

The cost of travel: How dispersal ability limits local adaptation in host–parasite interactions

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Abstract

Classical theory suggests that parasites will exhibit higher fitness in sympatric relative to allopatric host populations (local adaptation). However, evidence for local adaptation in natural host–parasite systems is often equivocal, emphasizing the need for infection experiments conducted over realistic geographic scales and comparisons among species with varied life history traits. Here, we used infection experiments to test how two trematode (flatworm) species (*Paralechiorchis syntomentera* and *Ribeiroia ondatrae*) with differing dispersal abilities varied in the strength of local adaptation to their amphibian hosts. Both parasites have complex life cycles involving sequential transmission among aquatic snails, larval amphibians and vertebrate definitive hosts that control dispersal across the landscape. By experimentally pairing 26 host-by-parasite population infection combinations from across the western USA with analyses of host and parasite spatial genetic structure, we found that increasing geographic distance—and corresponding increases in host population genetic distance—reduced infection success for *P. syntomentera*, which is dispersed by snake definitive hosts. For the avian-dispersed *R. ondatrae*, in contrast, the geographic distance between the parasite and host populations had no influence on infection success. Differences in local adaptation corresponded to parasite genetic structure; although populations of *P. syntomentera* exhibited ~10% mtDNA sequence divergence, those of *R. ondatrae* were nearly identical (<0.5%), even across a 900 km range. Taken together, these results offer empirical evidence that high levels of dispersal can limit opportunities for parasites to adapt to local host populations.

KEYWORDS

coevolution, host, infectious disease, parasite evolution, trematode

1 | INTRODUCTION

Because parasites typically have shorter generation times and larger effective population sizes than their hosts, theory suggests that parasites should have greater evolutionary potential to adapt to local host populations (Gandon & Van Zandt, 1998; Lively & Dybdahl, 2000). Thus, a likely outcome of long-term host-parasite coevolution is that parasites will exhibit higher fitness on local (or current) rather than foreign host genotypes (Gandon et al., 2008). However, empirical support for parasite local adaptation is decidedly mixed (Kaltz et al., 1999; Lemoine et al., 2012); in a meta-analysis of 54 host-parasite experiments, Greischar and Koskella (2007) reported that fewer than half showed support for parasite local adaptation (see also Lemoine et al., 2012). Such heterogeneity in outcomes is often attributed to the relative evolutionary potential of hosts and parasites, for which gene flow is thought to dictate how effectively parasite populations can track evolutionary change in their hosts (Kawecki & Ebert, 2004; Lagrue et al., 2016; Morgan et al., 2005). Although research on host-parasite coevolution has often emphasized the importance of migration in influencing local adaptation (e.g. Lively, 1999; Mazé-Guilmo et al., 2016), high dispersal rates can also homogenize host and parasite populations and prevent local adaptation (Gandon, 2002; Holt & Gomulkiewicz, 1997; Morgan et al., 2005). Thus far, few studies have explicitly examined how variation in parasite dispersal affects the genetic structure and extent of local adaptation in natural host-parasite systems, particularly over the geographic scales relevant to animal movement (Andras et al., 2018; Louhi et al., 2010).

Detection of local adaptation in host-parasite systems is also highly sensitive to the experimental approach employed (Greischar & Koskella, 2007; Hoeksema & Forde, 2008), complicating efforts to predict when and at what scale local adaptation is likely to occur. Because infection is inherently the outcome of interactions between host and parasite, experiments are necessary to disentangle the influences of host adaptation (e.g. resistance) and parasite adaptation (e.g. infectivity). Classical experimental approaches involve reciprocal infections in which hosts from a local population are exposed to sympatric or allopatric parasite populations (i.e. the 'local vs. foreign' design), or parasite performance is compared between sympatric and allopatric host populations (i.e. the 'home vs. away' design) (Greischar & Koskella, 2007; Kawecki & Ebert, 2004). However, detection of local adaptation with either approach may be limited by the presence of strong main effects for the host or parasite population, especially when the number of replicate populations is low (Blanquart et al., 2013; Thrall et al., 2002). Thus, experimental designs that incorporate variation in host and parasite population sources simultaneously—although infrequently used—have advantages for isolating the interactive effect between environment (e.g. host source) and genotype (e.g. parasite source) in determining performance (Blanquart et al., 2013; Hoeksema & Forde, 2008). Understanding the mechanisms underlying spatial variation in patterns of local adaptation can be further informed

with concurrent estimation of genetic structure across host and parasite populations (Mazé-Guilmo et al., 2016; Thompson, 2005), which is becoming increasingly tractable with modern sequencing approaches.

Here, we used interactions between multiple amphibian host species and their trematode parasites to test how large-scale variation among host and parasite populations interact to drive infection success. These parasites have complex life cycles involving aquatic snails and larval amphibians as intermediate hosts, and vertebrate predators as definitive hosts. We selected trematode species that varied in dispersal capacity as a function of their definitive host use and compared the strength of their local adaptation within amphibian hosts by experimentally infecting 26 unique host-by-parasite population combinations from the western USA (Table 1). We generated complementary population genetic data for both hosts and parasites to examine the links among geographic distance, host genetic dissimilarity, and the extent of local adaptation between parasite species. We hypothesized that increasing geographic distance between host and parasite populations would negatively influence infection success under standardized experimental conditions. However, we predicted that the magnitude of this effect would depend on the degree of parasite genetic divergence across distance and therefore on parasite dispersal ability. We expected that the parasite dispersed by highly vagile avian hosts (*Ribeiroia ondatrae*) would exhibit less genetic structure and weaker local adaptation relative to the more dispersal-limited parasite (*Paralechriorchis syntomentera*), which depends on snakes for movement among sites. This work highlights the importance of comparative, multi-species approaches to understand large-scale patterns of local adaptation in natural host-parasite systems, including those involving parasites with complex life cycles dependent on multiple species (Betts et al., 2016; Penczykowski et al., 2016).

2 | MATERIALS AND METHODS

2.1 | Study system

Studies of the interactions between trematode parasites and their hosts have been foundational in advancing coevolutionary research, facilitating tests of hypotheses about local adaptation and reciprocal selection stemming from species interactions (Bryan-Walker et al., 2007; Lively & Dybdahl, 2000; Thompson, 2005). The basic life cycle of digenetic trematodes involves sequential transmission among multiple host species (Galaktionov & Dobrovolskij, 2003). The trematodes *Ribeiroia ondatrae* (Echinostomatidae) and *Paralechriorchis syntomentera* (Reniferidae) both use pulmonate snails as first intermediate hosts (*Helisoma trivolvis* and *Physa* spp., respectively) and a wide range of amphibian species as second intermediate hosts (Ingles, 1933; Johnson et al., 2004). Amphibians become infected when mobile infectious stages (cercariae) are released by snails and penetrate amphibian larvae, forming encysted metacercariae that mature into sexually reproductive adults only

Host species	Parasite species	Sympatric crosses	Allopatric crosses
<i>P. regilla</i>	<i>P. syntomentera</i>	27 km, <i>n</i> = 13	871 km, <i>n</i> = 11
		22 km, <i>n</i> = 6	696 km, <i>n</i> = 13
<i>P. regilla</i>	<i>R. ondatrae</i>	0 km, <i>n</i> = 6	324 km, <i>n</i> = 8
		27 km, <i>n</i> = 13	201 km, <i>n</i> = 10
		17 km, <i>n</i> = 15	479 km, <i>n</i> = 15
		14 km, <i>n</i> = 15	903 km, <i>n</i> = 14
			903 km, <i>n</i> = 6
			229 km, <i>n</i> = 25
			695 km, <i>n</i> = 15
			725 km, <i>n</i> = 15
			351 km, <i>n</i> = 15
			205 km, <i>n</i> = 22
<i>A. boreas</i>	<i>R. ondatrae</i>	7 km, <i>n</i> = 15	876 km, <i>n</i> = 15
		30 km, <i>n</i> = 14	
<i>T. torosa</i>	<i>R. ondatrae</i>	78 km ^a , <i>n</i> = 15	836 km, <i>n</i> = 14

TABLE 1 Summary of hosts and parasites used for cross-infection experiments

Note: Parasites (either *Paralechiorchis syntomentera* or *Ribeiroia ondatrae*) collected from locations across the western United States (see Table S1 for details) were used to infect amphibian hosts (*Pseudacris regilla*, *Anaxyrus boreas*, or *Taricha torosa*). Geographic distance (km) between host and parasite origin is given for particular host–parasite crosses (sympatric or allopatric), as well as the number of replicate host individuals exposed per cross.

^aAlthough host and parasite source in this cross was both from within the Bay Area Region of California, their straightline distance could alternatively be considered ‘allopatric’. For statistical analyses, we used distance as a numeric variable.

after the amphibian host is consumed by a suitable vertebrate predator (Koprivnikar et al., 2012). The definitive hosts for *R. ondatrae* are predatory birds (Johnson et al., 2004), including waterfowl, raptors, herons, pelicans and kingfishers, which have the potential to disperse parasites over large geographic ranges. For instance, individual herons and egrets can disperse 100–200 km annually within California (Gill & Mewaldt, 1979). For *P. syntomentera*, the definitive hosts are garter snakes (*Thamnophis* spp.), which are more constrained in their dispersal range (Rossman et al., 1996), with limited gene flow among populations separated by more than ~5 km (Manier & Arnold, 2005).

Although both parasites are relative generalists that encyst beneath the skin of their amphibian hosts, they differ in virulence: *R. ondatrae* causes amphibian mortality and malformations in a dose-dependent manner (i.e. more cercariae lead to higher risk) (Johnson et al., 2012), whereas *P. syntomentera* is not known to cause substantial pathology in amphibians (Gilliland & Muzzall, 2002; Johnson et al. unpublished) (note: although *P. syntomentera* was initially linked to amphibian limb deformities in Sessions and Ruth (1990), this account was almost certainly due to *R. ondatrae* based on resurveys (e.g. Johnson et al., 2003)). For instance, although exposure to 40 *R. ondatrae* cercariae can reduce survival of Pacific treefrog (*Pseudacris regilla*) larvae by ~40%, we have not detected any survival effects of *P. syntomentera* even at dosages of 100–200 cercariae per tadpole. Although hosts can use multiple strategies to mitigate infection by parasites (e.g. avoidance behaviours to reduce infection as well as tolerance mechanisms to limit pathology) (Fantham & Porter, 1954), we focus here on the proportion of

administered parasites establishing infections (i.e. infection success) as our primary measure of parasite adaptation. Infection success is a useful metric for local adaptation in parasites because it is a consistently quantifiable outcome of host–parasite interactions.

2.2 | Experimental design and parasite exposures

To test for variation in local adaptation between parasite species and among host and parasite populations, we collected amphibian hosts and trematode parasites across the western United States (Figure 1, see Table 1 and the Appendix S1 for detailed information on collection locations, sample sizes and animal maintenance). Although we considered the absolute distance between host and parasite populations in our analyses (see below), this approach included host–parasite combinations that were sympatric—i.e. both host and parasite were collected from ponds within 30 km—as well as those that were allopatric and separated by geographic distances of 201–903 km (Figure 2). This definition of allopatry was selected to encompass distances that far exceed the lifetime movements of amphibian or snake hosts (e.g., Gregory & Stewart, 1975; Smith & Green, 2005). After isolating trematode-infected snails in 50 ml centrifuge tubes, we collected infectious cercariae within ~2 hr of peak emergence (see Appendix S1). For *R. ondatrae*, we collected marsh rams horn snails (*H. trivolvis*); for *P. syntomentera*, we used snails in the genus *Physa* (possible combination of *P. acuta* and *P. gyrina*). Cercariae were counted under a microscope and administered

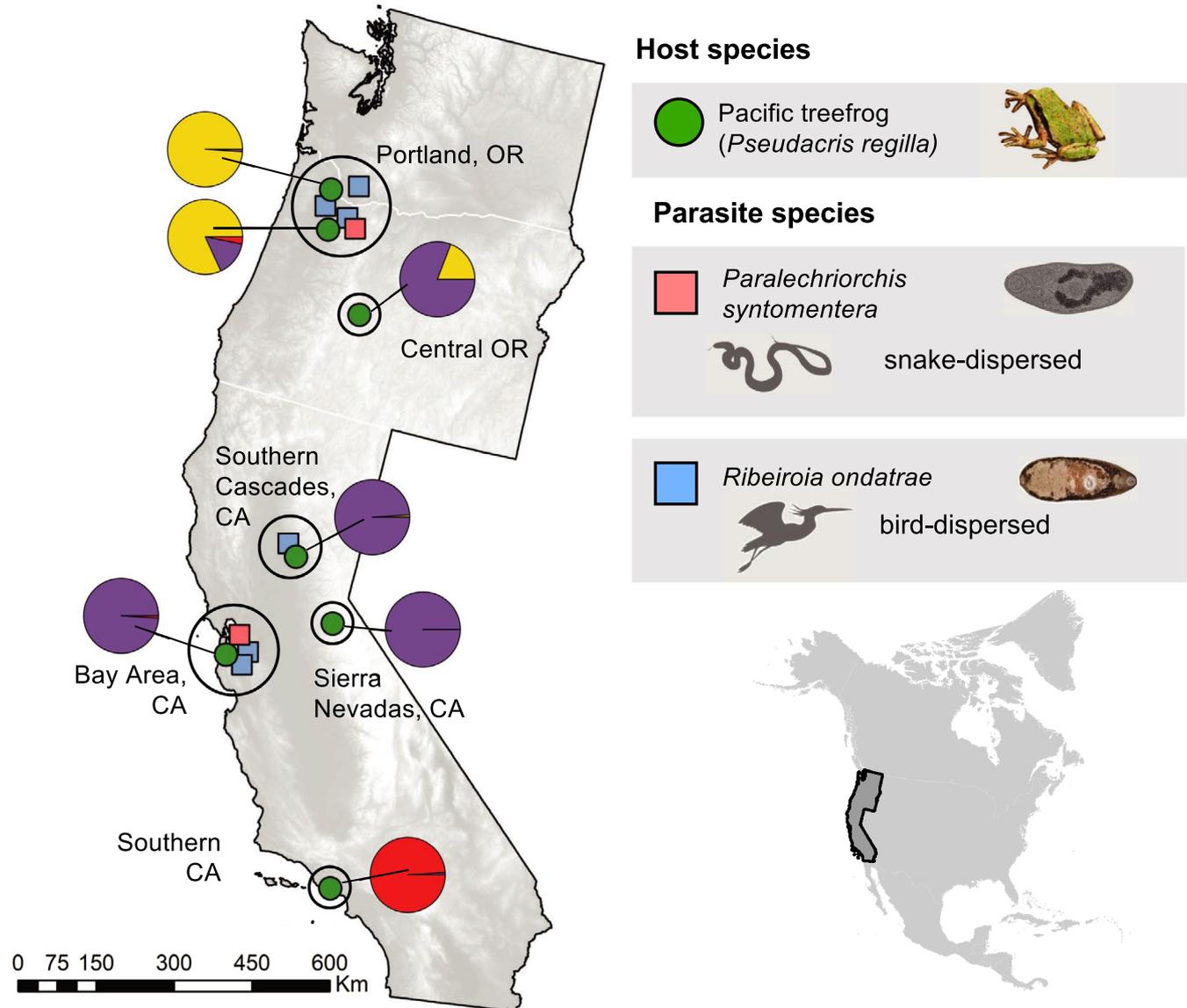


FIGURE 1 Sampling locations of amphibian hosts (Pacific treefrog complex; *Pseudacris regilla*, green triangles) and parasites (*Paralechriorchis syntomentera*, pink squares or *Ribeiroia ondatrae*, blue squares). Hosts and parasites were sampled along the western USA and used in cross-infection experiments. Points are adjusted slightly to avoid overlap. For *P. regilla* populations, individuals were assigned to one of three genetic clusters [yellow cluster (Pacific Northwest clade), purple cluster (Central California, Eastern Oregon clade), or red cluster (Southern California clade)]. The average ancestry coefficients from entropy for each population are represented with pie charts. Image credits: *P. regilla* (The High Fin Sperm Whale), parasites (www.aquaticparasites.org), host silhouettes (www.thenounproject.org)

into amphibian containers using a Pasteur pipette. We exposed each amphibian larva to 30 cercariae of either *R. ondatrae* or *P. syntomentera*. This number of cercariae was selected based on previous experimental work (e.g. Johnson & Hoverman, 2014) and a desire to maximize statistical power whereas managing the risk of mortality (i.e. with low exposure dosages, even small differences in infection represent a large proportional difference). Based on data from 79 field sites sampled in 2017, the average number of metacercariae per Pacific treefrog (*Pseudacris regilla*) metamorph ± 1 SE at ponds with infection was 4.2 ± 0.5 for *R. ondatrae* ($n = 33$ ponds; range:

1 – 233 per frog) and 0.3 ± 0.07 for *P. syntomentera* ($n = 12$ ponds; range: 1–59 per frog).

To ensure that amphibian hosts used in experiments were free of trematode infection, we collected egg masses from field sites and raised larvae to a standardized developmental stage prior to exposure (see Appendix S1). For *R. ondatrae*, we exposed larvae of the Pacific treefrog complex (*P. regilla*) from seven populations to cercariae collected from one of six locations distributed from southern California to southern Washington (Figure 1). For *P. syntomentera*, treefrog hosts from six populations were

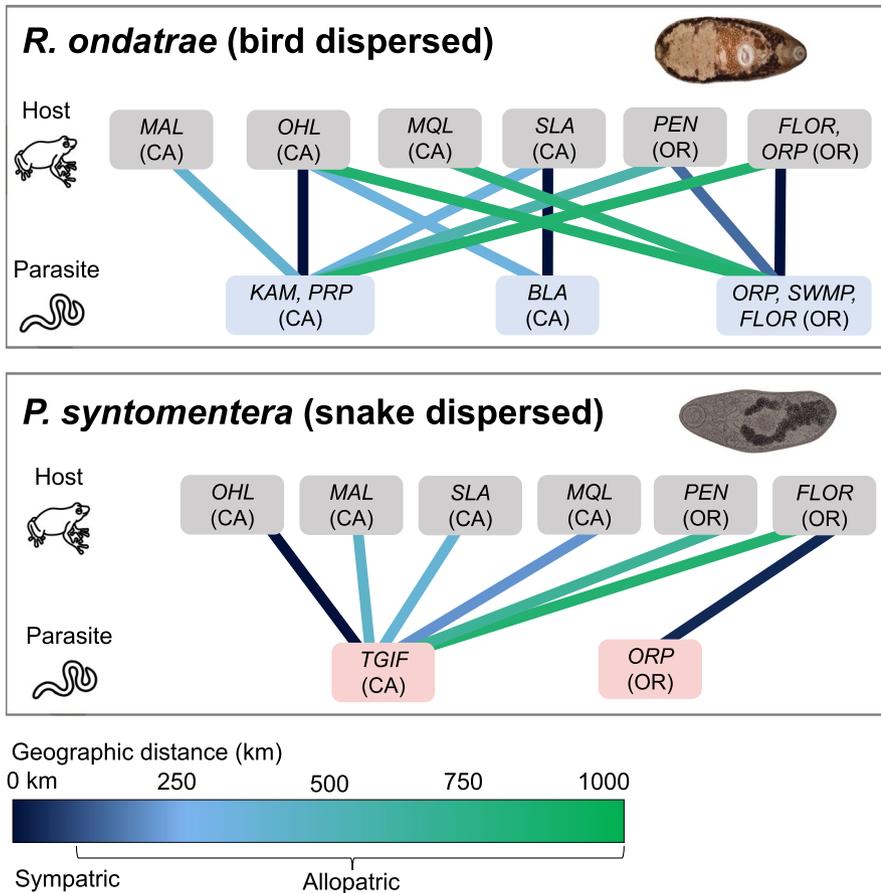


FIGURE 2 Experimental crosses between hosts (Pacific chorus frogs; *Pseudacris regilla*) and parasites (either *Ribeiroia ondatrae* [top] or *Paralechriorchis syntomentera* [bottom]). Hosts collected from a variety of locations within the western USA (grey boxes) were exposed to parasite cercariae from multiple sources (pink and blue boxes). Host-parasite crosses were either sympatric (within 30 km) or allopatric (>30 km), up to distances of nearly 1,000 km. We examined how infection success was related to the geographic distance between host and parasite source (color of line)

exposed to cercariae from either the Bay Area of California or the Portland Area of Oregon (Table 1). To extend our analysis to additional host species, we exposed western toads (*Anaxyrus boreas*) and California newts (*Taricha torosa*) collected from the Bay Area to *R. ondatrae* cercariae from either the same area or from Portland (a distance of ~850 km) (Unfortunately, we were unable to concurrently obtain snails infected with *P. syntomentera* to expose *A. boreas* or *T. torosa*). These three species represent some of the most abundant and ubiquitous amphibians in the western USA (Stebbins 2003); within ponds that support *R. ondatrae* or *P. syntomentera*, for instance, *P. regilla* is one of the most commonly infected species (e.g., Johnson et al., 2013, unpublished). After thirty-six hours of exposure, amphibian hosts were killed, measured (snout-vent length in mm and wet mass in mg) and necropsied to quantify infection success (number of established metacercariae relative to the number of cercariae administered) (e.g., Johnson et al., 2019; LaFonte et al., 2015). This time frame is appropriate as trematode cercariae rarely survive longer than 24 hr (Pechenik & Fried, 1995). However, this design only allowed for a test of differences in initial infection success (i.e., cercariae penetration and initial establishment); future studies would be needed to evaluate whether metacercariae were equally likely to persist through time (i.e., the inverse of clearance, see Holland, 2009). We also collected tissue for genetic analysis from a subsample of hosts and parasites (see below).

2.3 | Host population genetic analysis

We extracted genomic DNA from 121 *P. regilla* host larva from all seven host populations using Qiagen DNeasy Blood & Tissue kits (Qiagen, Inc.). We then employed a reduced representation ddRAD-seq approach previously used for a wide range of taxa to simultaneously discover and genotype single nucleotide polymorphisms (SNPs) (Gompert et al., 2012; Parchman et al., 2012; Peterson et al., 2012). We used the restriction enzymes *EcoRI* and *MseI* to digest genomic DNA, and ligated pairs of modified Illumina adaptors to the sticky-ended fragments. Adaptors ligated to the *EcoRI* cut sites included unique 8, 9 or 10 base barcodes to facilitate the post-sequencing identity of each individual. We PCR-amplified each restriction-ligation product using standard Illumina primers and a high-fidelity proofreading polymerase (iProof polymerase, BioRAD; Hercules, CA, USA). The adaptor barcoded PCR products were pooled and size-selected for fragments ranging from 350–450 bases in length using a Pippin Prep quantitative electrophoresis unit (Sage Science). We quality-checked libraries using a BioAnalyzer (Agilent Inc.) and sequenced samples on two lanes of an Illumina HiSeq 2500 at the University of Wisconsin Bioinformatics Center. Filtering, alignment and bioinformatic processing steps that we followed to identify and subsequently filter SNPs are detailed in the Appendix S1.

To quantify population structure, we estimated genotype probabilities and ancestry coefficients (q) using a hierarchical Bayesian model that incorporated uncertainty from sequencing and mapping

error as well as variable coverage depth across individuals and loci (entropy; Gompert et al., 2014). First, using genotype likelihoods generated in bcftools, we calculated a genotype covariance matrix and ran principal components analysis (PCA) (prcomp in R version 3.6.1; R Development Core Team, 2019). To speed convergence of MCMC chains, we conducted *k*-means clustering and linear discriminant analyses (MASS package in R) on the resulting PCA axes to provide starting values of cluster membership probability for each level of *k*. We then ran entropy for 100,000 MCMC (Markov Chain Monte Carlo) iterations following a 30,000 iteration burn-in. We ran five independent MCMC chains for each value of *k* across preset values of *k* = 2–7 and evaluated model fit using deviance information criterion (DIC).

We additionally summarized patterns of genetic variation across the sampled region with a model-free approach using PCA of the genotype probabilities generated by entropy (prcomp function in R). To generate metrics of genetic differentiation among all pairs of populations, we calculated population mean values of Hudson's F_{ST} and Nei's genetic distance (Nei's *D*). We visualized genetic distances among populations by generating a neighbour-joining tree using the ape package in R (Paradis et al., 2004) and calculated observed heterozygosity (H_o) and expected (H_e) heterozygosity from allele frequencies based on Hardy–Weinberg Equilibrium (HWE) expectations. We quantified patterns of isolation-by-distance (IBD) using Mantel tests based on matrices of pairwise geographic and genetic (Nei's *D* and F_{ST}) distances among populations.

2.4 | Parasite population genetic analysis

We used partial sequences of the variable mitochondrial cytochrome *c* oxidase subunit 1 (*CO1*) gene to analyse parasite genetic divergence within and between source populations. Although sequence variation at a single mitochondrial gene queries a small fraction of information compared with the genome-wide collection of SNPs generated above, this approach remains the benchmark for determining the genetic structure of macroparasite populations, such as trematodes (e.g. Blasco-Costa et al., 2016; Keeney et al., 2009; Lagrue et al., 2016). Furthermore, the minimal amounts of DNA obtained from parasite extractions precluded our ability to generate genome-wide SNP data using high throughput sequencing as above.

Following preliminary morphological identification, we isolated genomic DNA from several pooled cercariae or a single metacercaria using a ZR Genomic DNA™ Tissue Micro Prep kit (Zymo Research) or according to the protocol described by Tkach and Pawlowski (1999). We obtained genomic DNA from 19 samples of *R. ondatrae* cercariae from five locations and 20 samples of *P. syntomentera* cercariae or metacercariae from three locations (Table S3). We then PCR-amplified an approximately 425-base-pair fragment of *CO1* using the OneTaq Quick-Load Master Mix (New England Biolabs) according to the manufacturer's protocol, using an annealing temperature of 45°C with forward primer JB3 (Bowles et al., 1992: 5'-TTT TTT

GGG CAT CCT GAG GTT TAT-3') and reverse primer JB5 (Derycke et al., 2005: 5'-AGC ACC TAA ACT TAA AAC ATA ATG AAA-3').

We purified PCR products using the ExoSAP-IT PCR clean-up enzymatic kit (Affymetrix) and cycle-sequenced purified products in both directions using the amplification primers (JB3 and JB5) with the BrightDye Terminator Cycle Sequencing Kit (MCLAB). We purified the products of the sequencing reactions using magnetic beads from MCLAB and ran them on an ABI 3130 automated capillary sequencer (Life Technologies). We assembled contiguous sequences using Sequencher version 4.2 software (GeneCodes Corp.) and aligned them using Clustal W (Larkin et al., 2007), as implemented in BioEdit version 7.0.5.3 software (Hall, 1999); we then used pairwise sequence comparisons to calculate genetic distances between the 19 sequences of *R. ondatrae* and 20 sequences of *P. syntomentera* using BioEdit. We deposited all sequences in GenBank under accession numbers MW042959–MW042997 (Table S3).

2.5 | Statistical analyses of experimental data

Our analytical framework focused on generalized linear mixed models (GLMMs) because they accommodate (a) unbalanced experimental designs, (b) a variety of response variable distributions and (c) a combination of fixed and random effect terms (Bolker et al., 2009; Zuur et al., 2009). Importantly, the use of a mixed-modelling framework helps overcome previous analytical constraints by incorporating variation in host and parasite populations simultaneously, thus combining 'home versus away' and 'local versus foreign' approaches. Our primary response variable was the proportion of metacercariae observed per amphibian host out of the 30 administered, which we modelled using a binomial distribution with a logit-link function. We also included an observation-level random effect. As fixed effects, we included host body size (snout-vent length), the geographic distance between sampled host and parasite populations (calculated as the straight-line Euclidean distance), parasite species identity, and the interaction between parasite species and distance. As an alternative to amphibian body size, we also explored the influence of developmental stage [following Gosner (1960)], for which results were comparable. We used geographic distance as a predictor variable because this information was available for all host-parasite combinations, and it correlated strongly with genetic distance (see Results). We centred and scaled continuous variables prior to inclusion in analyses, and we incorporated the source population of hosts and parasites each as random intercept terms. For *R. ondatrae* only, we conducted an additional analysis evaluating the effect of amphibian host species (*P. regilla*, *A. boreas* and *T. torosa*), infection combination (sympatric or allopatric) and their interaction on infection success. We implemented models using the glmer function within the lme4 package (Bates et al., 2015) in R (R Core Team, 2019) and assessed the significance of individual terms using likelihood-ratio tests between full and reduced models. We excluded one host from analyses that died shortly after exposure.

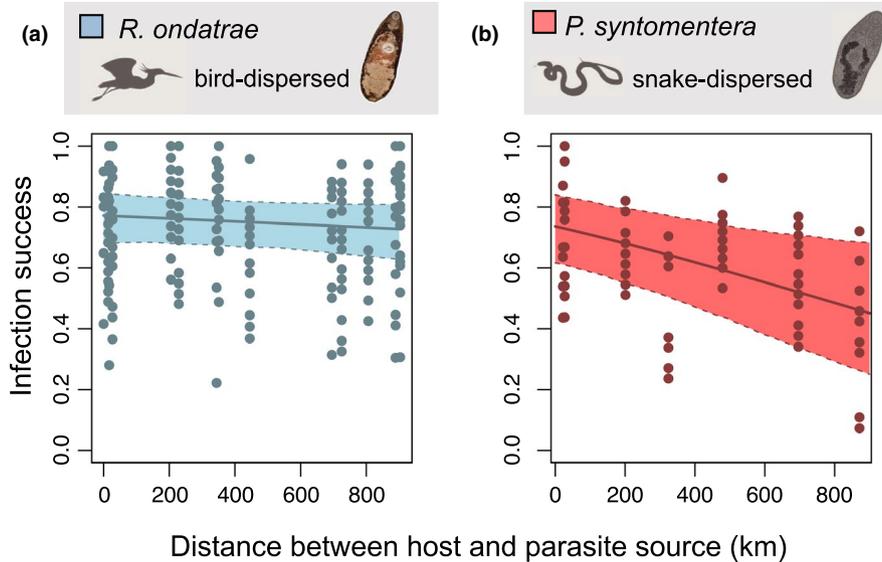


FIGURE 3 Effect of geographic distance on the infection success (proportion of exposed cercariae that successfully established) of each trematode in experimental crosses. Host species (*Pseudacris regilla*) were exposed to cercariae of either *Paralechthorichis syntomentera* (pink) or *Ribeiroia ondatrae* (blue), originating from source populations at varying geographic distances relative to the host. The dispersal-limited parasite *P. syntomentera* showed evidence of local adaptation, with decreasing infection success when parasites and hosts were separated by greater distances ($\beta_{\text{distance}} = -0.43 \pm 0.14$; $p < .01$). For *R. ondatrae*, which are dispersed by birds, there was no relationship between distance and infection success ($\beta_{\text{distance}} = -0.08 \pm 0.08$; $p = .30$). Best-fit lines with 95% confidence intervals are shown. Plotted points are residual parasite infection success, after correcting for estimated population-level random effects

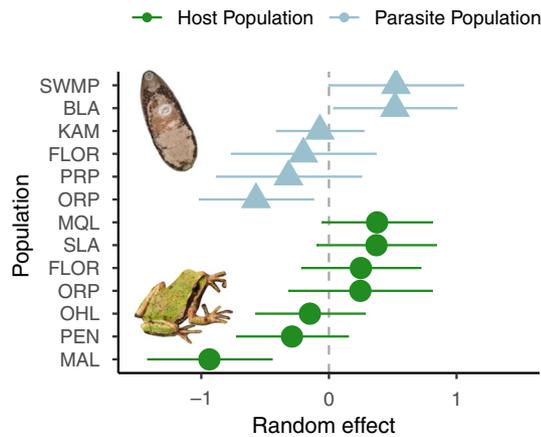


FIGURE 4 Magnitude of random effects on log-parasite load for populations of host (*P. regilla*) and parasite (*R. ondatrae*) used in experimental infection crosses. Horizontal values show the estimated random effect for a given host population (green circles) or parasite population (blue triangles) on the log-parasite load (error bars: ± 1 SD). Populations with estimates greater than 0 have a greater-than-average parasite load. Host populations accounted for more of the variance in parasite load than did parasite populations, likely driven by the Malibu population of *P. regilla*, which had low parasite loads across all crosses

3 | RESULTS

3.1 | Parasite exposure experiment

Geographic distance interacted significantly with parasite species identity to determine infection success (proportion of cercariae

that successfully infected the host) within experimentally exposed *P. regilla* hosts (GLMM; parasite \times distance \pm SE = 0.35 ± 0.16 ; likelihood ratio test: $\chi^2_1 = 4.80$; $p = .03$). The distance between host and parasite source locations had no influence on *R. ondatrae* infection success, even for crosses separated by over 900 km (Figure 3a). In contrast, increasing geographic distance led to a decrease in the proportion of establishing *P. syntomentera* parasites (GLMM; distance \pm SE = -0.43 ± 0.14 ; likelihood ratio test: $\chi^2_1 = 8.56$; $p = .003$; Figure 3b). On average, the odds of *P. syntomentera* infection decreased by 35% for every 300 km between host and parasite origin. Neither host body size (snout-vent length) nor host developmental stage affected infection success (GLMM; snout-vent length \pm SE = 0.02 ± 0.07 ; likelihood ratio test: $\chi^2_1 = 0.12$; $p = .73$; developmental stage \pm SE = 0.10 ± 0.08 ; likelihood ratio test: $\chi^2_1 = 1.66$; $p = .20$).

We also detected a strong main effect of parasite species on infection success (GLMM; parasite \pm SE = 0.65 ± 0.31 , likelihood ratio test: $\chi^2_1 = 6.16$; $p = .03$). *Ribeiroia ondatrae* exhibited a 91% higher odds of infection success relative to *P. syntomentera*. On average, hosts exposed to 30 *R. ondatrae* cercariae were predicted to support 74% of the cercariae, or 22.6 metacercariae per host (95% CI: 20.3–24.3), relative to 61% or 18.4 metacercariae for hosts exposed to *P. syntomentera* (95% CI: 14.0–22.3). For *R. ondatrae*, which had a larger number of source populations relative to *P. syntomentera*, a variance components analysis with only random intercept terms (no fixed effects) indicated that host location accounted for 53% of variation relative to 47% for parasite location (i.e. individual variation in *R. ondatrae* infection levels was driven by variation in both host and parasite populations). Hosts from Malibu, CA, for instance, had the

largest magnitude random effect, with a 72% lower odds of infection than other host populations (Figure 4).

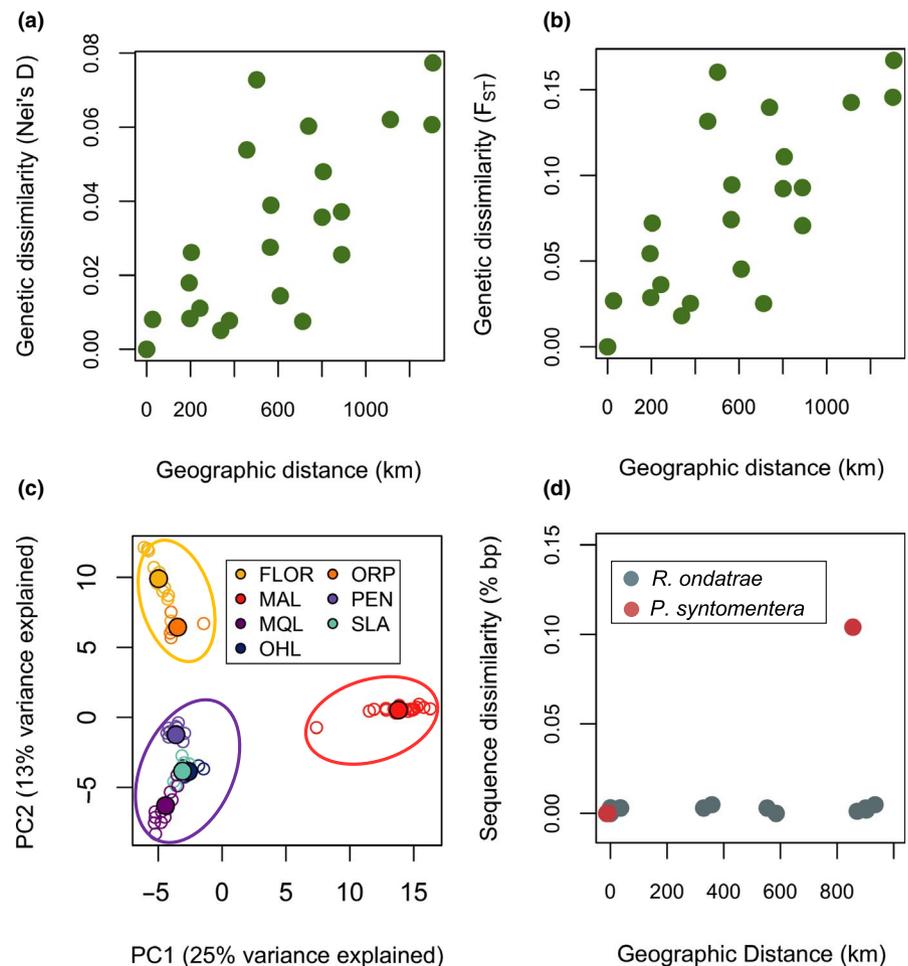
Analyses of *R. ondatrae* infection in other amphibian species suggested a similar lack of local adaptation. Overall infection success was greatest in *P. regilla*, which was 20% greater than in *A. boreas* (Tukey pairwise comparisons, *A. boreas*–*P. regilla* \pm SE = -0.47 ± 0.11 ; $p = .001$) and 31% greater than in *T. torosa* (although this difference was nonsignificant due to higher variance in *T. torosa* infections; -0.66 ± 0.58 ; $p = .47$). There was no effect of location (i.e. host-parasite sympatry vs. allopatry), or its interaction with amphibian host species identity (likelihood-ratio test, $\chi^2_3 = 1.75$; $df = 3$, $p = .63$). Thus, we found no statistical influence of host location on the number of parasites per host, regardless of amphibian host species, or whether hosts and parasites were derived from the same or allopatric location (separated by up to 536 km).

3.2 | Host and parasite genetic structure

After initial filtering, demultiplexing and removal of individuals with read counts below the 0.25 quantile of the read count distribution, we retained a total of 211,608,960 sequences from 83 *P. regilla* individuals across all seven sites. After employing stringent filtering of variable positions identified in alignments, we retained 1,943 SNPs

with a mean coverage depth of 19.9 \times per individual per locus. Our analyses revealed a pronounced pattern of hierarchical population structure across the sampled geographic area. Across model-based and model-free analyses, host individuals from each population formed tight and mostly nonoverlapping groupings, illustrating clear differentiation among even geographically proximate populations along with more accentuated divergence among groups of populations from three geographic regions (northern Oregon, northern California, and southern California). The PCA clustered populations into three, strongly separated genetic clusters (Figures 1 and 5c), as did the Bayesian clustering approach (entropy), which suggested three clusters ($k = 3$) fit the data best and assigned individuals into three differentiated ancestral populations (Figure 1). These three groups correspond to the three previously established lineages within the *P. regilla* complex (Recuero et al., 2006). Pairwise genetic differentiation was predicted by geographic distance among populations (Figure 5a,b), consistent with expectations of an isolation-by-distance model. Nonetheless, specific populations (e.g. Malibu, CA) exhibited higher than expected differentiation from all others. Estimates of both expected and observed heterozygosity varied across populations (Table S4), but without a clear relationship to geography. There was no pattern of heterozygote deficit, which is consistent with a lack of inbreeding (H_o mean: 0.146; range: 0.090–0.231; H_e mean: 0.161; range: 0.148–0.194).

FIGURE 5 Genetic structure of host and parasite populations from the western United States. (a) Genetic dissimilarity (Nei's D) correlated positively with geographic distance for larvae of the *Pseudacris regilla* complex (Mantel test, $p = .003$); (b) Population genetic subdivision (F_{ST}) correlated positively with geographic distance for *P. regilla* (Mantel test, $p = .007$); (c) principal components analysis (PCA) based on genotype data from *P. regilla* individuals, colored by collection location (see Table S1 for location codes) demonstrates genetic structure across the western USA, corresponding to three distinct groups ('yellow clade', 'red clade', 'purple clade'); (d) Average pairwise sequence dissimilarity (raw sequence divergence) increased with geographic distance for the snake-dispersed parasite *Paralechriorchis syntomentera* (pink), but not for the bird-dispersed *Ribeiroia ondatrae* (blue)



For parasites, the final mtDNA sequence alignments of CO1 (trimmed to the length of the shortest sequences) were 348 base pairs (bp) long for *P. syntomentera* and 412 bp for *R. ondatrae*; alignments translated to coding sequence and neither alignments contained gaps.

Both parasite species exhibited little genetic variability across samples collected from the same population. Sequences of *P. syntomentera* cercariae from locations in California and Oregon were identical within populations (0% dissimilarity). The within-population genetic variability in *R. ondatrae* varied from zero (BLA, ORP) to 0.3–0.5% (Table S3).

Among populations, we detected greater sequence divergence between the three source populations of *P. syntomentera* than among all sampled populations of *R. ondatrae*. Pairwise comparison of the CO1 sequences between *P. syntomentera* populations separated by 872 km showed 10.4% difference. Sequences of *R. ondatrae* demonstrated only minimal variation (<0.5%), even among populations separated by as much as 900 km (Table S3). Thus, although our degree of resolution was lower for parasite than host population genetics, the two parasites appeared to differ dramatically in genetic variation and structure.

4 | DISCUSSION

By infecting hosts with parasites from multiple populations across the western USA, our results highlight how dispersal ability can shape the evolution of host–parasite interactions. The success of complex life cycle trematodes in infecting amphibian intermediate hosts decreased with increasing geographic distance between host and parasite origin only for the trematode *P. syntomentera*, which has a lower dispersal capacity and consists of populations that are more genetically differentiated across geographic space. Thus, infection success by *P. syntomentera* was greatest when parasites and hosts were collected from close proximity, consistent with predictions of local adaptation for this parasite. For *R. ondatrae*, however, which is dispersed by bird definitive hosts, there was no such decrease in infection success with geographic distance, despite clear differences in amphibian host population genetic structure across the 900 km study range. This same lack of parasite local adaptation in infection success was evident for two additional amphibian host species exposed to *R. ondatrae* using an identical protocol, neither of which exhibited differential infection success between sympatric and allopatric populations (~500 km). Correspondingly, results of the parasite mtDNA sequence analyses highlighted the influence of dispersal on population genetic structure; whereas snake-dispersed *P. syntomentera* samples exhibited up to 10.4% mtDNA sequence divergence, bird-dispersed *R. ondatrae* were nearly identical (<0.5% sequence divergence). Although these findings are consistent with the differences in dispersal ability between the two parasites, it is important to note that these parasites also differ in other characteristics, such as virulence (see below).

The observed negative relationship between dispersal ability and local adaptation strength stands in contrast to previous findings that parasites will locally adapt whenever they have greater dispersal opportunities relative to their hosts (Gandon, 2002; Greischar & Koskella, 2007; Kawecki & Ebert, 2004; Morgan et al., 2005). This is because sufficient gene flow among parasite populations enhances genetic diversity and thus the evolutionary potential for parasites to track evolution in their local host populations (Gandon, 2002). Theoretically, however, sufficiently high levels of gene flow can eventually limit the capacity of parasites to locally adapt and can even lead to maladaptation when maladapted migrant genomes are introduced into populations (Dybdahl & Storfer, 2003; Lively, 1999; Thompson et al., 2002). Although this outcome has been supported through modelling and laboratory experiments (Gandon, 2002; Gandon & Michalakis, 2002; Vogwill et al., 2008), we are not aware of any previous studies demonstrating that high dispersal and gene flow in natural parasite populations impedes local adaptation. The lack of detectable genetic divergence among *R. ondatrae* populations is consistent with high gene flow due to the wide-ranging dispersal potential of bird definitive hosts (e.g. Johnson et al., 2004), similar to the findings of other studies with complex life cycle parasites dependent on hosts with high dispersal (Blasco-Costa & Poulin, 2013; Louhi et al., 2010; Mazé-Guilmo et al., 2016). In contrast, although *P. syntomentera* samples collected from both California and Oregon were similar morphologically and corresponded to the published description of this parasite (e.g. Ingles, 1933), the level of genetic differentiation between locations was surprisingly pronounced.

For complex life cycle parasites with avian definitive hosts, the latitudinal distribution of our study sites along the Pacific migratory flyway likely affords numerous opportunities for bird-mediated dispersal (Figure 1). In parallel, Louhi et al. (2010) reported that the bird-dispersed trematode *Diplostomum pseudospathaceum* exhibited no evidence of genetic structure across a relatively large geographic range (300 km), whereas Blasco-Costa et al. (2012) detected genetic differentiation following a pattern of isolation-by-distance only in a trematode species with low dispersal ability. Yet experimental investigations into the role of migration on parasite performance and local adaptation—as done here—remain limited (but see Morgan et al., 2005; Vogwill et al., 2008), with most comparisons relying on meta-analytic approaches across very different systems. Ultimately, the influence of parasite migration rate on genetic variation and local adaptation will likely be maximized at some intermediate value (Vogwill et al., 2008), particularly when there is environmental or temporal variation in species interactions (Blanquart et al., 2013). The focus of empirical studies on specialist parasites with relatively simple life cycles (e.g., direct) have restricted opportunities for characterizing parasite local adaptation within a more complex landscape of host populations (Tack et al., 2012).

Across the western USA, host populations (*P. regilla*) exhibited clear genetic structure, subdividing into three distinct groups. Our estimates of pairwise genetic dissimilarity (as F_{ST} or Nei's D) increased as a function of geographic distance, consistent with the expectation of isolation-by-distance (Figure 5). This indicates that

parasites crossed with amphibian hosts from greater geographic distances from their source origin encountered more novel host genotypes. Despite the lack of a distance effect on *R. ondatrae* infection, host population source was nonetheless influential. Based on the variance components analysis, host population source accounted for slightly more of the heterogeneity (53%) in infection success relative to parasite source (47%). Estimates of the random intercept terms from the mixed-modelling analytical framework can also be used to identify specific source populations with higher or lower values; for instance, the Southern California (Malibu) population of *P. regilla* was the least susceptible to *R. ondatrae* and had the most divergent genotype. Such population-level effects, which are strong across many systems (e.g. Schulte et al., 2011), have the potential to 'mask' local adaptation and underscore the need for experimental designs that include replicate source populations.

In addition to dispersal ability, the two parasites used in this study also differed in virulence. Although *R. ondatrae* often causes mortality or developmental malformations among exposed amphibian larvae, no such effects have been documented for *P. syntomentera* (e.g. Johnson et al., 2012, 2013, unpublished data). Highly virulent parasites are hypothesized to exert stronger selection on their hosts, leading to more heterogeneity in infection success among parasite populations and greater adaptation to local host genotypes (Gandon, 2002; Greischar & Koskella, 2007; Tack et al., 2012). However, although *P. syntomentera* had greater infection success on sympatric rather than allopatric host genotypes, we detected no evidence for such local adaptation in the more virulent *R. ondatrae*. This suggests that observed population-level differences in infection success between the two parasites are more consistent with their varying life cycles and dispersal abilities (as supported by the parasite genetic results), rather than to virulence. We acknowledge that our experiments measured only infection success, which is inherently the product of both host and parasite properties. Future studies that incorporate multiple epidemiological response metrics of both the host and parasite would be a valuable extension of local adaptation research in relation to disease. For instance, beyond variation in resistance, host populations may differ in tolerance, or their ability to mitigate pathology following infection (Parker et al., 2011; Råberg et al., 2007), which may in turn further drive parasite adaptation to local host genotypes.

Unlike commonly employed model systems, parasites in natural systems often use multiple host species, either alternatively or sequentially, making it challenging to predict the situations in which parasites are likely (or unlikely) to be locally adapted (e.g. Lajeunesse & Forbes, 2002). Parasites that use multiple, alternative host species, for instance, may exhibit less local adaptation relative to highly host-specific parasites (Poulin & Forbes, 2012). Correspondingly, in comparing infection results among three amphibian host species commonly infected with *R. ondatrae* in the western USA, we found no evidence for an effect of the parasite source population (sympatric vs. allopatric).

Given that these host species differ in life history and geographic range, it is likely that the observed lack of local adaptation by *R. ondatrae* was not an artefact of using a particular host species. Importantly, for parasites with complex life cycles dependent on multiple host species, selection intensity may also vary over space and throughout the life cycle, with selective pressure strongest in certain host species (Barrett et al., 2008; Louhi et al., 2010). Host specificity in trematodes is generally highest for first intermediate hosts (mollusks) and lowest for second intermediate hosts (Sapp & Loker, 2000), such as the larval amphibians used in this study. Thus, the selection exerted by amphibian hosts on these two trematodes could be relatively weak, leading to a lack of local adaptation when paired with high gene flow. This may also help explain why previous research on snail-trematode interactions has often documented significant local adaptation (e.g., Dybdahl & Lively, 1996; Lively et al., 2004), even when the definitive hosts had high dispersal potential (e.g., birds). Thus, the strongest selection pressure should operate on the 'bottleneck' stage in the life cycle where host specificity is highest, potentially trading off with a lack of local adaptation for other host stages. In addition, such differences in detection of parasite population structure may stem from variation in life cycle complexity (e.g. two-host vs. three-host life cycles) as well as whether hosts reproduce clonally or sexually (Mazé-Guilmo et al., 2016).

Studies of local adaptation in host-parasite systems have revealed fundamental insights about coevolutionary processes in dynamic systems (e.g., Gandon, 2002; Lively, 2017; Thompson, 2005). By experimentally exposing host and parasite populations across a geographic range with corresponding genetic data, results of the current study help to illustrate how the magnitude of local adaptation varies with parasite dispersal capability, population genetic structure and geographic distance. Intriguingly, and in contrast to comparative meta-analyses, our findings suggest that exceptionally high parasite dispersal can limit or constrain opportunities for local adaptation, helping to validate previously untested predictions from theory. We highlight the value of a deeper understanding of parasite-host coevolution, including the influence of host and parasite traits in mediating disease outcomes, for managing and predicting the results of novel species interactions as global translocations of both host and parasite species intensify.

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AUTHOR CONTRIBUTIONS

PTJJ, DMC and JK designed the study; PTJJ, DMC, TR, TM and JC ran the experimental infection studies and collected field samples; TLP, CF, JMH, TJA and VVT processed and analysed genetic data; PTJJ and WEM analysed experimental results; all authors helped write the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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