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Pathogen biology

Parasite-associated mortality in birds: the roles of specialist parasites and host evolutionary distance

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The factors that influence whether a parasite is likely to cause death in a given host species are not well known. Generalist parasites with high local abundances, broad distributions and the ability to infect a wide phylogenetic diversity of hosts are often considered especially dangerous for host populations, though comparatively little research has been done on the potential for specialist parasites to cause host mortality. Here, using a novel database of avian mortality records, we tested whether phylogenetic host specialist or host generalist haemosporidian blood parasites were associated with avian host deaths based on infection records from over 81 000 examined hosts. In support of the hypothesis that host specialist parasites can be highly virulent in novel hosts, we found that the parasites that were associated with avian host mortality predominantly infected more closely related host species than expected under a null model. Hosts that died tended to be distantly related to the host species that a parasite lineage typically infects, illustrating that specialist parasites can cause death outside of their limited host range. Overall, this study highlights the overlooked potential for host specialist parasites to cause host mortality despite their constrained ecological niches.

1. Introduction

Free-living organisms commonly serve as hosts to a diverse array of parasites without suffering major fitness consequences over the short term, though severe illness or death can occur rapidly such as when naïve hosts encounter novel parasites [1–4]. Generalist parasites with low host specificity, or the ability to infect and develop in a phylogenetically diverse suite of host species, are often the sources of such emerging infectious diseases [5,6]. Host generalists can also be the most abundant parasites in host communities [7] and may be more likely to become invasive than specialist parasites [8]. As a result, the ecology and evolution of host generalist parasites have received a great deal of attention relative to parasites with more restricted host ranges [9,10].

In contrast, the potential for specialist parasites with high host specificity to cause harm to naïve hosts has rarely been considered due to the constrained ecological niches that limit the ability of specialists to establish infections in a broad array of host species. However, specialist parasites do have the potential to cause significant harm to naïve hosts without establishing a transmissible infection (i.e. 'dead-end' infections [11]) due to immunopathological effects of the host immune system responding inappropriately to a pathogen to which it is not adapted [11]. As highly host-specific parasites are common in many systems [12], the potential for specialist parasites to serve as a source of host mortality may currently be underappreciated.

Table 1. Summary of the 33 studies that documented avian host mortality that was associated with infection by a haemosporidian *cytb* lineage.

reference	location of death	no. host deaths	host species	sampling context
Schrenzel *et al*. [25]	California, USA	7	seven species (Passeriformes)	aviary
Ferrell *et al*. [26]	Texas, USA	6	three species (Passeriformes and Phoenicopteriformes)	zoo
Donovan *et al*. [27]	California, USA	10	six species (Passeriformes)	zoo
Bueno *et al*. [28]	Sao Paulo, Brazil	2	*Spheniscus magellanicus*	zoo
Hill *et al*. [29]	Stewart Island, New Zealand	1	*Megadyptes antipodes*	wild
Dinhopl *et al*. [30]	Vienna, Austria	4	*Spheniscus humboldti*	zoo
Olias *et al*. [31]	Switzerland/Germany	3	three species (Psittaciformes)	aviary
Howe *et al*. [32]	New Zealand	3	three species (Passeriformes and Apterygiformes)	wild
Argilla *et al*. [33]	Enderby Island, New Zealand	1	*Megadyptes antipodes*	wild
Cannell *et al*. [34]	Penguin Island, Australia	4	*Eudyptula minor*	wild
Chagas *et al*. [35]	Sao Paulo, Brazil	1	*Alpochen aegyptica*	zoo
Silveira *et al*. [36]	Florianopolis, Brazil	2	*Spheniscus magellanicus*	rehabilitation centre
Vanstreels *et al*. [37]	Florianopolis, Brazil	4	*Spheniscus magellanicus*	rehabilitation centre
Dinhopl *et al*. [38]	Vienna, Austria	7	five species (Passeriformes and Piciformes)	Wild
Vanstreels *et al*. [39]	multiple locations, Brazil	20	*Spheniscus magellanicus*	rehabilitation centre
Martinsen *et al*. [40]	New Hampshire, USA	2	*Gavia immer*	wild
Sijbrandra *et al*. [41]	Multiple locations, New Zealand	4	*Eudyptula minor*	wild (2) and zoo (2)
Jia *et al*. [42]	Beijing, China	8	four species (Gruiformes)	zoo
Niedringhaus *et al*. [43]	California/Louisiana, USA	8	*Bubo virginianus*	wild
Rouffaer *et al*. [44]	Flanders, Belgium	4	*Turdus merula*	wild
Verwey *et al*. [45]	Queensland, Australia	2	two species (Psittaciformes)	aviary
Galosi *et al*. [46]	Italy	1	*Poicephalus robustus*	aviary
Groff *et al*. [47]	Washington, USA	1	*Picoides albolarvatus*	wild
Ortiz-Catedral *et al*. [48]	multiple locations in Europe	21	12 species (Psittaciformes)	aviary
Taunde *et al*. [49]	Rio Grande do Sul, Brazil	2	*Spheniscus magellanicus*	rehabilitation centre
Vanstreels *et al*. [50]	Espirito Santo, Brazil	4	*Spheniscus magellanicus*	rehabilitation centre
Himmel *et al*. [51]	Vienna, Austria	137	two species (Passeriformes)	wild
Spottiswoode *et al*. [52]	New York, USA	31	two species (Charadriiformes and Anseriformes)	zoo
Vanstreels *et al*. [53]	Espirito Santo, Brazil	1	*Puffinus puffinus*	rehabilitation centre
Cocumelli *et al*. [54]	Central Italy	2	*Agapornis roseicollis*	zoo
Meister *et al*. [55]	Berne Animal Park, Switzerland	4	*Fratercula arctica*	zoo
Thorel *et al*. [56]	ZooParc de Beauval, France	1	*Somateria mollissima*	zoo
Yoshimoto *et al*. [57]	Saitama Prefecture, Japan	1	*Bubo scandiacus*	zoo

Birds are an excellent host group for the study of the effects of specialist and generalist parasites on mortality, as birds that die naturally are often investigated intensively post-mortem. Avian haemosporidian parasites, relatives of the parasites that cause malaria in humans [13], are abundant throughout the world and have the potential to cause rapid morbidity and death in their hosts [14,15]. Avian haemosporidians have been heavily studied over the past 20 years [16] following the development of a robust cytochrome *b* (*cytb*) sequencing protocol, which has resulted in the development of a large global database that can be used to assess haemosporidian distributions and host specificity [17].

Here, we use a novel database of avian mortality records and analysis of haemosporidian parasite–host specificity that incorporates host phylogeny to test whether deadly infections in birds are caused primarily by generalist or specialist parasites. We tested two alternative hypotheses: (i) generalist parasites are more likely to be associated with host mortality due to their ability to initiate infection in a broad phylogenetic diversity of hosts, and (ii) specialist parasites are

more likely to be associated with host mortality because of their potential to be highly virulent in non-adapted host species. We find that haemosporidians that infect more closely related host species than expected under a null model were the primary source of avian mortalities, and that these parasites were found to often cause mortality in hosts that are distantly related to the host species that each parasite normally infects. Our findings illustrate that specialist parasites have the potential to be a significant source of host mortality.

2. Material and methods

We conducted a literature search for studies published since August 2021 that documented the death of at least one bird associated with infection by parasites in the order Haemosporida (see electronic supplementary material, methods for search queries). We considered studies that documented avian mortality due to natural infection of either wild birds or captive birds that were kept in outdoor facilities. In the final database, we retained only studies for which a necropsy and/or histological examination was performed post-mortem, and the authors stated that haemosporidian infection was definitively the cause of death or where the host exhibited internal damage from haemosporidian infection that was consistent with the cause of death. The final database only included studies for which the authors generated *cytb* sequence data for each haemosporidian that was implicated in a bird's death, which allowed for comparison to the global haemosporidian database MalAvi [17]. For each study, we recorded the host species that died, whether the host was native to the location in which the death occurred, and whether each host that died was naïve to the parasite that was associated with its death (see electronic supplementary material, methods for how native distributions and naiveté were classified).

We estimated the host specificity of each haemosporidian lineage that was associated with an avian death using a global database of haemosporidian infections of birds. This dataset was based primarily on the 'Hosts and Sites Table' of the MalAvi database ([17]; v. 2.5.0 downloaded 10 August 2021), which consisted of at least 80 037 sampled avian hosts. We also generated novel haemosporidian records from 1641 avian hosts sampled in temperate North America (Pennsylvania and New York, USA; electronic supplementary material, methods), for a total of 81 678 sampled hosts. We constructed a parasite by host interaction matrix, with the cells containing the number of times each parasite was found within each host species.

As host specificity reflects a continuum [18], we tested whether parasites were more or less phylogenetically host-specific than expected by chance using a null model approach [19]. We characterized the host specificity of each haemosporidian lineage using metrics that measure the phylogenetic diversity of communities using the R package *picante* [20]. We calculated mean pairwise distance (MPD) of the hosts infected by each parasite and its standardized effect size using the 'ses.mpd' function in *picante* with 1000 randomizations, the independent swap algorithm and abundance weighting to account for host sampling bias. This method has been widely used to characterize host specificity in a diversity of symbionts (e.g. [21]) and has the advantage of reporting estimates that are intuitive and directly comparable. We restricted the analysis for each haemosporidian lineage to include only the hosts found within the continents in which the parasite occurs, based on the records in the MalAvi database. The avian host phylogeny was obtained from www.birdtree.org [22] (electronic supplementary material, methods).

We also tested how distantly related the hosts that died were to the hosts that are typically infected by each haemosporidian lineage by calculating the 'host evolutionary isolation' metric of Farrell & Davies [23], which measures the mean phylogenetic distance of each host species within a parasite's host range to a focal host species (here the focal species is the host species that died). We modified this metric by weighting by infection frequencies per host species, so that all previously documented host infection records were considered in the calculation (electronic supplementary material, methods). We used a phylogenetic ANOVA to test whether host species that died with a haemosporidian infection differed in their mean phylogenetic distance to surviving hosts from host species that were infected with the same lineages but were otherwise healthy at the time of sampling using the phylANOVA function from the *phytools* package in R [24] with 1000 simulations.

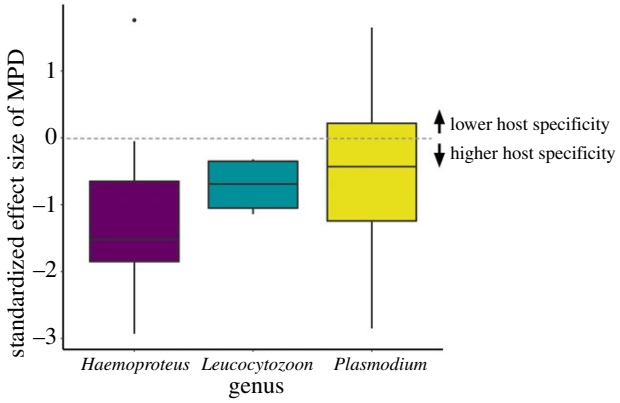

Figure 1. Boxplots of standardized effect size of MPD for haemosporidian lineages in the genera *Leucocytozoon*, *Haemoproteus* and *Plasmodium* associated with a host mortality event.

3. Results

We found 33 studies consisting of 303 total records from the years 2003–2021 that fulfilled our criteria for inclusion in this analysis (table 1). The 303 records were associated with 49 different haemosporidian *cytb* evolutionary lineages that are represented in the MalAvi database. We assembled a global database of haemosporidian infection records to characterize the phylogenetic host specificities of the parasites that were associated with host mortality, which resulted in identifying 6771 records of the 49 focal haemosporidian lineages from at least 81 678 sampled individual avian hosts. Out of the 34 haemosporidian lineages for which we had adequate sample size to measure phylogenetic host specificity, 25 lineages exhibited negative standardized effect sizes of MPD (SES-MPD), indicating a tendency towards higher host specificity (figure 1 and table 2). Eight haemosporidian lineages exhibited significantly lower SES.MPD *z*-score values (higher host specificity) than expected under a null model ($p < 0.05$). Overall, 15 lineages exhibited *z*-scores that were more than one standard deviation below the mean (indicating higher host specificity), while only three lineages exhibited *z*-scores that were more than one standard deviation above the mean (indicating low host specificity or generalism). The haemosporidian lineages that infected captive versus wild hosts showed similarly high host specificity ($t = -0.65$, $p = 0.52$), as did the lineages that infected naïve versus not naïve hosts ($t = -0.29$, $p = 0.78$) (electronic supplementary material, Results).

Phylogenetic ANOVA revealed that there was a significant difference in mean phylogenetic distance to surviving hosts between the host species that died with a

Table 2. Estimates of standardized effect size of MPD for 34 haemosporidian cytb lineages that were recorded as associated with mortality in at least one avian host. Lineages denoted with an asterisk and in italics had higher host specificity than expected by chance using a randomization approach.

cytb lineage	genus	no. records	distribution	MPD	*z*-score	*p*-value
BUVIR06	*Leucocytozoon*	2	N. America	24.6	−0.36	0.427
COCOR09	*Leucocytozoon*	95	Asia, Europe	12.9	−1.14	0.17
STOCC16	*Leucocytozoon*	2	N. America	24.6	−0.32	0.43
TUMER01	*Leucocytozoon*	27	Africa, Europe	6.4	−1.02	0.18
EUMIN01	*Haemoproteus*	5	Oceania, S. America	103.6	1.76	0.97
MELSTR01	*Haemoproteus*	3	N. America	21.8	−0.85	0.23
PYERY01	*Haemoproteus*	30	Africa, Asia, Europe, N. America, S. America	62.7	−0.05	0.41
*SIAMEX01**	*Haemoproteus*	*49*	*N. America*	*38.5*	*−1.61*	*0.019*
*STVAR01**	*Haemoproteus*	*148*	*Africa, N. America*	*11.7*	*−1.79*	*0.035*
*TASCH01**	*Haemoproteus*	*33*	*S. America*	*34.8*	*−2.93*	*0.001*
TUPHI01	*Haemoproteus*	41	Asia, Europe, N. America, S. America	20.9	−1.43	0.10
*TURDUS2**	*Haemoproteus*	*139*	*Africa, Asia, Europe, N. America, S. America*	*24.9*	*−2.03*	*0.04*
AFTRU5	*Plasmodium*	23	Africa, Asia, Europe, N. America	47.2	−0.37	0.32
CATUST05	*Plasmodium*	81	N. America, S. America	66.3	−0.69	0.28
DENPET03	*Plasmodium*	132	N. America, S. America	90.5	0.03	0.59
*DENVID02**	*Plasmodium*	*59*	*Asia, S. America*	*6.9*	*−1.69*	*0.035*
FANTAIL01	*Plasmodium*	16	Asia, Europe, Oceania	85.3	1.65	0.98
GASAN01	*Plasmodium*	3	N. America	38.7	−0.13	0.47
GRW04	*Plasmodium*	442	Africa, Asia, Europe, N. America, Oceania, S. America	64.2	−1.22	0.1
GRW06	*Plasmodium*	181	Africa, Asia, Europe, N. America, Oceania, S. America	104.2	1.26	0.90
GRW11	*Plasmodium*	414	Africa, Asia, Europe	56.6	−0.49	0.25
LAIRI01	*Plasmodium*	59	N. America, S. America	83.8	0.50	0.68
LINN1	*Plasmodium*	198	Africa, Asia, Europe, N. America, Oceania	26.7	−1.56	0.08
PADOM09	*Plasmodium*	154	N. America, S. America	93.5	0.41	0.71
*PADOM11**	*Plasmodium*	*355*	*N. America, S. America*	*68.9*	*−1.70*	*0.008*
PHPAT01	*Plasmodium*	20	N. America, S. America	87.6	0.82	0.77
SEIAUR01	*Plasmodium*	311	N. America	65.0	−1.03	0.12
SGS1	*Plasmodium*	3204	Africa, Asia, Europe, N. America, Oceania, S. America	68.5	0.09	0.56
SPMAG04	*Plasmodium*	3	S. America	42.2	−0.13	0.46
SPMAG06	*Plasmodium*	6	S. America	28.4	−1.25	0.14
SPMAG08	*Plasmodium*	9	S. America	80.0	0.26	0.57
*SYAT05**	*Plasmodium*	*422*	*Africa, Asia, Europe, N. America, Oceania, S. America*	*27.0*	*−1.79*	*0.039*
*TURALB01**	*Plasmodium*	*20*	*S. America*	*8.4*	*−2.85*	*0.001*
WW3	*Plasmodium*	81	Africa, Europe, N. America, S. America	65.4	−0.56	0.24

haemosporidian infection and host species that were infected with the same parasite lineages but appeared to be healthy at the time of sampling ($F = 42.8$, $p = 0.039$; figure 2). We found no relationship between the host specificity of a lineage and the mean evolutionary distance of the host it infected to surviving hosts (phylogenetic generalized least squares (PGLS), $\beta = -0.12$, $R^2 = -0.03$, $p = 0.98$; electronic supplementary material, figure S2).

4. Discussion

Using a novel database of fatal blood parasite infections in birds and estimates of parasite phylogenetic host specificity, we have shown that documented instances of avian host mortality are most commonly associated with parasites that have higher host specificity than expected under a null model. Supporting the hypothesis that specialist parasites can be highly virulent to non-adapted hosts, we found that hosts that died tended to be more distantly related to a parasite's typical hosts than hosts that appeared to be healthy at the time of sampling.

It is important to acknowledge potential limitations of our analysis, as our avian mortality database included deceased hosts that varied in condition (some were kept in rehabilitation centres) and native distribution (some captive hosts were not native to the location in which they were kept). However, we found an overwhelming signal of specialization in the lineages

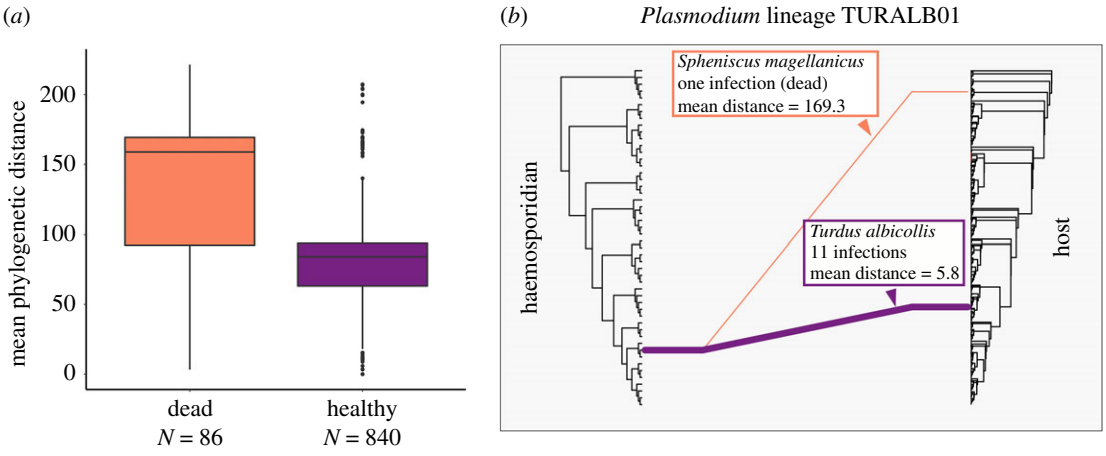

Figure 2. (*a*) Boxplots depicting variation in mean phylogenetic distance among deceased avian hosts and hosts that were infected with the same haemosporidian lineages but appeared to be healthy at the time of sampling. (*b*) Host associations for lineage TURALB01 depicting mean phylogenetic distance of a host that died (*Spheniscus magellanicus*) relative to hosts in the wild (genus *Turdus*). Line width reflects host infection frequency.

that were associated with avian host mortality, irrespective of whether hosts were kept in potentially stressful environments, whether we removed distantly related hosts such as penguins and whether hosts were naïve to the parasites that were associated with their deaths, indicating that this was not a significant limitation of our study (see electronic supplementary material, Results for analysis of data subsets). And while eight parasite lineages in total exhibited statistically significant ($p < 0.05$) specificity, it should be noted that several other parasite lineages exhibited striking patterns of high host specificity but did not reach the threshold for statistical significance (e.g. COCOR09). The inability of the SES-MPD randomization approach to classify this lineage and others as specialists highlights that this method is conservative when sample sizes are small and outlier infections occur in distantly related hosts, which has been documented previously [58]. Though it was somewhat surprising to find that some *Plasmodium* lineages such as GRW04 that can infect dozens of host species were classified as having higher host specificity than expected under a null model, closer inspection of infection patterns reveals that most infections of this lineage occur in a small number of related passeriform families, which explains the finding of phylogenetic specialization in this analysis. Overall, the statistical and taxonomic patterns reveal a consistent association between avian mortality and infection with host specialist parasites.

The strong signal of high host specificity in our dataset was striking considering that specialist parasites have been historically overlooked as potential sources of host mortality. The lack of attention to specialist parasites may be due in part to research suggesting that specialists suffer from a trade-off between efficient use of resources on a limited breadth of host species and the ability to initiate infection in hosts outside of this range [59]. Individual specialist parasite species may also simply be less abundant and widespread than generalists at the community level [7,60,61]. On the contrary, generalists that can infect many host species may have low virulence in these hosts; for instance, [62] found experimentally that generalist *Plasmodium* lineages were not more likely to cause host mortality than lineages with higher host specificity. We show here that specialists are clearly capable of causing mortality in hosts both within and outside of their typical host range.

Hosts that died had higher mean phylogenetic distance to other species within a parasite's host range than host individuals that were apparently healthy at the time of sampling, indicating that phylogenetic distance from a parasite's typical hosts can influence the outcome of host–parasite interactions. This result broadly supports several recent studies that have found that the more distantly related a species is from a parasite's typical hosts, the more susceptible that species seems to be to severe disease or death [23,63]. One possible explanation for this association is an increase in parasite virulence without a correlated increase in transmission as host phylogenetic distance increases, whereby parasites are capable of developing infections that are damaging to the host but result in a transmission 'dead-end' [11]. Decoupled transmission and virulence are apparent in several studies that contributed to our database, such as the study by Ortiz-Catedral *et al.* [48], which documented high virulence of thrush (genus *Turdus*)-specific haemosporidian lineages infecting captive Psittaciformes (parrots and their relatives) despite no evidence for the transmissible life stage in the infected hosts. Because our database included species that were not native to the location in which they died, phylogenetic distance estimates could have been biased towards higher values. However, there was no difference in mean phylogenetic distance to surviving hosts in native hosts that died and non-native hosts that died (phylogenetic ANOVA, $p = 0.86$).

A major goal of future research on host–parasite interactions will be to determine the functional mechanisms that explain why specific host–parasite pairs result in extremely high virulence, and why this effect is accentuated the more phylogenetically 'isolated' a host is with respect to a parasite's typical host range. A deep understanding of this interaction could potentially help inform our ability to predict virulence in novel host–parasite interactions, as is anticipated with the continuation of rapid global change and human-mediated movement of pathogens throughout the world.

Ethics. Samples from Pennsylvania were collected under Federal Bird Banding permit no. 23 679 and sample collection was approved by the Institutional Animal Care and Use Committee of Drexel University (protocol nos. 20 369 and 20 689). Samples from New York were collected under United States Fish and Wildlife Service Federal permit no. MB779035-1 and New York State Department of Environmental Conservation permit 1480, and approved by the Institutional Animal Care and Use Committee of the American Museum of Natural History.

Data accessibility. Novel parasite records from Pennsylvania and New York, data files and associated R code (avian deaths database, host records for host specificity analysis, host and parasite phylogenies, and R code) are currently available from the Dryad Digital Repository: https://doi.org/10.5061/dryad.c59zw3r8t [64].

Authors' contributions. S.C.G.: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, visualization, writing—original draft and writing—review and editing; S.R.: data curation, methodology and writing—review and editing; M.H.: data curation, methodology and writing—review and editing; J.D.W.: resources and writing—review and editing.

All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

Competing interests. We declare we have no competing interests.

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