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

Erin Sauer[1], Matthew Venesky[2], Taegan McMahon[3], Jeremy M. Cohen[4], Scott Bessler[5], Laura Brannelly[6], Forest Brem[7], Neal Halstead[8], Oliver Hyman[9], Pieter Johnson[10], Corinne Richards-Zawacki[11], Samantha Rumschlag[12], Brittany Sears[5], and Jason Rohr[13]

[1]University of Arkansas Fayetteville
[2]Allegheny College
[3]Connecticut College
[4]Yale University
[5]University of South Florida
[6]The University of Melbourne
[7]Memphis State University
[8]Wildlands Conservation
[9]James Madison University
[10]University of Colorado at Boulder
[11]University of Pittsburgh
[12]US Environmental Protection Agency
[13]University of Notre Dame

June 13, 2023

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 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 strikingly variable consequences with the greatest risk occurring when susceptible hosts and virulent strains interacted. 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.

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 (Daszak *et al.* 2000; Anderson *et al.* 2004). Pathogen pollution is also a primary threat to public health, as it has contributed to several recent deadly epidemics and pandemics (e.g. SARS CoV2) (Daszak *et al.* 2000; Morens *et al.* 2020).

Understanding how hosts respond to novel 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 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 defenses against these pathogens, resulting in high host mortality and host population suppression (Carey *et al.*1999; Anderson *et al.* 2004; Taraschewski 2006; McKenzie & Peterson 2012; Lymbery *et al.* 2014). In contrast, there is also a very rich literature indicating that pathogens are generally better adapted to infect and replicate in local rather than novel host species (Lively & Jokela 1996; Gandon & Van Zandt 1998; Kaltz & Shykoff 1998; Lively & Dybdahl 2000; Torchin *et al.* 2003; Torchin & Mitchell 2004; Morran *et al.* 2011; Strauss *et al.* 2012; Lymbery*et al.* 2014; Parker *et al.* 2015; Bolnick & Stutz 2017; Johnson *et al.* 2021). 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 (Lively & Jokela 1996; Gandon & Van Zandt 1998; Kaltz & Shykoff 1998; Lively & Dybdahl 2000; Torchin *et al.* 2003; Torchin & Mitchell 2004; Morran *et al.* 2011; Strauss*et al.* 2012; Lymbery *et al.* 2014; Parker *et al.*2015; Bolnick & Stutz 2017; Johnson *et al.* 2021) (Figure 1). Rarely do local adaptation and naïve host syndrome studies cite one another or acknowledge their ostensibly mixed messages.

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 to pose substantial risk that an especially virulent host-pathogen combination will occur given sufficient pathogen introduction events (Torchin & Mitchell 2004; Lloyd-Smith *et al.*2005; Reeder *et al.* 2012; Cohen *et al.* 2018; Golas*et al.* 2021). 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 (Fig. 1). Researchers might be biased towards the assumption that 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 20$^{\text{th}}$ century, possibly with the expansion of trade (O'Hanlon *et al.* 2018), and thus is an invasive pathogen in much of its range with host-parasite outcomes that vary greatly in virulence. 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*et al.* 2019b) and can even adversely affect co-occurring non-amphibian species (Brannelly *et al.* 2012; McMahon *et al.* 2013; Nordheim *et al.* 2021). Further, Bd is considered endemic in many regions (Venesky *et al.* 2014), with some evidence that this endemicity is driven by amphibian hosts adapting to local Bd strains (Voyles *et al.* 2018; Waddle *et al.* 2019; Fisher & Garner 2020; McDonald *et al.* 2020). While many host-pathogen systems exhibit a trade-off between virulence and transmission, field and laboratory evidence suggest transmission is not significantly limited by virulence, at least in part due to non-amphibian reservoir hosts (Fisher *et al.* 2012; McMahon *et al.* 2013). Further, high Bd loads lead to greater host mortality, suggesting that mortality is likely a suitable measure for pathogen performance in this system (Greischar & Koskella 2007; Fisher *et al.* 2012; Fu & Waldman 2019; Scheele *et al.* 2019b).

To test the hypotheses described above, we identified six populations 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 and abundance when the toads were exposed to their local strain of a chytrid fungus, *Batrachochytrium dendrobatidis* (Bd), five non-local strains, and a sham control (Table S2). We define a novel strain as one that is not from the same host population. 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.

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) were shipped overnight to Tampa, Florida. Although the experiment was designed to cross six host populations with six Bd strains (a 6x6 design), we could not collect enough Quebec (QC) hosts and the experiment was reduced to a 5x6 design. Breeding times varied across collection locations and so we used a randomized block design in which identical protocols were employed 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. 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 variation 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 d 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 and quantification

All toads received 1.5 x 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 either were Bd+ (strain specific Bd exposure) or Bd-free (control, sham exposure). All toads were swabbed before, two weeks after, and 70 d 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 -80º 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).

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) two 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 (stats package). In the Cox regression and both GLM models, we controlled for potential effects of host mass (g) as a covariate.

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.(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 analyzed 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, a metric for host-pathogen novelty (hereafter, distance), was negatively associated with host mortality (β = -0.06, SE = $\pm$0.03, z = -2.10, p = 0.04; Figure 2A & Table S3), Bd prevalence (β = -0.53, SE = $\pm$0.23, z = -2.33, p = 0.02, Table S5), and pathogen abundance on the host (β = -0.03, SE = $\pm$0.02, z = -2.01, $p <$ 0.05, Figure S1 & Table S4). 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; β= -0.77, SE = $\pm$0.25, t = -3.05, $p < 0.01$; Figures 2B & Table S4).

While local host-pathogen interactions generally result in worse outcomes for hosts, there was substantial variation among host-pathogen outcomes. 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 & 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 & 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: χ^2 = 9.95, p = 0.04; and pathogen load = $\chi^2 = 12.36$, p = 0.01; Figures 3 & S2). Specifically, when averaging across Bd strains, toads from Arizona and Tennessee had the highest mortality and infection prevalence (Figure S2). Consistent with the experimental results, in the meta-analysis, we found significant variation in mortality among taxonomic groups with Bufonoidea species being especially susceptible to Bd-induced mortality ($\chi^2 = 29.92$, $p < 0.001$; Figure 3).

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. Finally, our log-likelihood ratio test of proportional hazard model fits 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 ($\chi^2 = 4.19$, $df = 1$, $p = 0.0406$).

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 (Lively & Jokela 1996; Kaltz & Shykoff 1998; Lively & Dybdahl 2000; Morran *et al.* 2011; Strauss *et al.* 2012; Lymbery *et al.* 2014; Urban *et al.* 2020; Johnson *et al.* 2021). However, the rise of catastrophic modern pandemics from pathogen pollution has led to speculation that introduced pathogens are especially devastating to naïve hosts (Carey *et al.* 1999; Cunningham *et al.* 2003; Anderson *et al.* 2004; Mastitsky *et al.* 2010). While we did find substantial variation among host-pathogen outcomes, there was no evidence that novel host-pathogen interactions generally cause especially high mortality. Thus, the major concern with pathogen pollution is not that naïve hosts are especially vulnerable but that increasing introductions of novel pathogens increases the chance that virulent pathogens will encounter highly vulnerable hosts. This perception that novel and introduced pathogens are especially deadly might be because of detection bias – most introduced pathogens might 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 >8,000 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.

We found significant variation in mortality, infection success, and pathogen load among Bd strains (Figure 3 & S2), consistent with other studies showing variation in the traits of Bd strains within the global panzootic lineage (Lambertini *et al.* 2016; Becker *et al.*2017). 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 & S2). We also found significant variation in mortality, prevalence, and pathogen load among host species (Figures 3 & S2). Specifically, when averaging across Bd strains, toads from Arizona and Tennessee had the highest mortality and infection prevalence (Figure S2). 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 (Figures 3B & S3). Further, our meta-analysis revealed that Bufonoidea species (toads and relatives) were especially susceptible to Bd-induced mortality compared to other host taxa, confirming previous research (Scheele *et al.* 2019a) (Figure 3 & S2).

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 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 policy makers mitigate the risk of pathogen spillover and dispersal (Altmann & Kolby 2017; Aguirre *et al.* 2021). Policies regarding surveillance, biosafety, and security of wildlife and livestock trade that utilize One Health approaches are especially promising for reducing risk (Cunningham *et al.* 2017; Aguirre *et al.* 2021).

Acknowledgments

Funds for this project were provided by grants to J.R.R. from the National Science Foundation (DEB-2109293, DEB-2017785, IOS 1754868), the National Institutes of Health (R01TW010286), and the US Department of Agriculture (2020-08148), to T.A.M. from the National Science Foundation (IOS 1754862),

National Institutes of Health (1R01GM135935-01, Subaward KK2022) and the University of Tampa (Dana and Delo Faculty Development Grants), and to P.J. from the California Department of Fish and Wildlife and United States Fish and Wildlife Service (Section 6 Grant: P188010 and California State Wildlife Grant: P1830601), and the National Science Foundation (DEB-0841758, DEB-1149308, DEB-1754171), the National Institutes of Health (R01GM109499, 5R01GM135935), and the David and Lucile Packard Foundation. We thank Daniel Lenger, Nicholas Croy, Kaitlin Deutsch, Danielle Vermilyea, Danny Reyes, and Shawna Mulherin for their assistance in sample collection.

References

1.

Aguirre, A.A., Gore, M.L., Kammer-Kerwick, M., Curtin, K.M., Heyns, A., Preiser, W. *et al.* (2021). Opportunities for transdisciplinary science to mitigate biosecurity risks from the intersectionality of illegal wildlife trade with emerging zoonotic pathogens. *Frontiers in Ecology and Evolution* , 9, 604929.

2.

Altmann, M.C. & Kolby, J.E. (2017). Trends in US imports of amphibians in light of the potential spread of chytrid fungus,*Batrachochytrium dendrobatidis* (Bd), and implications for conservation. *Journal of International Wildlife Law & Policy* , 20, 226-252.

3.

Anderson, P.K., Cunningham, A.A., Patel, N.G., Morales, F.J., Epstein, P.R. & Daszak, P. (2004). Emerging infectious diseases of plants: pathogen pollution, climate change and agrotechnology drivers. *Trends in Ecology & Evolution* , 19, 535-544.

4.

Becker, C., Greenspan, S., Tracy, K., Dash, J., Lambertini, C., Jenkinson, T. *et al.* (2017). Variation in phenotype and virulence among enzootic and panzootic amphibian chytrid lineages. *Fungal Ecology* , 26, 45-50.

5.

Bolnick, D.I. & Stutz, W.E. (2017). Frequency dependence limits divergent evolution by favouring rare immigrants over residents.*Nature* , 546, 285-288.

6.

Boyle, D.G., Boyle, D.B., Olsen, V., Morgan, J.A.T. & Hyatt, A.D. (2004). Rapid quantitative detection of chytridiomycosis (*Batrachochytrium dendrobatidis*) in amphibian samples using real-time Taqman PCR assay. *Diseases of Aquatic Organisms* , 60, 141-148.

7.

Brannelly, L.A., Richards-Zawacki, C.L. & Pessier, A.P. (2012). Clinical trials with itraconazole as a treatment for chytrid fungal infections in amphibians. *Diseases of Aquatic Organisms* , 101, 95-104.

8.

Carey, C., Cohen, N. & Rollins-Smith, L. (1999). Amphibian declines: an immunological perspective. *Developmental and Comparative Immunology* , 23, 459-472.

9.

Chatfield, M.W.H. & Richards-Zawacki, C.L. (2011). Elevated temperature as a treatment for *Batrachochytrium dendrobatidis* infection in captive frogs. *Diseases of Aquatic Organisms* , 94, 235-238.

10.

Chung, Y., Rabe-Hesketh, S., Dorie, V., Gelman, A. & Liu, J. (2013). A nondegenerate penalized likelihood estimator for variance parameters in multilevel models. *Psychometrika* , 78, 685-709.

11.

Cohen, J.M., Civitello, D.J., Venesky, M.D., McMahon, T.A. & Rohr, J.R. (2018). Thermal mismatches explain how climate change and infectious disease drove widespread amphibian extinctions. *Global Change Biology* 25, 927–937.

12.

Cunningham, A., Daszak, P. & Rodriguez, J. (2003). Pathogen pollution: defining a parasitological threat to biodiversity conservation. *J Parasitol* , 89, S78-S83.

13.

Cunningham, A.A., Daszak, P. & Wood, J.L. (2017). One Health, emerging infectious diseases and wildlife: two decades of progress?*Philosophical Transactions of the Royal Society B: Biological Sciences* , 372, 20160167.

14.

Daszak, P., Cunningham, A.A. & Hyatt, A.D. (2000). Emerging infectious diseases of wildlife: Threats to biodiversity and human health.*Science* , 287, 443-449.

15.

Fisher, M.C. & Garner, T.W. (2020). Chytrid fungi and global amphibian declines. *Nature Reviews Microbiology* , 18, 332-343.

16.

Fisher, M.C., Henk, D.A., Briggs, C.J., Brownstein, J.S., Madoff, L.C., McCraw, S.L. *et al.* (2012). Emerging fungal threats to animal, plant and ecosystem health. *Nature* , 484, 186-194.

17.

Fu, M. & Waldman, B. (2019). Ancestral chytrid pathogen remains hypervirulent following its long coevolution with amphibian hosts.*Proceedings of the Royal Society B* , 286, 20190833.

18.

Gandon, S. & Van Zandt, P.A. (1998). Local adaptation and host–parasite interactions. *Trends in Ecology & Evolution* , 13, 214-216.

19.

Golas, B.D., Goodell, B. & Webb, C.T. (2021). Host adaptation to novel pathogen introduction: Predicting conditions that promote evolutionary rescue. *Ecology Letters* , 24, 2238-2255.

20.

Greischar, M.A. & Koskella, B. (2007). A synthesis of experimental work on parasite local adaptation. *Ecology letters* , 10, 418-434.

21.

Johnson, P., Calhoun, D.M., Moss, W.E., McDevitt-Galles, T., Riepe, T.B., Hallas, J.M. *et al.* (2021). The cost of travel: How dispersal ability limits local adaptation in host–parasite interactions. *Journal of Evolutionary Biology* , 34, 512-524.

22.

Kaltz, O. & Shykoff, J.A. (1998). Local adaptation in host–parasite systems. *Heredity* , 81, 361-370.

23.

Lambertini, C., Becker, C.G., Jenkinson, T.S., Rodriguez, D., da Silva Leite, D., James, T.Y. *et al.* (2016). Local phenotypic variation in amphibian-killing fungus predicts infection dynamics. *Fungal Ecology* , 20, 15-21.

24.

Lively, C.M. & Dybdahl, M.F. (2000). Parasite adaptation to locally common host genotypes. *Nature* , 405, 679.

25.

Lively, C.M. & Jokela, J. (1996). Clinal variation for local adaptation in a host-parasite interaction. *Proceedings of the Royal Society of London. Series B: Biological Sciences* , 263, 891-897.

26.

Lloyd-Smith, J.O., Cross, P.C., Briggs, C.J., Daugherty, M., Getz, W.M., Latto, J. *et al.* (2005). Should we expect population thresholds for wildlife disease? *Trends in Ecology & Evolution* , 20, 511-519.

27.

Longo, A.V., Rodriguez, D., da Silva Leite, D., Toledo, L.F., Mendoza Almeralla, C., Burrowes, P.A. *et al.* (2013). ITS1 copy number varies among *Batrachochytrium dendrobatidis* strains: implications for qPCR estimates of infection intensity from field-collected amphibian skin swabs. *PLoS One* , 8, e59499.

28.

Lymbery, A.J., Morine, M., Kanani, H.G., Beatty, S.J. & Morgan, D.L. (2014). Co-invaders: the effects of alien parasites on native hosts.*International Journal for Parasitology: Parasites and Wildlife* , 3, 171-177.

29.

Mastitsky, S.E., Karatayev, A.Y., Burlakova, L.E. & Molloy, D.P. (2010). Parasites of exotic species in invaded areas: does lower diversity mean lower epizootic impact? *Diversity and Distributions* , 16, 798-803.

30.

McDonald, C., Ellison, A., Toledo, L., James, T. & Zamudio, K.R. (2020). Gene expression varies within and between enzootic and epizootic lineages of Batrachochytrium dendrobatidis (Bd) in the Americas.*Fungal Biology* , 124, 34-43.

31.

McKenzie, V.J. & Peterson, A.C. (2012). Pathogen pollution and the emergence of a deadly amphibian pathogen. *Molecular Ecology* , 21, 5151-5154.

32.

McMahon, T.A., Brannelly, L.A., Chatfield, M.W.H., Johnson, P.T.J., Joseph, M.B., McKenzie, V.J. *et al.* (2013). Chytrid fungus*Batrachochytrium dendrobatidis* has nonamphibian hosts and releases chemicals that cause pathology in the absence of infection.*Proceedings of the National Academy of Sciences of the United States of America* , 110, 210-215.

33.

McMahon, T.A., Sears, B.F., Venesky, M.D., Bessler, S.M., Brown, J.M., Deutsch, K. *et al.* (2014). Amphibians acquire resistance to live and dead fungus overcoming fungal immunosuppression. *Nature* , 511, 224-227.

34.

Morens, D.M., Daszak, P., Markel, H. & Taubenberger, J.K. (2020). Pandemic COVID-19 joins history's pandemic legion. *MBio* , 11, e00812-00820.

35.

Morran, L.T., Schmidt, O.G., Gelarden, I.A., Parrish, R.C. & Lively, C.M. (2011). Running with the Red Queen: host-parasite coevolution selects for biparental sex. *Science* , 333, 216-218.

36.

Nordheim, C.L., Grim, J.M. & McMahon, T.A. (2021).*Batrachochytrium dendrobatidis* (Bd) exposure damages gill tissue and inhibits crayfish respiration. *Diseases of Aquatic Organisms* , 146, 67-73.

37.

O'Hanlon, S.J., Rieux, A., Farrer, R.A., Rosa, G.M., Waldman, B., Bataille, A. *et al.* (2018). Recent Asian origin of chytrid fungi causing global amphibian declines. *Science* , 360, 621-627.

38.

Parker, I.M., Saunders, M., Bontrager, M., Weitz, A.P., Hendricks, R., Magarey, R. *et al.* (2015). Phylogenetic structure and host abundance drive disease pressure in communities. *Nature* , 520, 542-544.

39.

R Core Team, R. (2013). R: A language and environment for statistical computing.

40.

Raffel, T.R., Halstead, N.T., McMahon, T., Romansic, J.M., Venesky, M.D. & Rohr, J.R. (2013). Disease and thermal acclimation in a more variable and unpredictable climate. *Nature Climate Change* , 3, 146-151.

41.

Reeder, D.M., Frank, C.L., Turner, G.G., Meteyer, C.U., Kurta, A., Britzke, E.R. *et al.* (2012). Frequent arousal from hibernation linked to severity of infection and mortality in bats with white-nose syndrome. *PloS One* , 7, e38920.

42.

Sauer, E.L., Cohen, J.M., Lajeunesse, M.J., McMahon, T.A., Civitello, D.J., Knutie, S.A. *et al.* (2020). A meta-analysis reveals temperature, dose, life stage, and taxonomy influence host susceptibility to a fungal parasite. *Ecology* , 101, e02979.

43.

Scheele, B.C., Foster, C.N., Hunter, D.A., Lindenmayer, D.B., Schmidt, B.R. & Heard, G.W. (2019a). Living with the enemy: Facilitating amphibian coexistence with disease. *Biological Conservation* , 236, 52-59.

44.

Scheele, B.C., Pasmans, F., Skerratt, L.F., Berger, L., Martel, A., Beukema, W. *et al.* (2019b). Amphibian fungal panzootic causes catastrophic and ongoing loss of biodiversity. *Science* , 363, 1459-1463.

45.

Strauss, A., White, A. & Boots, M. (2012). Invading with biological weapons: the importance of disease-mediated invasions. *Functional Ecology* , 1249-1261.

46.

Taraschewski, H. (2006). Hosts and parasites as aliens. *Journal of Helminthology* , 80, 99-128.

47.

Therneau, T. (2014). A package for survival analysis in S. R package version 2.37-7.

48.

Torchin, M.E., Lafferty, K.D., Dobson, A.P., McKenzie, V.J. & Kuris, A.M. (2003). Introduced species and their missing parasites.*Nature* , 421, 628-630.

49.

Torchin, M.E. & Mitchell, C.E. (2004). Parasites, pathogens, and invasions by plants and animals. *Frontiers in Ecology and the Environment* , 2, 183-190.

50.

Urban, M.C., Strauss, S.Y., Pelletier, F., Palkovacs, E.P., Leibold, M.A., Hendry, A.P. *et al.* (2020). Evolutionary origins for ecological patterns in space. *Proceedings of the National Academy of Sciences* , 117, 17482-17490.

51.

Venesky, M.D., Raffel, T.R., McMahon, T.A. & Rohr, J.R. (2014). Confronting inconsistencies in the amphibian-chytridiomycosis system: implications for disease management. *Biological Reviews* , 89, 477-483.

52.

Voyles, J., Woodhams, D.C., Saenz, V., Byrne, A.Q., Perez, R., Rios-Sotelo, G. *et al.* (2018). Shifts in disease dynamics in a tropical amphibian assemblage are not due to pathogen attenuation.*Science* , 359, 1517-1519.

53.

Waddle, A.W., Levy, J.E., Rivera, R., van Breukelen, F., Nash, M. & Jaeger, J.R. (2019). Population-level resistance to chytridiomycosis is life-stage dependent in an imperiled anuran. *EcoHealth* , 16, 701-711.

Figures

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 gray 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 result in very high performance in a new host (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 10000 points while panel B displays a random subset of 25 points for simplicity.

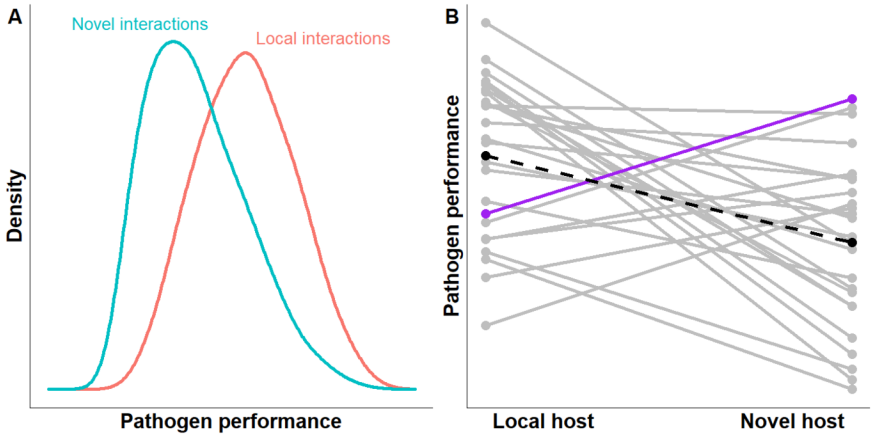

Figure 2 | Model prediction plots showing the significant negative correlations between distance between amphibian host and *Batrachochytrium dendrobatidis* (Bd) strain collection locations and host mortality. **A)** Cox-proportional hazards model of experimental exposures of five North American toad species to six North American Bd strains (β = -0.06, z = -2.10, p= 0.04). **B)** Mixed-effects meta-analysis of Bd experiments using the Sauer et al. (2020) database (β = -0.77, t = -3.05,p = 0.01). Points are predicted model values and gray 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).

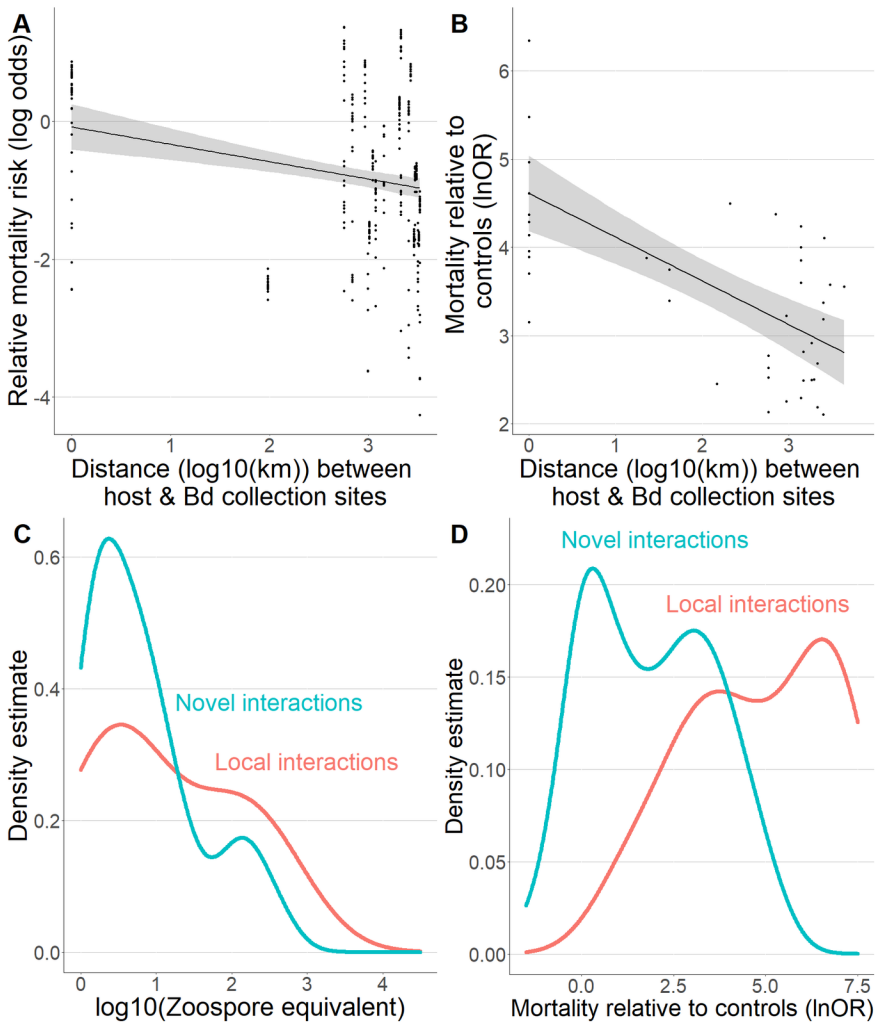

Figure 3 | Experimental exposures of five North American toad species to six North American *Batrachochytrium dendrobatidis* (Bd) strains revealed strong effects of host population and Bd strain on host mortality. Heat maps show treatment-level**A)** host mortality probability and **B)** mean days alive. 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.