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RESEARCH

Co-infection with *Leucocytozoon* and Other Haemosporidian Parasites Increases with Latitude and Altitude in New World Bird Communities

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Abstract

Establishing how environmental gradients and host ecology drive spatial variation in infection rates and diversity of pathogenic organisms is one of the central goals in disease ecology. Here, we identified the predictors of concomitant infection and lineage richness of blood parasites in New Word bird communities. Our multi-level Bayesian models revealed that higher latitudes and elevations played a determinant role in increasing the probability of a bird being co-infected with *Leucocytozoon* and other haemosporidian parasites. The heterogeneity in both single and co-infection rates was similarly driven by host attributes and temperature, with higher probabilities of infection in heavier migratory host species and at cooler localities. Latitude, elevation, host body mass, migratory behavior, and climate were also predictors of *Leucocytozoon* lineage richness across the New World avian communities, with decreasing parasite richness at higher elevations, rainy and warmer localities, and in heavier and resident host species. Increased parasite richness was found farther from the equator, confirming a reverse Latitudinal Diversity Gradient pattern for this parasite group. The increased rates of *Leucocytozoon* co-infection and lineage richness with increased latitude are in opposition with the pervasive assumption that pathogen infection rates and diversity are higher in tropical host communities.

Keywords Co-infection · Disease macroecology · Elevational gradient · Host migration · Latitudinal diversity gradient · Parasite macroecology

Introduction

The Latitudinal Diversity Gradient Hypothesis (LDGH) postulates that species diversity increases towards the equator [1, 2]. This longstanding and pervasive macroecological pattern has been documented for a myriad of free-living species [3, 4] and parasitic and infectious organisms in human hosts [5]. Although hotspots of zoonotic diseases are concentrated in tropical sites and emerging infectious disease risks are expected with higher frequency at lower latitudes [6, 7], many parasitic and pathogenic organisms are more prevalent and diverse at higher latitudes [8, 9].

Parasitic and pathogenic organisms rarely occur in isolation in their hosts, meaning that most individual hosts may harbor concomitant infections with at least two genetically different infectious agents [10, 11]. Therefore, parasitic organisms must optimize their transmission by interacting with competing parasites while circumventing the host's immune system [10]. Although infections by multiple disease agents are ubiquitous in wild populations, spatial

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patterns of concomitant infections (hereafter co-infections) have received considerably less attention in comparison with that of single infections and focused mainly on macroparasites or vector-transmitted microparasites in human hosts [11, 12].

As temperature can affect parasite development and vector distribution, it may be among the most influential factors driving infection risk with vector-transmitted pathogens across altitudinal and latitudinal gradients [13, 14]. For instance, hotspots for human malaria risk are predicted to shift towards higher elevations across Africa with warming temperature [15]. However, hotspots for co-infection with two common avian blood protozoan parasites (genera *Leucocytozoon* and *Trypanosoma*) cannot be driven solely by temperature across a latitudinal gradient in Alaska [16].

Infection probability may vary across host communities not only in response to climate filters, but also from shifting contact opportunities in response to changing host species composition and functional traits [17, 18]. Host functional traits such as migratory behavior can enhance contact rates between parasites and new avian hosts across their flyways, and, in turn, increase parasite prevalence and richness [17]. In fact, migratory species had a higher probability of being co-infected with haemosporidian parasites than sedentary species in a palearctic bird community [19]. Moreover, body mass has been uncovered as a universal predictor of parasite richness because larger hosts provide more niche availability for parasite colonization and a more stable habitat for parasite reproduction [20]. Although host body mass has been identified as a global driver for infection probability in avian malaria parasites and related haemosporidians [21], we do not know whether this host trait may impact co-infection with *Leucocytozoon* and related haemosporidian parasites.

Haemosporidians from the genera *Leucocytozoon*, *Plasmodium*, *Parahaemoproteus*, and *Haemoproteus* are a diverse group of vector-transmitted parasites that infect blood cells and other avian tissues where they develop and reproduce [22]. The prevalence for each haemosporidian genus exhibits broad variation among and within avian host clades as well as across zoogeographical regions, but the drivers of such variation in infection probability are studied mainly for single infections of each parasite genus [21]. For example, elevation is a strong predictor of *Plasmodium* and *Leucocytozoon* infection probability at a global scale, but in opposite directions. Whereas single infection probability can be influenced by environmental features [21], the presence of one virulent parasite lineage could modulate the avian host immune system, making the host more susceptible to multiple infections [23].

Co-infections are frequent in the bird-haemosporidian systems [e.g., 16, 19, 24–26] and phylogenetic conservatism seems to play a determinant role in co-infection variation among host species in the same host community [19]. This may be explained because avian host traits that influence host immune response and potentially restrict parasite invasion, such as body mass [27], are strongly affected by phylogenetic relationships [28]. Few studies have explored variation in haemosporidian co-infection rates of birds across environmental gradients ranging from local to regional scales [e.g., 16, 19, 24–26]. The drivers of such variation in co-infection probability among avian clades are only partially known from region-level studies and with conflicting results. For example, *Leucocytozoon* co-infection prevalence decreased with latitude in temperate South America [26], whereas increased in North America [25]. A synthesis across multiple local bird communities sampled along a large latitudinal gradient that can accommodate regional uncertainty is necessary to quantify robust abiotic, biotic, and historical drivers of co-infection probability permitting an exploration of macroecological patterns in haemosporidian co-infection prevalence.

Here we assess the influence of latitude, elevation, climate, and host functional traits on *Leucocytozoon* co-infection and lineage richness across avian communities in the New World. We predicted an increased probability of co-infection and lineage richness in avian communities at higher elevations and latitudes, where *Leucocytozoon* is more prevalent [9, 21]. Based on evidence of environmental filters for the distribution of this parasite genus across the New World [9], we also predicted an elevated prevalence of *Leucocytozoon* co-infections in colder regions. If host functional traits influence infection by multiple pathogens, we would expect an increased probability of a bird being co-infected and harboring higher lineage richness with increased body mass and migratory distance [17, 19, 20].

Methods

Avian Host and Parasite Sampling

Our analyses are based on 11,585 blood and tissue samples from 1208 avian species collected between 1999 and 2019 from Alaska to Patagonia (Fig. 1). This dataset includes 838 localities surveyed across Argentina, Brazil, Chile, Honduras, Mexico, Nicaragua, Peru, and the USA. We gathered geolocation and date for each bird screened for haemosporidian parasites from [9, 18, 24, 29–31]. We also included the results of screening 962 unpublished samples from Alaska and Brazilian Amazonia (see raw data in Supporting Information Table S1).

Parasite lineages were identified from avian tissue samples using a standard molecular barcoding approach. Briefly, DNA extracted from host tissues underwent PCR-based detection targeting a 477-bp barcoding fragment of the cytochrome *b* (cyt-*b*) gene from the haemosporidian

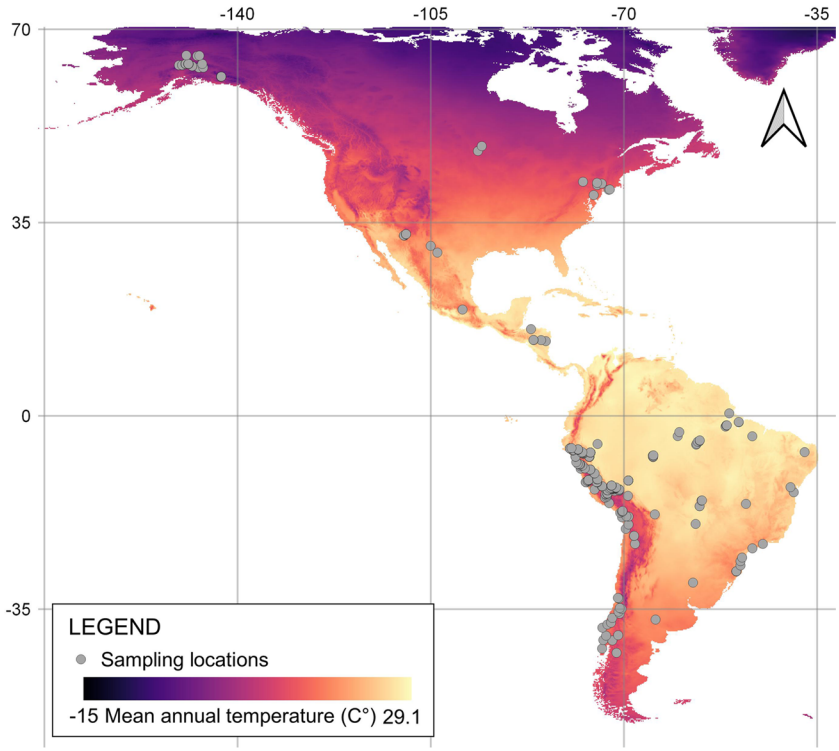

Fig. 1 Sampling localities distributed along a New World latitudinal and temperature gradient

mitochondrial genome. Details on primers used, reaction protocols, and cycling conditions can be found in [32, 33]. Sequence chromatograms with overlapping peaks were considered as co-infections and individual haplotypes were delineated following one of following two methods. First, co-infections with overlapping peaks that differed consistently in both sequencing directions were manually delineated following the protocols of [24]. Second, in co-infections where haplotypes could not be identified manually, we used the program PHASE 2.1.1 [34, 35] following the protocol of [36]. As evidence indicates that avian haemosporidian haplotypes differing by one cyt-*b* nucleotide may be reproductively isolated entities [37], we used the conventional practice of referring to each unique cyt-*b* haplotype as a unique parasite lineage following the standard naming scheme for this group of parasites [38].

Host Functional Traits and Climatic Data

We used the variables of annual mean temperature (Bio1) and annual rainfall (Bio12) to account for climate aspects previously shown to influence haemosporidian prevalence [9, 21]. These climatic variables were obtained from the WorldClim database [39; http://worldclim.org/version2] and were calculated using resolution of 30 arc-seconds (~ 1 km) for each georeferenced individual bird. We considered host body mass (i.e., average species mass) and migratory behavior in our analyses, following previous analyses, to explain prevalence and richness of haemosporidian parasites in the New World [17, 21, 40]. We obtained host species functional traits from the AVONET database [41].

Statistical Analyses

To test our hypotheses, we ran multi-level Bayesian models using the software R [42]. Prior to the Bayesian models, we calculated the phylogenetic signal present in our sample for *Leucocytozoon* prevalence (infection only with this parasite genus), *Leucocytozoon* lineage richness, and co-infection (concomitant infection with *Leucocytozoon* and any other haemosporidian parasite, including the genera *Leucocytozoon*, *Haemoproteus*, *Parahaemoproteus*, or *Plasmodium*). To do so, we filtered bird species with less than five individuals sampled to account for only well sampled species ($n = 10{,}207$). We estimated phylogenetic signal using a full avian phylogenetic tree (AllBirdsHackett1.tre) downloaded from the https://birdtree.org/ project [43]. We filtered this phylogenetic tree to include only the species present in our dataset and then calculated how much of the *Leucocytozoon* prevalence, co-infection rates, and lineage richness present in each bird species could have evolved randomly or was based on the phylogenetic distance among bird species (i.e., Brownian motion). Phylogenetic signal was low in all cases (< 0.15), and, for this reason, phylogeny was not included in the models.

Bayesian models used our full dataset ($n = 11{,}585$) and were implemented using the "brms" package from R [44]. Models evaluating *Leucocytozoon* prevalence, co-infection,

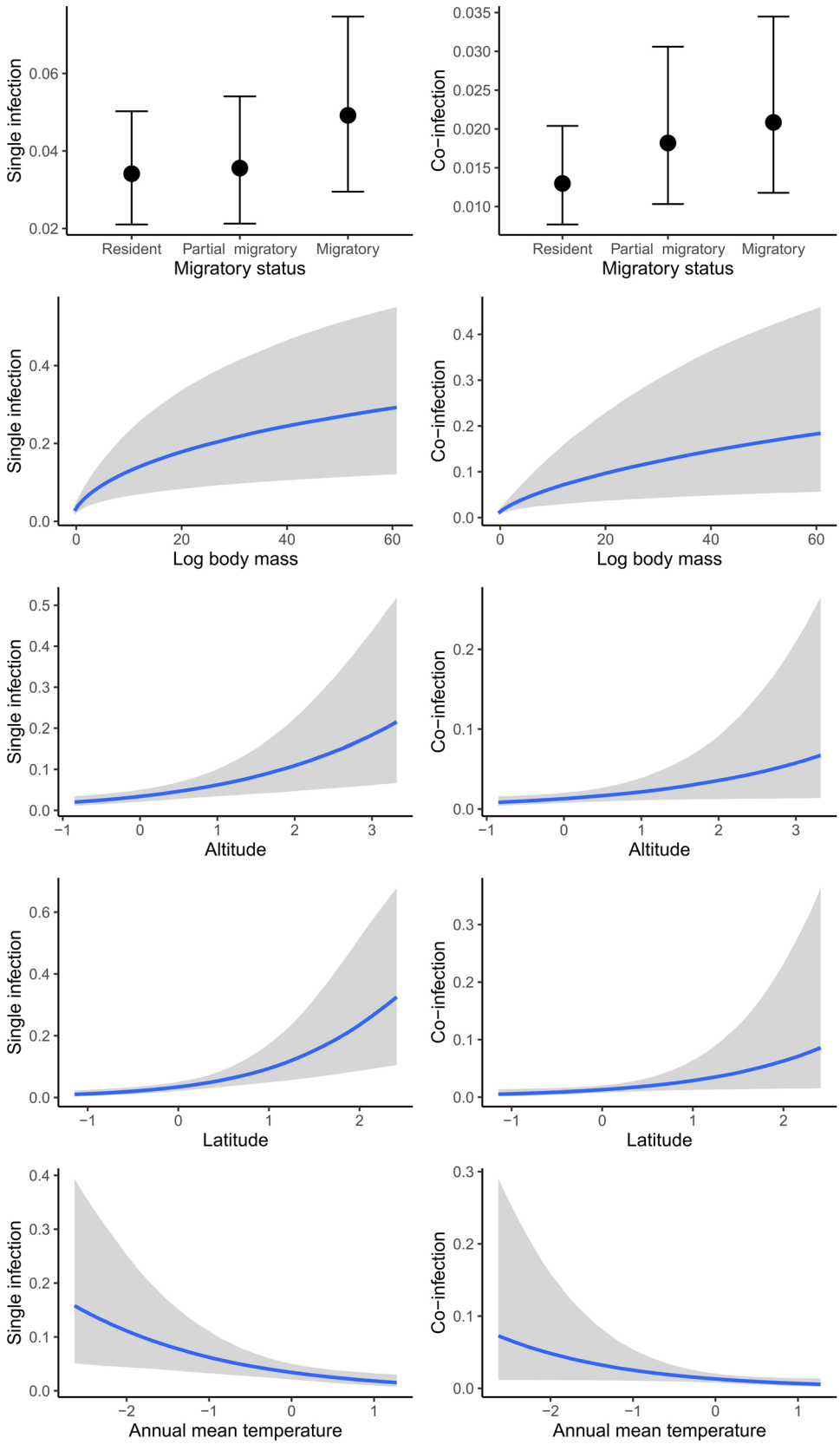

Fig. 2 Mean (±credible intervals) of *Leucocytozoon* single infection and co-infection according to migratory status, host body mass, altitude, latitude, and annual mean temperature

Table 1 Parameter estimates, standard errors, and credible intervals for the Bayesian model testing the relationship between *Leucocytozoon* prevalence and host migratory status, body mass, altitude, annual mean temperature, annual precipitation, and latitude (reference level = resident)

	Estimate	St. deviation	Credible interval	
Intercept	–3.38	0.23	–3.86	–2.95
Partial migrants	0.05	0.12	–0.20	0.29
Full migrants	0.38	0.13	0.14	0.63
Body mass (log)	0.60	0.12	0.36	0.84
Altitude	0.62	0.19	0.25	1.00
Temperature	–0.63	0.23	–1.07	–0.18
Precipitation	0.01	0.19	–0.37	0.37
Latitude	1.10	0.30	0.51	1.70

and *Leucocytozoon* lineage richness per bird species (i.e., response variables) were run with migration status, body mass (log scale), altitude, latitude, annual mean temperature (Bio1), and annual precipitation (Bio12) as explanatory variables. Explanatory variables were all included together; therefore, we ran a total of three models, one for each response variable. All numeric variables were converted to the scales of standard deviations due to the distinct measure scales used in this study (e.g., meters, geographical coordinates, grams). Community ID (i.e., the identification of each bird-parasite community) was set as a random variable. Response and explanatory variable distributions were visually checked. Priors were set using "get_prior" function from the "brms" package and the distribution family was Bernoulli for both *Leucocytozoon* prevalence and co-infection models and negative binomial for the model evaluating *Leucocytozoon* lineage richness. A total of four chains with 2000 iterations were run per model. All models were posteriorly subject to model diagnosis and selection by (i) a visual check of model convergence; and (ii) cross-validation via Pareto-smoothed importance sampling ("loo" function). Plotted results illustrate the predicted values of the response extracted from the Bayesian model.

Results

In total, 1408 of 11,585 birds analyzed were infected with *Leucocytozoon* (overall prevalence of 12%, see Supporting Information Table S1). There was broad variation in *Leucocytozoon* prevalence (ranging from zero to 95%) among the 150 well sampled localities ($n \geq 10$ screened individuals). Co-infections were detected in 50 out of 150 avian host communities (co-infection prevalence ranging from 0 to 73%). The lineage richness of *Leucocytozoon* was heterogeneous across the 150 bird communities, ranging from 0 to 91 (Supporting Information Table S2).

Leucocytozoon prevalence and co-infection seem driven by similar factors (Fig. 2, Tables 1 and 2). In both scenarios, single and co-infection were positively associated with latitude (i.e., distance from the Equator), altitude, and body mass, and negatively associated with annual mean temperature (Tables 1 and 2). Furthermore, co-infections were more common among both partially and fully migratory birds than resident birds, whereas single infection with *Leucocytozoon* was higher only among fully migratory species (Tables 1 and 2). Again, in both cases, no effect of precipitation was found on *Leucocytozoon* probability of infection or co-infection. Nonetheless, it is important to note that the probability of co-infection is close to half (6%, $n = 729$) the probability of single infection with *Leucocytozoon* (i.e., prevalence, 12%, $n = 1408$).

Leucocytozoon lineage richness was negatively related to host body mass, annual mean temperature, annual precipitation, and altitude, whereas latitude was still positively associated with parasite richness (Fig. 3, Table 3). Here, both partially and fully migratory bird species harbored higher *Leucocytozoon* lineage richness when compared to resident birds (Table 3).

Discussion

We demonstrated that co-infection with haemosporidian parasites increased towards high latitudes and elevations supporting our prediction that the higher prevalence of *Leucocytozoon* in cooler environments would influence the susceptibility of avian hosts and enhance co-infection by other haemosporidian lineages. This unusual disease macroecological pattern could be explained by two factors that are not mutually exclusive.

Table 2 Parameter estimates, standard errors, and credible intervals for the Bayesian model testing the relationship between *Leucocytozoon* co-infection and host migratory status, body mass, altitude, annual mean temperature, annual precipitation, and latitude (reference level = resident)

	Estimate	St. deviation	Credible interval	
Intercept	–4.36	0.26	–4.89	–3.89
Partial migrants	0.34	0.17	0.01	0.68
Full migrants	0.48	0.15	0.18	0.78
Body mass (log)	0.69	0.16	0.38	1.00
Altitude	0.51	0.25	0.03	1.01
Temperature	–0.67	0.32	–1.28	–0.03
Precipitation	–0.05	0.24	–0.50	0.48
Latitude	0.85	0.39	0.07	1.59

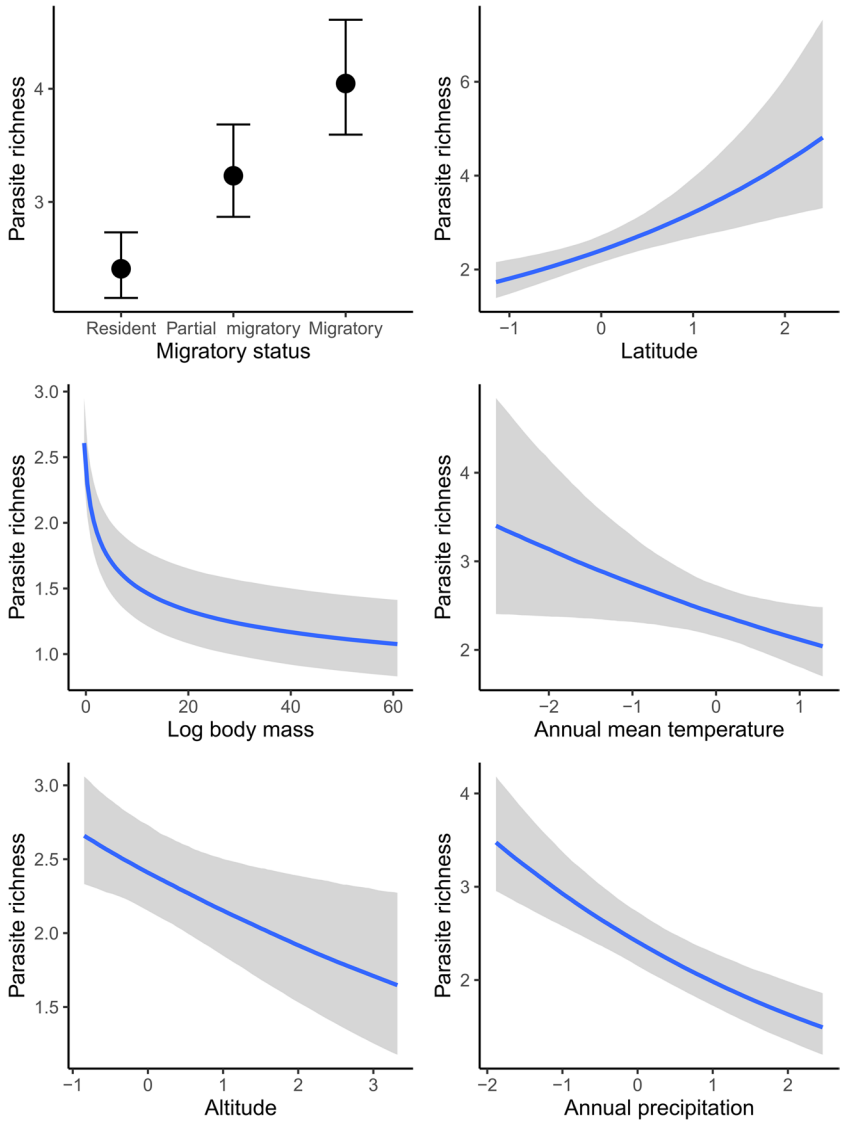

Fig. 3 Mean (± credible intervals) of *Leucocytozoon* lineage richness according to migratory status, host body mass, altitude, latitude, annual mean temperature, and annual precipitation

Table 3 Parameter estimates, standard errors, and credible intervals for the Bayesian model testing the relationship between *Leucocytozoon* richness and host migratory status, body mass, altitude, annual mean temperature, annual precipitation, and latitude (reference level = resident)

	Estimate	St. deviation	Credible interval	
Intercept	0.87	0.06	0.75	0.99
Partial migrants	0.29	0.05	0.24	0.34
Full migrants	0.52	0.03	0.46	0.57
Body mass (log)	–0.19	0.03	–0.25	–0.14
Altitude	–0.11	0.05	–0.20	–0.02
Temperature	–0.11	0.06	–0.26	–0.01
Precipitation	–0.20	0.04	–0.26	–0.12
Latitude	0.29	0.09	0.14	0.45

First, costly life history activities may cause host immunosuppression. For example, energetically costly activities, such as thermoregulation, have been shown to suppress bird immune response. Specifically, birds exposed to cold temperatures have lower antibody response to haemosporidian parasites [45]. Therefore, if cold temperatures have a negative impact on immunocompetence, suppressing host immune responses, then one might expect higher infection rates in birds from colder environments (e.g., higher latitudes and altitudes). This tradeoff between thermoregulation and immunocompetence may be a potential force increasing co-infection rates in bird hosts from colder regions such as Alaska, Patagonia, and the high elevations of the Andes. Long distance migration between breeding and wintering grounds is also a strenuous and physiologically demanding activity that may modulate the maintenance and activation

of the immune response in migratory bird species. Thus, if a tradeoff exists between these two energetically costly activities, migration and immune response, then during migration, birds may be in a poor immunological state leading to reduced resistance and increased susceptibility to co-infection. In fact, long distance migratory bird species exhibit a higher prevalence of *Leucocytozoon* and other haemosporidian parasites [17, 21] than resident species, and we have shown here that migratory birds are also more likely to harbor haemosporidian co-infections and have higher lineage richness of *Leucocytozoon* in the New World. Higher prevalence of co-infection may be explained because infected migratory birds are in a poor immunological state at stopover sites where they are exposed to a higher diversity of both vectors and parasites, which may drive an increase in host susceptibility to secondary infections. Alternatively, migratory bird species may harbor higher co-infection rates because they are exposed to an elevated diversity of *Leucocytozoon* during the breeding season in boreal and temperate grounds [21], and then could be co-infected by a second tropical parasite lineage while on their tropical wintering grounds.

Second, birds may experience greater exposure to *Leucocytozoon* parasites due to increased vector diversity and density at higher latitudes or altitudes. The probability of a bird being co-infected with *Leucocytozoon* consistently increased with increasing elevation in New Word bird communities. This pattern has been previously reported for *Leucocytozoon* prevalence along the tropical Andes in Colombia and Peru [29, 46, 47]. The decreasing *Leucocytozoon* lineage richness with elevation across New World reported here may be driven by the large *Leucocytozoon* diversity found in some mid and low-elevation boreal forest communities, where density and diversity of black flies, the main vectors for *Leucocytozoon* parasites, are also extremely high [48]. Nonetheless, the expected increase in black fly vector diversity [47, 48] and *Leucocytozoon* infection with increasing elevation and latitudes in the New World suggests that *Leucocytozoon* species have higher transmission rates and are therefore better adapted to cooler environments, leading to increased co-infection despite the lower diversity of avian host species in these regions.

Our correlational approach using wild hosts is consistent with an experimental study demonstrating that the presence of one malaria parasite lineage facilitates the invasion by a second lineage that utilizes the same resource in the vertebrate host [49]. This occurs when one generalist parasite species causes anemia in the vertebrate host, thus altering the availability of new red blood cells to sufficiently facilitate the replication of specialist parasites that preferentially infect young red blood cells [50]. Although we did not measure the parasitemia of *Leucocytozoon* or parasite specialization in each host bird, experimental evidence using competitive *Plasmodium* species in rodents showed that inoculation of a generalist parasite species facilitated the increase in abundance of a specialist species in the same host individual [49]. Thus, the presence of a *Leucocytozoon* lineage could facilitate the replication of another haemosporidian either by altering host red blood cell availability or by modulating the host immune response, making it more susceptible to new infections.

Host phylogenetic relatedness might constrain parasite host range expansion and thus promote similar infection rates among host taxa that share a common ancestor. However, host phylogenetic relationships played a negligible role in modulating co-infection in New World birds, confirming a pattern previously demonstrated for boreal birds [24]. This might suggest that *Leucocytozoon* parasite shifts among vertebrate host do not necessarily occur among phylogenetically related avian species [24], but instead through cross-species transmission mediated by generalist vectors. Some black flies do not exhibit strong preference for specific host clades [51]. In fact, these hematophagous insects are apparently generalists in their feeding habits at high elevations [47]. This reinforces the hypothesis that black fly vectors may play a critical role in determining the macroecology and macroevolution of *Leucocytozoon* across avian host communities.

A positive relationship between parasite richness and host body mass would be expected in most host-parasite systems [20]. However, we found that *Leucocytozoon* lineage richness decreased whereas co-infection rates increased in heavier host species. One possible explanation for this pattern is that larger avian species might better tolerate multiple infections by few *Leucocytozoon* lineages across host distributional ranges. Alternatively, intraspecific competition among both parasites and vectors to access avian hosts could be constraining the invasion by a second *Leucocytozoon* lineage in larger host species. Thus, the inferences above may explain the inverse relationship between *Leucocytozoon* co-infection and lineages richness with respect to avian host body mass. This can be conclusively confirmed through analysis of blood films to quantify parasitemia and assess the presence of infective stages of different parasite lineages within the same host. Most importantly, sampling black flies would be imperative to study vector competence and determine whether vectors significantly affect transmission rates and host range expansion within the avian host community.

Conclusion

Co-infection probability and diversity of *Leucocytozoon* parasites exhibit a strong decline towards the tropics, which is the opposite trend that one would predict given the LDGH. This reverse trend has been rarely documented in the literature and little is known about the underlying ecological and

evolutionary causes. Our understanding of this avian-parasite-vector system will improve with sampling and analysis of black flies across a latitudinal and elevational gradient to determine patterns of *Leucocytozoon* diversity and host specificity within the invertebrate hosts. This is imperative to confirm whether *Leucocytozoon* diversity is following vector diversity towards the poles and high elevations.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00248-023-02283-x.

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Author Contribution AF and DAD conceived the idea, designed the research, and wrote the manuscript. DAD ran the analyses. EJW, JDW, and JHD generated new data. JAB curated the data. All authors contributed critically to the manuscript drafts and gave final approval for publication.

Data Availability The bird infection data used in this study are available as Supporting Information Table S1. All parasite sequences are deposited in GenBank, and accession numbers can be found in the Supporting Information Table S1.

Data Accessibility The raw dataset is available in the Supporting Information. All unpublished DNA sequences will be available in Genbank and MalAvi.

Declarations

Competing interests The authors declare no competing interests.

Conflict of Interest The authors declare no competing interests.

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