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Are novel or locally adapted pathogens more devastating and why? Resolving opposing hypotheses

Erin L. Sauer[1,2] | Matthew D. Venesky[2,3] | Taegan A. McMahon[2,4] | Jeremy M. Cohen[2,5] | Scott Bessler[2] | Laura A. Brannelly[6,7] | Forrest Brem[8] | Allison Q. Byrne[9] | Neal Halstead[2,10] | Oliver Hyman[11] | Pieter T. J. Johnson[12] | Corinne L. Richards-Zawacki[6,13] | Samantha L. Rumschlag[14,15] | Brittany Sears[2] | Jason R. Rohr[2,16]

Correspondence
Erin L. Sauer, Department of Biological Sciences, University of Arkansas, 850 W. Dickson St. Fayetteville, AR 72701, USA.
Email: erinsauer10@gmail.com

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Abstract

There is a rich literature highlighting that pathogens are generally better adapted to infect local than novel hosts, and a separate seemingly contradictory literature indicating that novel pathogens pose the greatest threat to biodiversity and public health. Here, using *Batrachochytrium dendrobatidis*, the fungus associated with worldwide amphibian declines, we test the hypothesis that there is enough variance in "novel" (quantified by geographic and phylogenetic distance) host-pathogen outcomes to pose substantial risk of pathogen introductions despite local adaptation being common. Our continental-scale common garden experiment and global-scale meta-analysis demonstrate that local amphibian-fungal interactions result in higher pathogen prevalence, pathogen growth, and host mortality, but novel interactions led to variable consequences with especially virulent host-pathogen combinations still occurring. Thus, while most pathogen introductions are benign, enough variance exists in novel host-pathogen outcomes that moving organisms around the planet greatly increases the chance of pathogen introductions causing profound harm.

KEYWORDS
chytridiomycosis, coevolution, infectious disease, local adaptation, naïve host syndrome, pathogen pollution

INTRODUCTION

Human-facilitated pathogen dispersal (often termed pathogen pollution) has led to an increase in emerging infectious diseases over the last few decades (Cunningham et al., 2017) and is a major threat to global biodiversity and food security. Introduced pathogens can cause catastrophic animal (e.g. crayfish plague, avian malaria) and plant (e.g. chestnut blight, citrus greening) declines and economic losses (Anderson et al., 2004; Daszak et al., 2000). Pathogen pollution is also a primary threat to public health, as it has contributed to several recent deadly epidemics and pandemics (e.g. SARS-CoV-2) (Daszak et al., 2000; Morens et al., 2020).

Understanding how hosts respond to foreign or novel pathogens relative to local pathogens is necessary to predict and prepare for outbreaks of emerging pathogens, which are on the rise globally (Cunningham et al., 2017). However, there is a set of seemingly contradictory hypotheses on foreign/novel pathogens in the literature. The naïve host syndrome hypothesis asserts that hosts are especially vulnerable to novel pathogens because hosts have lower evolved immunological defences against these pathogens, resulting in high host mortality and host population suppression (Anderson et al., 2004; Carey et al., 1999; Lymbery et al., 2014; McKenzie & Peterson, 2012; Taraschewski, 2006). In contrast, there is also a very rich literature indicating that pathogens are generally better adapted to infect and replicate in local rather than foreign/novel host species (Bolnick & Stutz, 2017; Gandon & van Zandt, 1998; Johnson et al., 2021; Kaltz & Shykoff, 1998; Kawecki

For affiliations refer to page 8.

& Ebert, 2004; Lively & Dybdahl, 2000; Lively & Jokela, 1996; Lymbery et al., 2014; Morran et al., 2011; Parker et al., 2015; Strauss et al., 2012; Torchin et al., 2003; Torchin & Mitchell, 2004). Hence, the naïve host syndrome suggests that pathogens are able to invade novel hosts because of a lack of co-evolutionary history, whereas local adaptation suggests that pathogens are better able to invade local hosts because of their co-evolutionary history (Bolnick & Stutz, 2017; Gandon & van Zandt, 1998; Johnson et al., 2021; Kaltz & Shykoff, 1998; Lively & Dybdahl, 2000; Lively & Jokela, 1996; Lymbery et al., 2014; Morran et al., 2011; Parker et al., 2015; Strauss et al., 2012; Torchin et al., 2003; Torchin & Mitchell, 2004) (Figure 1). Rarely do local adaptation and naïve host syndrome studies cite one another or acknowledge their ostensibly mixed messages. This may be because the local adaptation literature largely focuses on the local-to-foreign/novel gradient as it pertains to pathogen adaptations, whereas the naïve host syndrome literature focuses on the local to foreign/novel gradient from a host perspective (i.e., immunity). However, host-pathogen outcomes are a product of host-pathogen interactions and thus both the hosts and the pathogens must be considered when trying to understand these complex relationships.

Here, we hypothesize that pathogens are generally better adapted to infect and replicate in local hosts, resulting in deadlier host-pathogen outcomes. However, we also hypothesize that enough variance exists in novel host-pathogen outcomes (i.e. considerable overlap with novel outcomes) to pose substantial risk that an especially virulent host-pathogen combination (i.e. one that is more virulent than the average local interaction) will occur given sufficient pathogen introduction events (Cohen et al., 2018; Golas et al., 2021; Lloyd-Smith et al., 2005; Reeder et al., 2012; Torchin & Mitchell, 2004), even if there is no greater variance in novel than local host-pathogen outcomes (Figure 1). Thus, we postulate that pathogen pollution is dangerous because, as pathogen introductions occur with increasing frequency, the probability increases that (i) a particularly deadly strain of a pathogen will devastate a naïve host population, (ii) a particularly vulnerable host population will be exposed to a new pathogen, and (iii) especially virulent host-pathogen combinations will occur (Figure 1). Researchers might be biased towards the assumption that foreign/novel pathogens are often devastating because they predominantly only observe pathogen introductions that establish and are problematic, even though most introductions might fail because of a lack of co-evolutionary history (Torchin et al., 2003; Torchin & Mitchell, 2004).

Amphibian-*Batrachochytrium dendrobatidis* (Bd) interactions are ideal to address these hypotheses for several reasons. Bd spread globally in the early 20th century, possibly with the expansion of trade (O'Hanlon et al., 2018), and this is an invasive pathogen in much of its range with host–parasite outcomes that vary greatly in virulence (Fisher & Garner, 2020; McDonald et al., 2020; Voyles et al., 2018; Waddle et al., 2019), and with higher Bd loads generally leading to greater host mortality (Fisher et al., 2012; Fu & Waldman, 2019; Greischar & Koskella, 2007; Scheele, Pasmans, et al., 2019). Bd represents one of the most urgent ecological disasters on the planet as it is implicated in the declines and extinctions of over 500 amphibian species around the globe (Scheele,

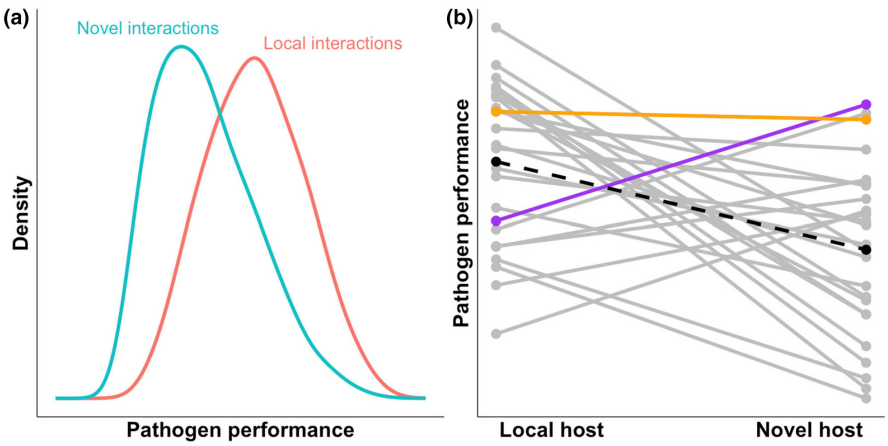

FIGURE 1 Local adaptation by the pathogen should result in pathogens being better adapted to invade and replicate within local hosts compared to novel hosts, on average. (a) Density plot showing theoretical distributions of pathogen performance when pathogens are locally adapted to their hosts, demonstrating that mean pathogen performance is higher during interactions with local hosts (solid red curve) relative to novel hosts (solid blue curve). (b) Theoretical changes in performance that a single pathogen might experience when shifting from a local to a random novel host population (each grey line). Mean performance (dashed black line) is lower in the novel host because the pathogen is not locally adapted to invade it. However, certain stochastic host–pathogen interactions can result in a particularly deadly pathogen being introduced to a novel host (orange line) or a particularly vulnerable host being exposed to novel pathogen (represented by the solid purple line). Panel b is modified from Kaltz and Shykoff (1998). Both panels were made using the same randomly generated datasets of theoretical host-pathogen outcomes. Each curve in panel a was generated using 10,000 points while panel b displays a random subset of 25 points for simplicity.

Pasmans, et al., 2019) and can even adversely affect co-occurring non-amphibian species (Brannelly et al., 2012; McMahon et al., 2013; Nordheim et al., 2021). Despite the global epizootic of Bd, there is also considerable evidence of isolation by distance among Bd isolates and Bd-infected host populations (Addis et al., 2015; Albert et al., 2015; Bai et al., 2012; Banks et al., 2020), indicating that distant Bd isolates are probably not experienced regularly by local host populations. In many regions, Bd is considered endemic (Venesky et al., 2014), with some evidence that this endemicity is driven by amphibian hosts adapting to local Bd strains (Fisher & Garner, 2020; McDonald et al., 2020; Voyles et al., 2018; Waddle et al., 2019). While many host-pathogen systems exhibit a trade-off between virulence and transmission, field and laboratory evidence suggest transmission of Bd is not significantly limited by virulence, at least in part because it is a multi-host system where vulnerable hosts can be continuously infected by pathogen populations maintained by more resistant or tolerant hosts (de Castro & Bolker, 2005; Fisher et al., 2012; McMahon et al., 2013). Given that the pathogen is not virulence-limited, movement of Bd has the potential of exposing host populations to highly virulent Bd isolates. Further, higher Bd loads generally lead to greater host mortality, suggesting that mortality is likely a suitable measure for pathogen performance in this system (Fisher et al., 2012; Fu & Waldman, 2019; Greischar & Koskella, 2007; Scheele, Pasmans, et al., 2019).

To test the hypotheses described above, we identified six populations (five species) of toads from across North America (Arizona, California, Louisiana, Ohio, Tennessee, and Quebec, Canada; Table S1) and, in a "common-garden" experiment, measured host mortality and infection prevalence (proportion of toads infected) and abundance (average number of pathogen zoospores per exposed toad based on a standardized swabbing effort) when the toads were exposed to their local strain of a chytrid fungus, *B. dendrobatidis* (Bd), five non-local strains, and a sham control (Table S2). We define a foreign/novel strain as one that is not from the same host species locale. To complement the common-garden experiment, we assembled a host mortality dataset of 84 experiments from 26 Bd studies that included 23 amphibian species, 22 unique Bd strains, and wide variability in local and novel host–parasite interactions. Using this dataset, we conducted a global-scale meta-analysis to test for evidence of local adaptation, particularly susceptible host populations, and especially deadly Bd strains and host-Bd strain combinations.

Importantly, pathogen foreignness or novelty (hereafter referred to as novelty) is a continuous variable, can be difficult to define, and can be measured in several ways (Kawecki & Ebert, 2004). For example, host populations can have 100% adaptive immunity to a pathogen or be entirely susceptible with little-to-no cross-protection from related pathogens and uniform age-at-first-infection distributions. Likewise, pathogen populations can be 100% to 0% infective to a host population. Additionally, new strains of a pathogen can be novel even if a pathogen species is endemic. For example, during the recent COVID pandemic, many people were exposed to early strains of SARS-CoV-2, but those exposures offered little resistance to later strains, such as the delta and omicron strains (Chavda et al., 2022), and SARS-CoV-2 reinfection can even increase risk of death and serious complications (Bowe et al., 2022). So, the fact that early strains of SARS-CoV-2 were found in a location did not mean that newer strains were not particularly deadly to individuals in those same populations. Hence, novelty is often a product of the degree of evolutionary history a host population has with a particular pathogen or pathogen strain and novel strains can appear over short periods of time depending on the generation time of and the selection pressures on the pathogen.

In this study, we estimate pathogen novelty to a host population in three different ways. First, we estimate the geographic distance between the host and pathogen collection sites and assume that the greater the distance between the two, the more novel (i.e., less evolutionary history) the pathogen might be to the host population. However, geographic distance might not be as important as phylogenetic distance in determining the resistance of a host to a new pathogen strain (Dennehy et al., 2006; Farrell & Davies, 2019; Guth et al., 2019; Longdon et al., 2014, 2015). This is because two distant pathogen isolates or hosts might be closely related and thus might be less unique or novel than predicted by geographic distance alone. Thus, the second variable we use as a proxy of novelty is the estimated phylogenetic distance between the non-local Bd isolate and the local isolate, with greater phylogenetic distance representing greater novelty of the isolate to the host. Finally, the third variable we test is the phylogenetic distance between the local host species and the host species found at the location of collection, with greater phylogenetic distance representing greater novelty of the host to the Bd isolate. Although it would also be nice to know the duration of time a given host and pathogen isolate have interacted, like for most host–parasite systems, this information is unknown for the host populations and Bd isolates that we studied.

METHODS

Common garden experiment

Experimental design and animal husbandry

Metamorphic toads (Bufonidae) collected from Arizona, California, Louisiana, Ohio, and Tennessee, USA, (see Table S1 for specific collection locations and times, experimental times, and the five host species) were shipped overnight to Tampa, Florida. Given that all the toads

were recent metamorphs, they were all of similar age. Although the experiment was designed to cross six host populations and five host species with six Bd strains (a 6 × 6 design), we could not collect enough Quebec (QC) hosts and the experiment was reduced to a 5 × 6 design with five species of hosts. Hereafter, we refer to these five host populations/species as host species. Identical protocols were employed for each host and pathogen isolate to minimize variation (see Supplemental Methods and Table S1 for details). To eliminate any existing Bd infections from field-collected animals, we subjected all animals to a 10-day 30°C Bd clearance treatment (Supplemental Methods) (Chatfield & Richards-Zawacki, 2011; McMahon et al., 2014). Toads were then maintained individually in containers at 18.5°C for a 7–10 day acclimation period (Raffel et al., 2013). We fed toads ad libitum with vitamin- and mineral-dusted crickets and provided a fresh container and bedding twice per week (Supplemental Methods).

We crossed 5 closely related North American toad species ($Host_{AZ}$, $Host_{CA}$, $Host_{LA}$, $Host_{OH}$, $Host_{TN}$) with 6 Bd strains (Bd_{AZ}, Bd_{CA}, Bd_{LA}, Bd_{OH}, Bd_{TN}, Bd_{QC}; Table S2) and one sham control (artificial spring water; ASW) for a total of 35 experimental treatment combinations. LA, OH, and TN strains were isolated from wild amphibians 1–2 years prior to host collection at those locals. QC, CA, and AZ strains were pulled from cryopreservation from the Bd isolate cryopreservation library of Dr. Joyce Longcore. The number of replicates per treatment varied between 6 and 18 because of variations in the availability of toads across the populations (Table S1). An experimental unit was an individual toad. Each toad population was split into seven treatments (6 Bd strains and one ASW sham). Mortality was monitored daily. All toads were weighed before the Bd exposure, and again at death or at 70 days post-exposure. At the end of the experiment, all remaining toads were swabbed for Bd load, euthanized with phosphate-buffered benzocaine, and stored at −20°C.

Bd isolation, quantification, and sequencing

All toads received 1.5×10^5 zoospores of their respective strain in a 5–8 mL inoculum pipetted onto their dorsal surface. The inoculum was composed of ASW that was rinsed from 1% tryptone agar plates that were either Bd+(strain-specific Bd exposure) or Bd-free (control, sham exposure). All toads were swabbed before, 2 weeks after, and 70 days after exposure or upon mortality. During each swabbing event, a sterile swab was passed over the ventral surface from snout to vent and each leg from hip to toe five times before being frozen at −80°C. Bd DNA was extracted from the samples using Prepman Ultra, and intergenic transcribed spacer 1 (ITS1) region copy numbers were quantified using quantitative-PCR (Boyle et al., 2004). To compare Bd loads across strains with differing ITS1 copy numbers, we transformed our qPCR results to zoospore equivalents (see Supplemental Methods and Results) (Longo et al., 2013). See the Supplemental Methods and Results for details on Bd sequencing and genomic analysis. Importantly, none of the isolates collected are known to occur in the other host species and our phylogeny reinforces the distinctness among these isolates (Figure S4).

Statistical analysis

All analyses were conducted in R 4.1.0 (R Core Team, 2013) and significance was based on log-likelihood ratio tests. To test if local pathogens are more deadly than novel pathogens, we conducted a Cox-proportional hazards survival analysis in which the response was mortality and the predictors were the additive terms: distance, host species, Bd strain, and host mass (survival package) (Therneau, 2014). Distance was a continuous variable defined as the log-linear Euclidean distance between the collection location of the host and Bd strain (log10(km)) (Johnson et al., 2021). We conducted a generalized linear model with a normal error distribution to determine the effect of the same predictors on Bd zoospore load (adjusted for copy number and $\log_{10}$ transformed) 2 weeks after exposure or on day of death if an animal died before day 14 (base package). This GLM included both infected and uninfected animals and a fixed effect for swab date. We conducted a GLM with a binomial error distribution to determine the effect of the same predictors on Bd prevalence rather than Bd load (stats package). Finally, we tested for effects of host species and pathogen novelty on Bd tolerance of infection (damage per pathogen) by repeating the aforementioned survival analysis with the inclusion of an interaction term between host species and Bd zoospore load (adjusted for copy number and $\log_{10}$ transformed) and an interaction term between distance and Bd zoospore load (Grogan et al., 2023; Rohr et al., 2010). The fits of all GLMs were assessed using residual plots and curvature tests in the car package. In the Cox regression and all GLM models, we controlled for potential effects of host mass (g) as a covariate.

To test the fit of alternative measures of strain novelty, the survival, Bd zoospore load, and Bd prevalence models described above were competed against (i.e., comparing AICs) identical models with either the inclusion of pairwise host or Bd strain phylogenetic distances or a simple two-level categorical predictor representing strain novelty to the host (novel or local) and the exclusion of geographic distance. The phylogenetic distance models examined a subset of the data, excluding treatments where hosts were exposed to the QC Bd strain as that location did not have a representative host in the experiment or an available Bd strain sequence. Those two

models were compared to models of the same subset that included geographic distance instead of host pairwise or Bd strain pairwise phylogenetic distances.

Global Bd meta-analysis

We conducted a meta-analysis to standardize and compare results across multiple experiments to draw broadly applicable conclusions regarding the effects of distance and host taxa on the outcomes of Bd infections. We used a subset of the data published in Sauer et al. (2020), restricting the database to metamorphic/juvenile amphibians for consistency. This refined database included 23 amphibian species from 7 families and 22 Bd strains (Database S1). Host species and strains were collected from North and Central America and Europe (see Supplemental Information for more details regarding data collection). The final database consists of 84 effect sizes from 26 Bd studies.

We analysed the database using a mixed-effects meta-analysis to determine the effect of distance (log-linear Euclidean distance between the collection location of the host and Bd strain; $\log_{10}$(km)) and host taxonomic group (superfamily, four-level categorical variable) on host mortality (blme package) (Chung et al., 2013). Mortality was measured using log odds ratios from Sauer et al. (2020) (where a log odds ratio significantly greater than zero represents greater mortality in the Bd-exposed than control group). We controlled for $\log_{10}$-transformed Bd zoospore dose by including it as a fixed effect and accounted for between-study random effects as well as non-independence among Bd strains by including Bd strain and host species as random intercepts in our models. For the full list of host species included in the meta-analysis, and more details regarding effect sizes, see Supplemental Methods and Table S5 for summary information. Model prediction plots were made using the predict function and the original conditions of the datasets.

RESULTS

The laboratory experiment revealed that geographic distance between the host and Bd collection locations was negatively associated with host mortality ($\beta = -0.06$, SE = ±0.03, $z = -2.10$, $p = 0.04$; Figure 2a; Table S3), Bd prevalence ($\beta = -0.53$, SE = ±0.23, $z = -2.33$, $p = 0.02$, Table S5), and pathogen abundance on the host ($\beta = -0.03$, SE = ±0.02, $z = -2.01$, $p = 0.045$, Figure S1; Table S4). However, geographic distance was not associated with tolerance to Bd (distance*Bd load: $\chi^2 = 0.76$, $p = 0.38$; Table S7). Geographic distance was also negatively associated with host mortality in the global-scale meta-analysis (while accounting for among-study variance, Bd strain, and host taxonomic group; $\beta = -0.77$, SE = ±0.25, $t = -3.05$, $p < 0.01$; Figure 2b; Table S6).

While local host-pathogen interactions generally result in worse outcomes for hosts, there was substantial variation among host-pathogen outcomes in both the experiment and meta-analysis. In the experiment, we found significant variation in mortality, infection success, and pathogen load among Bd strains (main effect of strain identity on mortality: $\chi^2 = 61.05$, $p < 0.001$; prevalence: $\chi^2 = 56.98$, $p < 0.001$; pathogen load: $\chi^2 = 351.65$, $p < 0.001$; Figure 3; Figure S2). Specifically, when averaging across host species, Bd from Louisiana was most deadly, most likely to cause infection, and produced the highest infection burdens (Figure 3; Figure S2). We also found significant variation in mortality, prevalence, and pathogen load among host species (main effect of host on mortality: $\chi^2 = 136.22$, $p < 0.001$; prevalence: $\chi^2 = 9.95$, $p = 0.04$; and pathogen load = $\chi^2 = 12.36$, $p = 0.01$; Figure 3; Figure S2). Specifically, when averaging across Bd strains, toads from Arizona and Tennessee had the highest mortality and infection prevalence (Figure S2). Further, we found variation in tolerance among hosts, specifically, toads from California and Ohio were more tolerant than toads from Tennessee, Arizona, and Louisiana, but all other pairwise comparisons were similar (Tukey pairwise comparisons: $p < 0.05$; Table S7; Figure S3). Consistent with the experimental results, in the meta-analysis, we found significant variation in mortality among taxonomic groups with species from superfamily Bufonoidea being especially susceptible to Bd-induced mortality ($\chi^2 = 29.92$, $p < 0.001$; Figure 3).

Models competing alternative measures of novelty, including geographic distance, host or Bd strain pairwise phylogenetic distances, or a simple two-level categorical predictor representing "novel" or "local" interactions were found to either be similar in fit (ΔAIC <2; Table S8) or the model with geographic distance better fit the data (ΔAIC >2; Table S8). Hence, geographic distance appears to be the best proxy of novelty in this case because it best predicted Bd transmission and virulence to hosts. Because no alternative predictors improved model fits, hereafter we present only the results of models including geographic distance as the metric of Bd strain novelty to the host. Results of these alternative models are described in Tables S9–S17.

Importantly, we compared fits of all models from the experiment with and without the inclusion of a two-way interaction between host and Bd identity and determined that models without the interaction fit better and thus did not include the interaction term in any model (ΔAIC >7). This means that the main effects of host and Bd strain are more important than any potentially idiosyncratic interactions between these two factors. Our proportional mortality hazard model from the laboratory experiment revealed that host species accounted for the most variation in the model ($\chi^2 = 140.91$, $df = 4$, $p < 0.001$), followed by Bd strain ($\chi^2 = 60.22$, $df = 5$, $p < 0.001$) and distance ($\chi^2 = 4.19$, $df = 1$, $p = 0.0406$). Finally, diagnostic tests revealed that the models were good fits to the data and

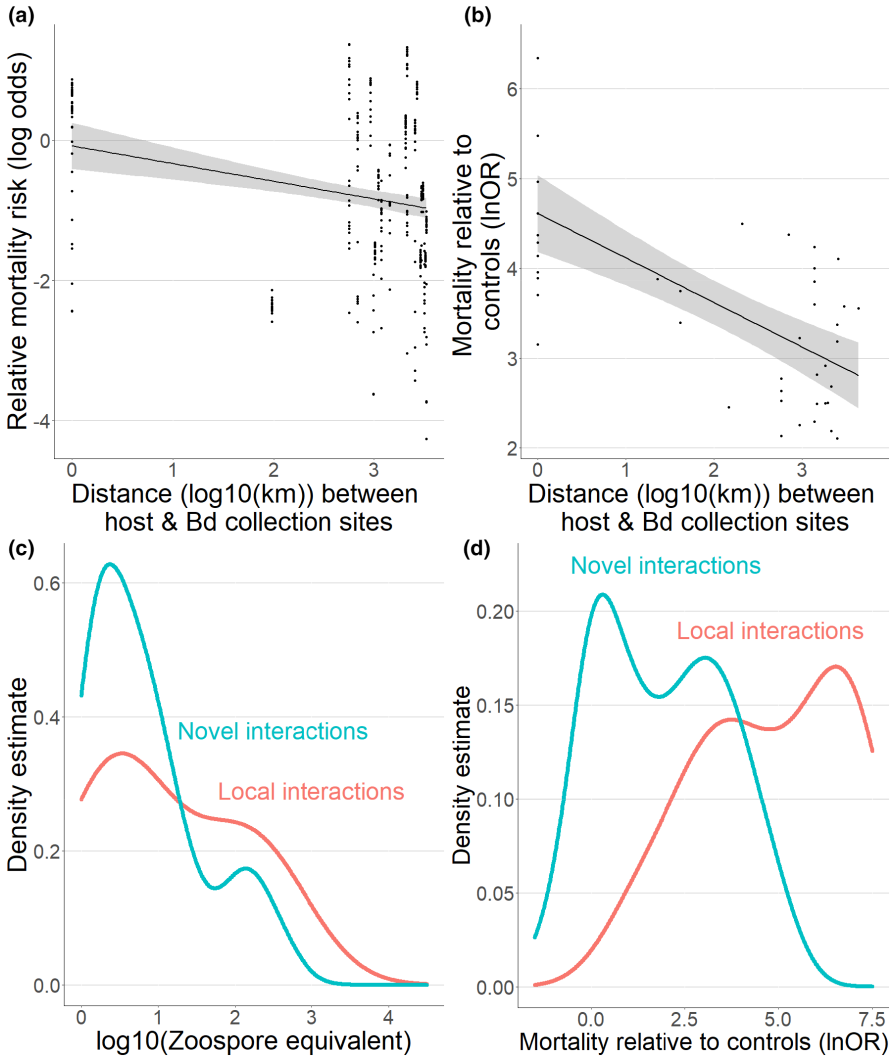

FIGURE 2 Model prediction plots showing the significant negative correlations between distance between amphibian host and *Batrachochytrium dendrobatidis* (Bd) strain collection locations and host mortality. (a) Cox-proportional hazards model of experimental exposures of five North American toad species to six North American Bd strains ($\beta = -0.06$, $z = -2.10$, $p = 0.04$). (b) Mixed-effects meta-analysis of Bd experiments using the Sauer et al. (2020) database ($\beta = -0.77$, $t = -3.05$, $p = 0.01$). Points are predicted model values and grey shading areas associated 95% (a) confidence and (b) credible bands. (c) Relative distributions of Bd load for novel and local interactions from the laboratory experiment showing that, on average, Bd loads were higher on local hosts (red) than on novel hosts (blue). (d) Relative distributions of Bd-induced mortality for novel and local interactions from the meta-analysis database showing that, on average, mortality was higher in local hosts (red) than in novel hosts (blue).

model assumptions were not violated. Additionally, there was no difference in the variation of the raw days alive or log zoospore load data between local and novel interactions (Levene's test: $F_1 = 0.545$ $p = 0.4609$, $F_1 = 0.1759$ $p = 0.6752$, respectively).

DISCUSSION

Our results demonstrate that Bd strains are typically more successful at infecting and replicating, and thus causing mortality, in local than novel hosts, supporting local adaptation or the hypothesis that pathogens are best adapted to take advantage of their local hosts (Johnson et al., 2021; Kaltz & Shykoff, 1998; Kawecki & Ebert, 2004; Lively & Dybdahl, 2000; Lively & Jokela, 1996; Lymbery et al., 2014; Morran et al., 2011; Strauss et al., 2012; Urban et al., 2020). However, the rise of catastrophic modern pandemics from pathogen pollution has led to speculation that introduced pathogens are especially devastating to naïve hosts (Anderson et al., 2004; Carey et al., 1999; Cunningham et al., 2003; Mastitsky et al., 2010). While we did find substantial variation among host-pathogen outcomes, there was no evidence that more foreign or novel host-pathogen interactions generally cause especially high mortality. Thus, the major concern with pathogen pollution is not that naïve hosts are especially vulnerable; the concern is that increasing introductions of novel pathogens increases the chance that virulent pathogens will encounter highly

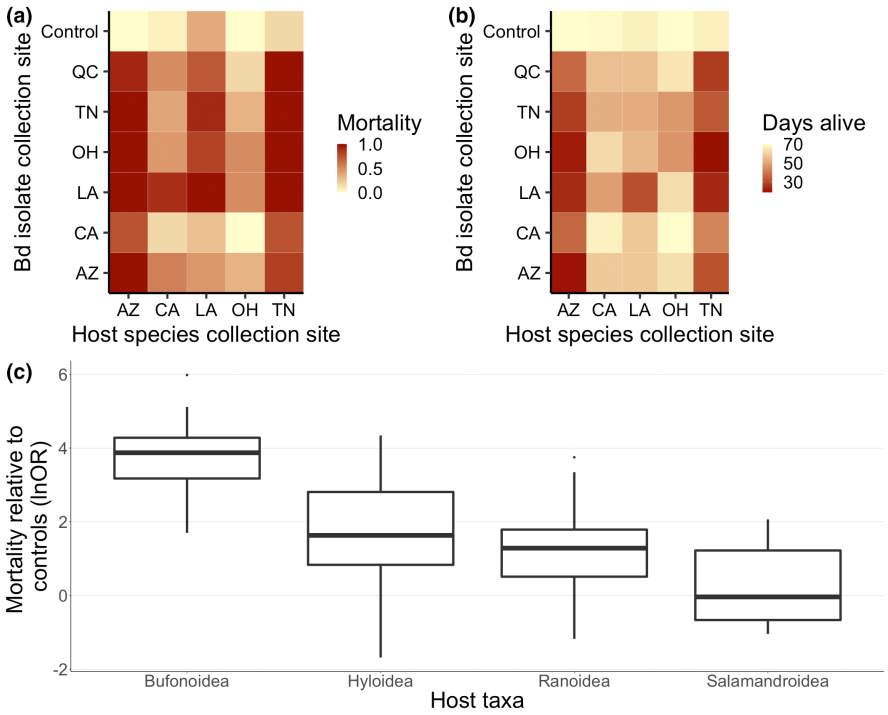

FIGURE 3 Experimental exposures of five North American toad species to six North American *Batrachochytrium dendrobatidis* (Bd) strains revealed strong effects of host species and Bd strain on host mortality. Heat maps show treatment-level (a) host mortality probability and (b) mean days alive. There were certain combinations of Bd strains and host species that resulted in extremely rapid mortality (e.g. host from Tennessee combined with Bd from Ohio). (c) Box plot showing evidence of host variation in susceptibility to Bd across broader taxonomic groups from the mixed-effects meta-analysis of Bd experiments.

vulnerable hosts. This perception that novel and introduced pathogens are especially deadly might be because of detection bias—most introduced pathogens probably go undetected because low pathogen fitness in novel host populations reduces the likelihood of establishment (Torchin et al., 2003; Torchin & Mitchell, 2004). However, there are >8000 species of amphibians and a multitude of Bd strains and thus the full strength of local adaptation and the scope of variation in host-strain outcomes remains unclear in this system.

Given that local versus novel interactions is a continuum and can be difficult to define (Dennehy et al., 2006; Farrell & Davies, 2019; Guth et al., 2019; Longdon et al., 2014, 2015), we measured novelty several ways. We compared the fits of pairwise (1) geographic distances between populations, (2) phylogenetic distances between host species, and (3) phylogenetic distances between fungal isolates on mortality, infection success, and pathogen load. Our models revealed that geographic distance accounted for more variation in host-pathogen outcomes than phylogenetic distance between fungal isolates or host species. Although other studies detected effects of host phylogenetic distance on pathogen virulence and transmissibility (Dennehy et al., 2006; Farrell & Davies, 2019; Guth et al., 2019; Longdon et al., 2014, 2015), they did not include geographic distance as an alternative explanation and we suspect that phylogenetic distance and geographic distance might often be correlated. Importantly, two distantly related pathogen species might actually be closely related in host invasion mechanisms through convergent evolution. Thus, functional relatedness rather than phylogenetic relatedness might be a more ideal metric for predicting the outcomes of species interactions (Mahon et al., 2021), such as pathogen virulence and transmissibility to hosts. We encourage future studies to better capture functional similarity but recognize that this is an even more challenging variable to quantify than phylogenetic similarity or geographic distance.

We found significant variation in mortality, infection success, and pathogen load among Bd strains (Figure 3; Figure S2), consistent with other studies showing variation in the traits of Bd strains within the global panzootic lineage (Becker et al., 2017; Lambertini et al., 2016). Specifically, when averaging across host species, Bd from Louisiana was most deadly, most likely to cause infection, and produced the highest infection burdens (Figure 3; Figure S2). We also found significant variation in mortality, prevalence, pathogen load, and tolerance among host species (Figure 3; Figure S2). Specifically, when averaging across Bd strains, toads from Arizona and Tennessee had the highest mortality and infection prevalence (Figure S2) and toads from Tennessee, Arizona, and Louisiana were least tolerant (Figure S3). Rapid mortality occurred in our experiment when highly susceptible hosts were exposed to especially virulent Bd

strains. Specifically, toads from Arizona and Tennessee died an average of 29 days sooner when exposed to Bd from Louisiana or Ohio relative to any other novel host-pathogen interactions (Figure 3b; Figure S3). Further, our meta-analysis revealed that species from superfamily Bufonoidea (toads and relatives) were especially susceptible to Bd-induced mortality compared to other host taxa, confirming previous research (Scheele, Foster, et al., 2019) (Figure 3; Figure S2).

The only scenario that would not make the movement of pathogens problematic is if there was less variance in novel than local host-pathogen outcomes and evidence of local pathogen adaptation (i.e., local pathogens are better at infecting hosts and deadlier), which was not shown here. Rather, we did not detect a difference in variance between novel and local host-pathogen outcomes. However, we are cautious to conclude that there is no difference in nature because we only tested 30 of potentially endless host genotype-by-pathogen genotype interactions. Importantly, greater variance in novel than local host-pathogen outcomes is not absolutely necessary for the movement of pathogens to be problematic as long as there is considerable overlap between the local and novel parasite infectivity and virulence distributions, as was shown here. If this is the case, then the movement of pathogens can increase (1) pathogen exposure for particularly susceptible host species and populations, (2) the chances of hosts being exposed to particularly virulent pathogen strains, and (3) the likelihood of particularly deadly host-pathogen combinations (genotype-by-genotype interaction), even though, on average, local parasites are significantly more infectious and virulent than novel parasites.

By combining a continental-scale factorial experiment with a global-scale meta-analysis, we show that local host-pathogen interactions typically resulted in higher host mortality, greater infection success, and higher pathogen loads. However, we also found that novel host-pathogen interactions do not always result in low mortality, infection success, and pathogen loads. There was substantial variation in novel host-pathogen outcomes, including pairings of especially vulnerable hosts and especially deadly pathogen strains that resulted in extremely rapid mortality. In fact, the host- and strain-level effects accounted for more variation in our models than any metric of strain novelty. Therefore, frequent introduction of novel strains increases the risk of especially vulnerable hosts encountering especially deadly pathogens despite pathogens being better adapted to invade and replicate in local hosts. Therefore, we provide support for both the local adaptation and naïve host syndrome hypotheses, highlight how the two hypotheses are complementary rather than conflicting, and emphasize the need for greater integration of these hypotheses and their associated semi-disparate literature. Stochastic encounters between deadly pathogen strains and vulnerable hosts will continue to rise as human connectivity and encroachment on and degradation of wildlife habitat increase. Thus, it is imperative that policymakers mitigate the risk of pathogen spillover and dispersal (Aguirre et al., 2021; Altmann & Kolby, 2017). Policies regarding surveillance, biosafety, and security of wildlife and livestock trade that utilize One and Planetary Health approaches are especially promising for reducing risk (Aguirre et al., 2021; Cunningham et al., 2017; Rohr et al., 2023).

AUTHOR CONTRIBUTIONS

The experiment was designed by MDV and JRR and implemented by MDV and ELS. The meta-analysis was designed by ELS. Data collection for the meta-analysis was conducted by ELS, MDV, TAM, JMC, SB, NH, BS, and JRR. Toad populations were provided by LAB, FB, OH, PTJ, CLR, and SLR. Statistical analyses for the experiment and meta-analysis were conducted by ELS. Copy number quantification was conducted by ELS. Bd genomic analysis was conducted by AQB. The first draft of the manuscript was predominantly developed by ELS with major contributions from JRR and MDV. All authors contributed substantially to the revisions. JRR provided funds and space for the project.

AFFILIATIONS

[1]Department of Biological Sciences, University of Arkansas, Fayetteville, Arkansas, USA
[2]Department of Integrative Biology, University of South Florida, Tampa, Florida, USA
[3]Department of Biology, Allegheny College, Meadville, Pennsylvania, USA
[4]Biology Department, Connecticut College, New London, Connecticut, USA
[5]Department of Ecology and Evolutionary Biology, Yale University, New Haven, Connecticut, USA
[6]Ecology and Evolutionary Biology, Tulane University, New Orleans, Louisiana, USA
[7]Faculty of Veterinary and Agricultural Sciences, University of Melbourne, Melbourne, Victoria, Australia
[8]Biology Department, University of Memphis, Memphis, Tennessee, USA
[9]Department of Environmental Science, Policy, and Management, University of California, Berkeley, California, USA
[10]Wildlands Conservation, Tampa, Florida, USA
[11]Biology Department, James Madison University, Harrisonburg, Virginia, USA
[12]Ecology and Evolutionary Biology, University of Colorado, Boulder, Colorado, USA
[13]Department of Biological Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
[14]Department of Biology, Miami University, Oxford, Ohio, USA
[15]U.S. Environmental Protection Agency, Office of Research and Development, Center for Computational Toxicology and Exposure, Great Lakes Toxicology and Ecology Division, Duluth, Minnesota, USA
[16]Department of Biological Sciences, University of Notre Dame, South Bend, Indiana, USA

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DATA AVAILABILITY STATEMENT

The data and code supporting the results are publicly archived on GitHub: https://github.com/erinsauer/Sauer-et-al.-Bd-novelty and on Dryad: https://doi.org/10.5061/dryad.jwstqjqhp.

ORCID

Erin L. Sauer https://orcid.org/0000-0002-8339-6498
Laura A. Brannelly https://orcid.org/0000-0003-2975-9494
Pieter T. J. Johnson https://orcid.org/0000-0002-7997-5390

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SUPPORTING INFORMATION

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

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