival	[132]
Pseudacris brachyphona	LC	FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival	[132]
Pseudacris feriarum	LC	FV3-like isolate	10^3 PFU/mL	Water bath	Embryo through metamorphosis	Reduced survival	[136]

Table 1. *Cont.*

c. Effects of ranavirus on amphibian hosts							
Species	IUCN Status	Rv Strain	Dose	Type of Exposure	Life-Stage	Effect on Host	Reference
		FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival	[132]
Pseudacris triseriata	LC	FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival	[132]
Rana capito (Lithobates capito)	NT	FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival	[132]
Rana clamitans (Lithobates clamitans)	LC	FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival	[132]
Rana latastei	VU	FV3	2.25×10^6 pfu/mL (aliquots of 10 mL) from 70 mL of stock solution with 5.5×10^8 PFU/mL added to aged tap water		Larvae	Reduced survival	[124]
		FV3	4.5×10^6 pfu/mL (aliquots of 10 mL), 4.5×10^5, 4.5×10^4, 4.5×10^3, 4.5×10^2		Larvae	Dose dependent survival and survival rates	[124]
		FV3	na, but feeder tadpoles infected with 4.5×10^6 PFU/mL	Consuming infected carcasses	Larvae	Exposure type dependent survival rate	[124]
		FV3	4.5×10^4 PFU/mL, 4.5×10^6 PFU/mL (this was achieved by adding 2.796×10^8 PFU of FV3 to 615 mL of aged water, low exposure was a 1:100 dilution of this.)		Larvae	Dose dependent survival, effect of genetic diversity on survival	[207]
Rana palustris (Lithobates palustris)	LC	FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival	[132]
Rana pipiens (Lithobates palustris)	LC	FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival	[132]
Rana sphenocephala (Lithobates Sphenocephala)	LC	FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival	[132]
Rana sylvatica (Lithobates sylvatica)	LC	FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival	[132]
		FV3-like isolates (from wood frog and spotted salamander)	10 fold dilutions from 2.36×10^1 through 2.36×10^5 PFU/mL for wood frog isolate and 2.51×10^1 through 2.51×10^5 PFU/mL for spotted salamander isolate)	Water bath	Larvae	Dose dependent survival rates, no strain differences in infection	[105]
		FV3-like isolate	2.36×10^3 PFU/mL	Water bath	Larvae	Higher stress hormone levels	[105]
		FV3	67; 670; and 6,700 PFU/mL	Water bath	Larvae	Horizontal transmission the most likely means of FV3 transmission	[60]

Table 1. *Cont.*

c. Effects of ranavirus on amphibian hosts							
Species	IUCN Status	Rv Strain	Dose	Type of Exposure	Life-Stage	Effect on Host	Reference
Rana temporaria	LC	RUK 11, RUK 13, BUK 2, BUK 3	10^6 pfu, 10^4 pfu [all exposures standardized to 30 mL]	Water bath	Larvae	Dose and strain dependent effects on survival	[272]
		BIV, DFV, ECV, EHNV, FV3, GV6, PPIV, REV, and SERV	10^4 TCID50/mL	Water bath	Larvae	Strain and temperature dependent effects on survival	[277]
		BIV, DFV, ECV, EHNV, FV3, GV6, PPIV, REV, and SERV	10^4 TCID50/mL	Water bath	Juveniles	Strain dependent effects on survival	[277]
		RUK11 and RUK13	0.25 mL intraperitoneally, 0.25 subcutaneously both from $10^{6.2}$ and $10^{5.6}$ TCID 50/mL stock	Injection	Adults	Reduced survival	[125] **
Scaphiopus holbrookii	LC	FV3-like isolate	10^3 PFU/mL	Water bath	Embryo through metamorphosis	Reduced survival	[136]
		FV3, FV3-like isolate	10^3 PFU/mL	Water bath	Larvae	Reduced survival	[132]
Taudactylus acutirostris	CR	BIV	10^3 TCID50/mL	Water bath	Adults	Reduced survival	[273] *
Xenopus laevis	LC	FV3	1×10^4 PFU in 10 uL	Injection	Larvae	Developmental stage differences in immune response to FV3	[278]
		FV3	5×10^6 PFU in 100 uL	Injection	Adults	Developmental stage differences in immune response to FV3	[278]
		FV3	1×10^4 PFU in 10uL for injection; 10 uL of 1×10^5 PFU for oral ingestion; and 2 mL of 5×10^6 PFU for water bath	Water bath, Injection, oral ingestion	Larvae	Developmental stage dependent immune function and infection rates	[134]
		FV3	0.1 mL volume of 1×10^6 PFU	Injection	Juveniles	Developmental stage dependent immune function and infection rates	[134]
		FV3	1×10^6 to 5×10^6 PFU in 300 uL	Injection	Adults	Host cell differences in viral clearance	[279]
		FV3	1×10^6 PFU	na	Adults	Immunocompromised adults can transmit infection within 3 h	[134]
		FV3	10^6 PFU	Injection	Larvae & Adults	Developmental stage differences in immune response to FV3	[280]

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