Interactions between Micro- and Macroparasites Predict Microparasite Species Richness across Primates

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ABSTRACT: Most wild animals face concurrent challenges by multiple infectious organisms, and immunological responses triggered by some parasites may increase susceptibility to other infectious agents. Immune-mediated interactions among parasites have been investigated among individuals in a population, but less is known about broader comparative patterns. We investigated the "macro-micro facilitation hypothesis" that higher helminth prevalence in a host species provides greater opportunities for intracellular parasites to invade, resulting in higher richness of intracellular microparasites. We obtained data on average helminth prevalence for 70 primate hosts, along with data on richness of intra- and extracellular infectious organisms. Using Bayesian phylogenetic methods, we found that primate species with higher overall helminth prevalence harbored more species of intracellular microparasites, while the positive association between helminth prevalence and extracellular microparasite species richness was weaker. The relationships held after controlling for potentially confounding variables, but associations were not found in focused tests of prevalence for six genera of well-studied helminths. The magnitude of support and effect sizes for overall helminth prevalence on intracellular microparasite species richness was similar to support for other well recognized ecological and life-history drivers of parasite species richness. Our findings therefore suggest that intrahost parasite interactions are as important as some ecological characteristics of hosts in accounting for parasite richness across host species.

Keywords: parasitism, comparative study, coinfection, immune response, immune trade-off.

Introduction

In comparative tests across species, host traits involving life history, ecology, and behavior have been linked to variation in the abundance or richness of parasites. For instance, host body size, geographic or home range size, and population density often emerge as key predictors of parasite species richness across mammalian taxa (Arneberg 2002; Nunn et al. 2003; Ezenwa et al. 2006; Lindenfors et al. 2007; Kamiya et al. 2013). Environmental factors such as latitude and rainfall also frequently predict parasite richness across geographical regions (Guernier et al. 2004; Nunn et al. 2005; Bordes et al. 2011). These patterns suggest that fundamental ecological processes, such as species-area relationships and latitudinal gradients, shape patterns of parasitism. Much of the variation in parasite species richness across hosts remains unexplained, however, even when multiple host and environmental traits are considered (Poulin 1997).

Recent evidence suggests that within-host parasite interactions can influence patterns of infection at the individual host level (Graham 2008; Ezenwa and Jolles 2011; Griffiths et al. 2011; Pedersen and Antonovics 2013). These findings therefore raise the possibility that parasites themselves may influence one another's patterns of diversity via interactions that occur within hosts. Despite the ubiquity of coinfection in the wild, however, the potential role of parasite interactions in shaping patterns of infection across species has yet to be considered. Such comparative studies are important because they reveal the generality of a phenomenon using a different level of variation—interspecific variation rather than variation among individuals or populations of the same species.

As with free-living species, indirect interactions among parasites can be mediated from the "bottom up" by competition for resources, or from the "top down" by shared predation. Bottom-up effects arise when multiple parasite species compete for a similar host resource, whereas top-down effects arise from immunological responses triggered

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by one parasite that indirectly affects other parasites in the same host (Pedersen and Fenton 2007). Because the immunological effects of certain parasites are known, it is possible to generate predictions for the potential outcome of immune-mediated interactions between specific combinations of parasites. For instance, immunological studies of laboratory rodents and humans suggest that helminth infections induce immunological changes within the host that facilitate infection by a number of microparasites, including viruses such as the human immunodeficiency virus, bacteria such as those that cause leprosy or tuberculosis, and protozoa such as *Plasmodium* (Co et al. 2007; Walson et al. 2008; Diniz et al. 2010; Metenou et al. 2011). In fact, a meta-analysis of laboratory mouse studies showed that helminth coinfection uniformly increased microparasite density in situations when the helminth and microparasite did not share similar resources (Graham 2008). The increase in microparasite density was strongly associated with helminth-induced suppression of microparasite-specific immune responses (Graham 2008). Through these and other mechanisms, helminth-microparasite interactions taking place within a host may scale up to influence broader scale patterns of infection.

Following previous research noted above, we also consider the impacts of helminths. We retained this focus because helminths are among the most widespread parasites of humans, wildlife, and domesticated mammals (Petney and Andrews 1998), and they share a long coevolutionary history with vertebrates (Jackson et al. 2009). Helminths also tend to be long-lived in their hosts and produce a suite of consistent responses in the mammalian immune system (Diaz and Allen 2007; Allen and Maizels 2011).

Indirect effects of helminths on microparasites can result from at least three well-described immune mechanisms. First, helminths typically induce a T-helper cell type 2 (Th2) immune response in the host, while intracellular parasites induce a T-helper cell type 1 (Th1) response (Mosmann and Sad 1996). Both types of immune responses result in distinct sets of messenger molecules (cytokines), and importantly, cytokines produced by Th2 cells suppress Th1 immune function and vice versa (Abbas et al. 1996). This cross-regulatory interaction between Th2 and Th1 responses is a major way that helminths can suppress immunity to intracellular parasites. Second, many helminths protect themselves from the host immune system by exploiting the host's immunoregulatory pathways. In these situations, helminths enhance the activity of regulatory T-cells (T regs) that stimulate the release of cytokines that suppress both Th1 and Th2 responses (Maizels et al. 2004, 2009). Thus, activity of helminths can result in generalized suppression of immune responses to both intracellular and extracellular microparasites. Third, a recently described lineage of immune cells—the T-helper cell type 17 (Th17) cells—orchestrates critical immune responses against extracellular bacteria and fungi and some intracellular parasites (Curtis and Way 2009). Like Th1 responses, Th17 responses are often suppressed during helminth infection (Elliott et al 2008; Walsh et al. 2009). Helminth-associated Th17 suppression may therefore influence the host immune response to both intracellular and extracellular parasites. Given this combination of suppressive effects that helminths have on the host immune system, these parasites may facilitate invasion of the host by a wide range of other infectious organisms.

We took a comparative approach to investigate how interactions among parasites influence cross-species patterns of infection in wild hosts. Specifically, we tested the hypothesis that helminth (macroparasite) infection provides an opportunity for intracellular and extracellular microparasites to establish within primate hosts due to helminth-induced suppression of antimicroparasite immunity (which we call the "macro-micro facilitation hypothesis"). In a comparative context, we predicted that increases in helminth prevalence (i.e., the proportion of individuals infected) lead to correlated increases in the species richness of microparasites. Thus, we explicitly tested the prediction that when more individual hosts of a species experience helminth infections, more microparasites will be documented in that species. We used microparasite richness because it captures susceptibility to a wide range of organisms without regard to transmission mode, and is commonly used in studies of ecological drivers of parasitism.

Although causality is difficult to assess in comparative studies, we undertook several additional analyses that help us to investigate the causal links in the macro-micro facilitation hypothesis. First, we investigated the association between helminth prevalence and microparasite richness separately for intra- versus extracellular microparasites. Based on our framework, we predict a positive, but weaker, association between helminth prevalence and extracellular microparasite richness because helminths affect extracellular parasites via only two of three potential suppressive mechanisms discussed above (i.e., by enhancing T-regulatory and suppressing Th17 responses) versus all three for intracellular parasites. Second, by including several key covariates in the statistical models, we evaluated the relative effects of helminths and host life-history/ecological traits as predictors of microparasite richness. These multivariate tests also enabled us to control for variables that may influence the richness of parasites and thus to reduce the risk that associations between microparasite richness and macroparasite prevalence are really driven by factors involving host ecology and behavior rather than by interactions among the parasites themselves. Finally, we examined relationships between the prevalence of the best-

studied helminth genera and microparasite richness to investigate whether particular groups of helminths drive effects at the aggregate level.

Material and Methods

Data on parasites of primates came from the Global Mammal Parasite Database (http://gmpd.nunn-lab.org/; Nunn and Altizer 2005). This database includes records of both microparasites (protozoa, viruses, bacteria, and fungi) and macroparasites (helminths and arthropods) but excludes known commensal organisms. The primate portion of the database continues to be updated and is substantially larger than it was in many of the original articles that used the database (Nunn et al. 2003, 2004, 2005). The version of the database used here contained 5,980 records of host-parasite relationships (including some cases of multiple records of the same host-parasite combination from different sampling periods or locations). These records represented 145 primate host species and 623 parasite species, and they came from 517 references. Importantly, data collation was restricted to studies of free-living primate populations; samples from zoo animals and those in other captive settings are excluded from the database.

For each parasite or infectious disease reported from a wild primate population, the type of parasite was recorded in the database (virus, protozoan, fungus, arthropod, helminth, bacterium), along with parasite genus and species names, host genus and species names (later revised according to Corbet and Hill 1991), and information on the location and method of sampling. Parasites with clear synonyms were collapsed into one species, taxonomic records were scanned in current textbooks and online databases, and parasites identified only to the genus level were included in the analysis if they represented a unique record for that genus in a host species.

To these core data, we added information on the type of infection (intracellular vs. extracellular) for viruses, bacteria, and protozoa. We classified parasites into four distinct categories: (1) obligate intracellular: organisms capable of reproducing only inside host cells, (2) obligate extracellular: organisms capable of reproducing only outside host cells, (3) facultative intracellular: organisms capable of reproducing both inside and outside of hosts cells independent of life stage, and (4) intra- and extracellular: organisms capable of living inside or outside host cells, depending on stage of growth. All viruses were classified as obligate intracellular parasites based on their exclusive intracellular reproduction. To classify bacteria and protozoa, we used the full Latin binomial to search the literature for studies documenting the characteristics of each parasite. In this way, we were able to classify 74% of bacteria and 90% of protozoa in our data set into one of the four categories. To test the macro-micro facilitation hypothesis, we compiled parasite species richness for obligate intracellular and obligate extracellular microparasites only, as this should provide the cleanest test of the hypothesis that effects differ for these two groups of parasites.

We quantified levels of helminth infection across primate species using prevalence (i.e., the proportion of individual hosts infected). We used prevalence rather than other measures of abundance, such as intensity, because prevalence provides a more comparable measure of the degree to which helminths may have shaped a host species' immune phenotype over evolutionary time. Thus, prevalence was interpreted as the relative fraction of individuals per species experiencing helminth-induced immunosuppression.

In a first analysis of "all-helminth prevalence," we extracted prevalence data for each host species in three ways: as a simple average of all estimates of prevalence in the database; as a weighted average of all estimates, with weights based on sample sizes from the individual studies; and averaging first by parasite genera documented in a host species and then creating a simple average of the estimates for each parasite genus found in that host. These variables were highly correlated, with the weakest correlation $r = 0.94$ (for the weighted average and genera average). We focused on the second of these (weighted average) because it most directly takes into account sample sizes in the underlying studies when estimating prevalence. We included results based on the other measures in the online enhancements and identify the rare cases when these results differ from the main conclusions.

In a more focused set of analyses, we also investigated our prediction at the level of the parasite genus ("generic-helminth prevalence"). For this, we calculated a weighted average based on sample sizes in individual studies. We then further restricted the data to parasite genera with information on at least 20 host species represented on our phylogeny. This ensured that we had an adequate number of data points in our simplest statistical models. Information on the six parasites is provided in table 1. We generally found positive associations among prevalence estimates in pairwise comparisons among the parasite genera examined, with correlation coefficients ranging from -0.09 to 0.73. While this finding is not critical to testing our hypothesis, it suggests that we should find similar patterns when the genera are examined separately. In addition, in the all-helminth prevalence analyses, a host with high relative prevalence of one helminth should generally show high prevalence of other helminths.

At the simplest level, we investigated the influence of helminth prevalence (p) on microparasite richness (R) using a regression model of the form $R = c + \beta_1 * p + \varepsilon$, where c is a constant (intercept), β_1 is a regression coeffi-

Table 1: Parasites with sufficient host sampling for analyses at the generic level

	No. hosts	Description
Strongyloides	42	Nematode: fecal-oral transmission and skin penetration
Trichuris	39	Nematode: fecal-oral transmission
Oesophagostomum	26	Nematode: fecal-oral transmission
Ascaris	25	Nematode: fecal-oral transmission
Enterobius	25	Nematode: fecal-oral transmission
Necator	21	Nematode: skin penetration

Note: Number of hosts reflects total number of host species with data that were also represented in our phylogeny (ver. 3 of 10kTrees; Arnold et al. 2010). We required prevalence data for at least 20 hosts to include a parasite in the analysis.

cient relating prevalence to richness, and ε is an error term that also reflects phylogenetic nonindependence (see below). Parasite richness reflects the number of microparasites of a particular class (i.e., intracellular or extracellular) that have been recorded for a given host species.

Due to the nature of the data, we took into account three additional issues in developing our statistical models to test the main hypothesis. First, sampling effort plays a major role in the number of parasites that are documented for a host species (Gregory 1990; Walther et al. 1995). In particular, a parasite may be correctly scored as absent from a host species because it does not occur or incorrectly scored as absent because the host has been insufficiently sampled to detect that parasite in the wild. Consequently, host species that are studied more intensively have more parasite records in the Global Mammal Parasite Database (Nunn and Altizer 2005). Following previous research that used this database (Nunn et al. 2003, 2004; Ezenwa et al. 2006; Lindenfors et al. 2007), we obtained citation counts for each host species as a measure of sampling effort. For these analyses, we used Primate Information Network's PrimateLit bibliographic database (http://primatelit.library.wisc.edu/), accessed in May 2010, because it includes journals, books, and book chapters (thus matching the types of sources also included in the primate portion of the Global Mammal Parasite Database). We assessed whether the relationship between $\log_{10}$ citation counts and $\log_{10}$ richness of intra- and extracellular microparasites was linear by comparing models with and without a squared (polynomial) term using the Akaike Information Criterion (AIC) and favored simpler models unless the more complex model was at least two AIC units lower than the simpler (linear) model. These analyses revealed no support for a nonlinear model for either group of parasite ($AIC_{intracellular,\ linear}$: 52.7; $AIC_{intracellular,\ polynomial}$: 51.4; $AIC_{extracellular,\ linear}$: 2.64; $AIC_{extracellular,\ polynomial}$: 4.63). Based on these tests, we included citation counts as a predictor variable in all statistical models using a linear model.

Second, to assess relative statistical support for the roles of immune-mediated interactions and standard host ecological factors, we included in the statistical models additional characteristics of hosts that have been shown to influence parasite richness (Poulin 1995; Morand 2000). Host ecological and behavioral traits—such as group size, range size, and body mass—are often correlated with (or predicted to correlate with) the number of parasites reported across populations or species (Gregory 1990; Morand and Harvey 2000; Nunn et al. 2003; Poulin and Morand 2004; Ezenwa et al. 2006; Lindenfors et al. 2007; Rifkin et al. 2012; Kamiya et al. 2013). Thus, for the overall analysis we included predictor variables reflecting group size (number of adults and immature animals per social group), female body mass (kg), and geographic range area (km^2) in the regression model. Data on group size were drawn mainly from Nunn and van Schaik (2002), while data on female body mass were means taken from Smith and Jungers (1997). Geographic range data were obtained from Nunn et al. (2003; 2005) and, to deal with additions and taxonomic revisions to the database, additional ranges were obtained from Schipper (2008) and Pantheria (Jones et al. 2009). We did not include latitude as a covariate because distance from the equator is not a strong predictor of primate parasitism (with the exception of protozoa; Nunn et al. 2005), and latitude was not found to have a consistent effect on parasite richness in a recent meta-analysis across all host groups studied (Kamiya et al. 2013). We were also concerned about collinearity among the predictor variables in the multivariate tests, including through ecological influences on helminth prevalence. To assess collinearity, we calculated variance inflation factors (VIF) for the full model. The highest VIF was only 1.7 (for geographic range size), and thus much less than 10, which is an upper cutoff that indicates problematic collinearity (Petraitis et al. 1996).

A final issue for our statistical model concerns the potential nonindependence of species data (Felsenstein 1985; Harvey and Pagel 1991; Nunn 2011). More closely related species are likely to exhibit more similar trait values for many morphological, life-history, and behavioral traits (Freckleton et al. 2002; Blomberg et al. 2003), and comparative approaches that control for host phylogeny generally assume that the traits in question are shared through common descent. Although parasite community diversity and the measures of sampling effort are not strictly heritable (genetic) traits in primates, they may follow phylogenetic lines of descent or be associated with other traits

that are shared through common descent (Nunn and Altizer 2006). If so, statistical tests of association may be invalid (Martins and Garland 1991).

To deal with this important statistical issue, we used phylogeny-based comparative methods to test our comparative predictions and, importantly, to assess the degree of phylogenetic signal in residuals from our regression model (Freckleton et al. 2002; Revell 2010). For this, we performed Bayesian Markov chain Monte Carlo (MCMC) analyses to generate a posterior probability distribution of statistical parameters using the program BayesTraits (Pagel and Meade 2007), and we assessed phylogenetic signal using the branch length scaling parameter λ (Freckleton et al. 2002). The MCMC approach is important in this context because it provides a principled way to control for phylogenetic uncertainty by integrating the statistical results across a sample of trees (Pagel and Lutzoni 2002; Pagel and Meade 2006), and it gives easily interpreted support values that can be compared across different analyses (in this case, we focus on the probability that regression coefficients are positive). The parameter λ scales internal branches on the tree. When $\lambda = 0$, all internal branches are set to zero, resulting in a "star phylogeny" with all branches emanating from a common node (Felsenstein 1985), while increasing phylogenetic nonindependence (based on the input tree) is modeled as λ increases to a value of 1. In addition to assessing phylogenetic signal of the residuals, we estimated λ in the estimates of prevalence used in these analyses. As most biological traits show evidence for phylogenetic signal, we expected that prevalence would also exhibit λ estimates greater than zero.

For Bayesian estimation of parameters, we conducted three independent MCMC analyses for each statistical model, sampling regression coefficients, λ, and other parameters every 100 generations and ensuring that results converged across runs. In the iterative process for proposing new values in the MCMC analysis, we obtained an acceptance rate of 20%–40%, which was achieved by adjusting the ratedev parameter in the BayesTraits software. We assumed a flat prior distribution of regression coefficients and ensured that analyses had reached burn-in (i.e., a stationary distribution of values in the MCMC sample). We sampled statistical parameters only from the post-burn-in sample.

To incorporate phylogenetic uncertainty, we used a sample of 100 dated trees from version 3 of the 10kTrees website (Arnold et al. 2010). This online resource provides up to 10,000 trees from a Bayesian posterior probability distribution. By using multiple inferences of phylogeny, our results are less sensitive to phylogenetic uncertainty for the primates in our sample, including uncertainty related to topology or branch lengths (Pagel and Lutzoni 2002). In our case, most uncertainty involved branch lengths rather than topology. We were able to match up all but one species, *Saguinus labiatus*, which we included in the focused tests (to maximize sample size) by relabeling it *Saguinus imperator*, its closest relative that was not used in the analysis, based on Bininda-Emonds et al. (2007). Three species that were unmatched to the phylogeny in the larger analysis were excluded (*Alouatta fusca*, *Alouatta pigra*, and *Saguinus labiatus*) because suitable unused sister species were not available for replacement.

We used a Bayesian approach to estimate regression coefficients in the following statistical model $R = c + \beta_1 * p + \beta_2 * s + \varepsilon$, where s is sampling effort, the βs are regression coefficients, and ε incorporates correlated error due to shared evolutionary history and is scaled by λ. In addition, for the all-helminth data set, we investigated a more complex model with additional covariates, $R = c + \beta_1 * p + \beta_2 * s + \beta_3 * g + \beta_4 * m + \beta_5 * G + \varepsilon$, where g is group size, m is mass, and G is geographic range size. We estimated the effect size of different predictor variables as $r = [t^2/(t^2 + df)]^{1/2}$, where t was obtained based on the mean regression coefficient and mean standard error for that coefficient. Data on number of parasites, number of citations, and host ecological traits were $\log_{10}$ transformed prior to analysis (after adding 1 to the raw data to avoid taking the logarithm of 0). We evaluated our hypotheses based on MCMC sampling of the regression coefficients in the posterior probability sample. When 90% or more of the regression coefficients were in the predicted direction, we considered this to be "support" for a particular prediction; when 95% or more coefficients were in the predicted direction we considered the evidence to be "strong support." We also assessed posterior probability distributions of λ to quantify phylogenetic signal, which was taken into account in BayesTraits when estimating regression coefficients.

Table 2: Microparasite richness in relation to sampling effort and overall helminth prevalence (weighted)

		Sampling effort		Prevalence		λ	
Response variable	R^2	Mean β	% support	Mean β	% support	Mean	95% CI
Intracellular richness	.24	.296	100	.255	91.1	.35	.12–.63
Extracellular richness	.09	.136	99.7	.087	72.3	.32	.05–.67

Note: λ is a measure of phylogenetic signal, and CI refers to the 95% Bayesian credible interval.

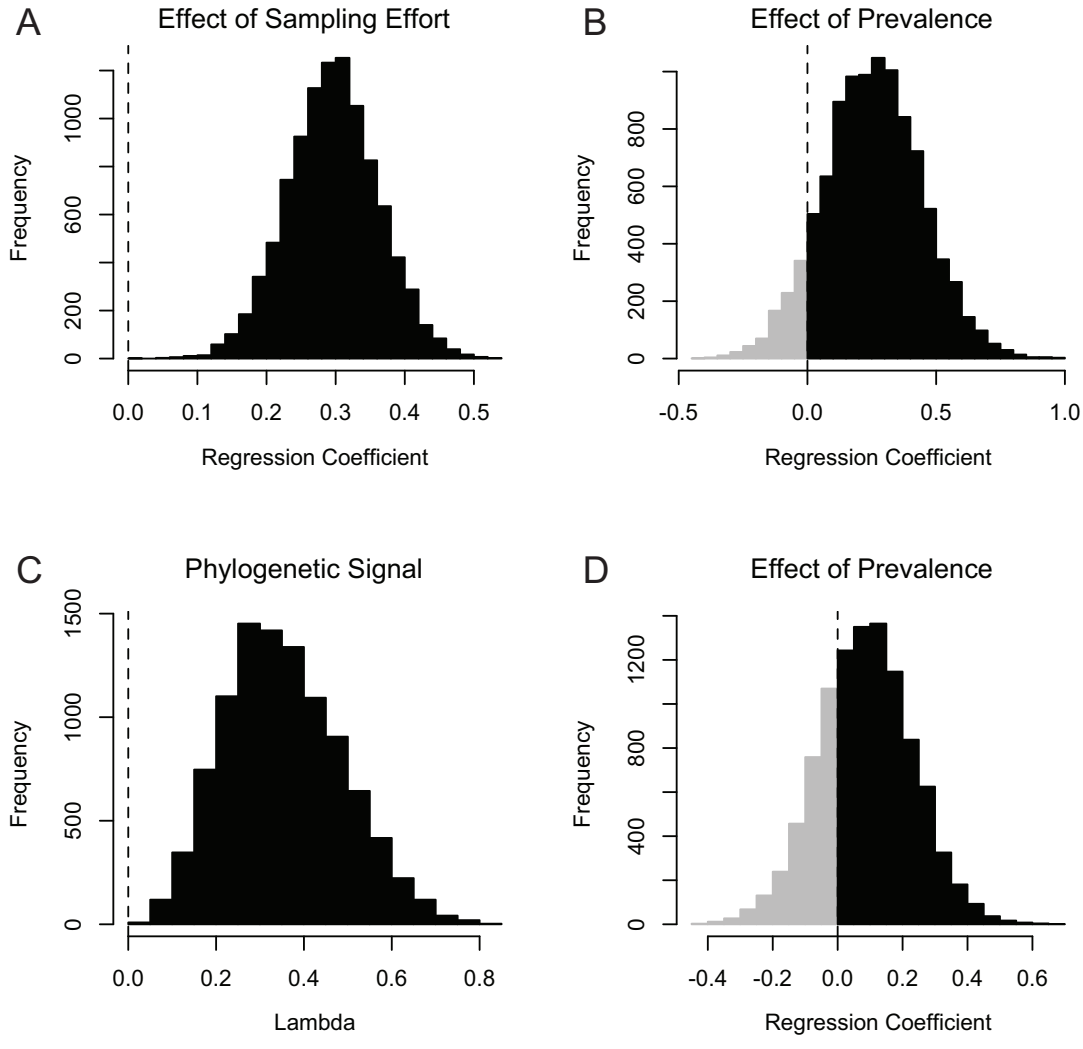

Figure 1: Parameter estimates (posterior probability distributions). Regression coefficients from the Markov chain Monte Carlo analysis of intracellular parasite richness regressed on sampling effort (*A*) and weighted helminth prevalence (*B*). In both cases, the analysis revealed support ("strong" in the case of sampling effort), with evidence for phylogenetic signal (*C*). Effects of weighted helminth prevalence were weaker in analyses of extracellular richness as the response variable (*D*). Black bars indicate positive values, gray bars negative values, and the dashed lines equal a value of zero.

Results

Overall Analysis: All-Helminth Prevalence

In bivariate tests using the all-helminth prevalence data set, we found strong support for an effect of both sampling effort and helminth prevalence on the richness of intracellular parasites (level of support: 100% and 91%, respectively, table 2; fig. 1*A*, 1*B*). We also found evidence for phylogenetic signal in residuals of the statistical model (i.e., $\lambda > 0$), although the estimates of λ showed a wide distribution (fig. 1*C*). Phylogenetic signal was somewhat weaker in the estimates of prevalence on their own (weighted prevalence: mean = 0.19, 95% credible interval: 0.01 to 0.53; similar results were obtained for other estimates of prevalence). In analyses of extracellular microparasite richness, sampling effort remained a strong positive predictor, with 99.7% of the MCMC samples supporting this effect (table 2). However, as predicted, helminth prevalence was a weaker predictor of extracellular richness, with only 72% of the MCMC samples showing a positive regression coefficient for this variable (table 2; fig. 1*D*). When using helminth prevalence estimates based on a simple average and averaged by genera we found similarly strong effects on intracellular parasite richness (level of support: 95%–98%). In these models, support for an effect of helminth prevalence on extracellular

microparasite richness increased to 85%–89% (tables A1, A2, available online), but this still fell short of our a priori cutoff of 90%.

These associations remained in multivariate tests that controlled for host ecological and life-history traits (table 3). For intracellular microparasite richness, sampling effort was strongly predictive, as was helminth prevalence, body mass, and geographic range size. Of these predictor variables, sampling effort had the largest effect size ($r = 0.35$), and the effect size for weighted helminth prevalence (0.20) was near the midpoint for effect sizes for other variables (0.11 to 0.31; table 3). For extracellular richness, only body mass and geographic range size reached support levels greater than 90%, and effect sizes for weighted helminth prevalence were lower (0.12, vs. 0.20 for analyses of intracellular richness) and low relative to other effect sizes for ecological variables (0.05 to 0.36; table 3). Use of different helminth prevalence estimates revealed some heterogeneity in the strength of effects but qualitatively similar patterns: helminth prevalence was always a relatively stronger predictor of intracellular than extracellular parasite richness. However, helminth prevalence also predicted extracellular microparasite richness at greater than 90% support in the additional tests (tables A3, A4, available online).

Table 3: Multivariate analyses: predictors of intracellular and extracellular microparasite richness

	Intracellular richness	Extracellular richness
R^2	.33	.22
Sampling effort:		
Mean β	.21	.06
% support	99.8	87
Effect size (r)	.35	.14
Weighted prevalence:		
Mean β	.30	.14
% support	95	84
Effect size (r)	.20	.12
Group size:		
Mean β	−.10	−.03
% support	18	34
Effect size (r)	.11	.05
Mass:		
Mean β	.19	.11
% support	98	94
Effect size (r)	.24	.19
Geographic range:		
Mean β	.14	.12
% support	99.4	99.97
Effect size (r)	.31	.36
λ:		
Mean	.27	.31
95% credible interval	.04–.60	.05–.66

Focused Analyses: "Generic Helminth" Prevalence

In most of the focused tests, we again found strong support for an effect of sampling effort on measures of parasitism, with support levels close to or equal to 100% in most tests, the exception being analyses of *Enterobius* (table 4). We also found evidence for phylogenetic signal in the residuals, indicated by $\lambda > 0$. However, the 95% credible interval for λ was extremely wide, typically ranging from just above 0 to 0.75 and with a mean of less than 0.5 in all but one case (table 4).

In these more focused tests, we found no support for the predicted positive association between helminth prevalence and intracellular parasite richness (table 4). While analyses of *Trichuris*, *Oesophogastomum* and *Enterobius* yielded positive coefficients for the effect of prevalence in more than 75% of the posterior samples, this level of support fell below our a priori cutoff of 90%. Only four of the six helminth genera showed evidence of a positive association with intracellular microparasite richness (based on the mean of the posterior distribution of regression coefficients, and ignoring support levels). In assessing patterns for extracellular microparasites (table 5), we again found a mixture of negative and positive effects for helminth prevalence, with mean coefficients negative in four cases and positive in two cases.

Discussion

Parasites and infectious diseases represent a major force shaping the ecology and evolution of free-living species. In recognition of this fact, a considerable amount of attention has focused on understanding the role these organisms play in natural systems (Tompkins et al. 2011). Nevertheless, we still lack a satisfactory understanding of the factors that drive patterns of parasite diversity across host species or geographic locations. A number of studies have identified both intrinsic host traits and extrinsic environmental characteristics as key drivers of parasite richness across hosts. Here, for the first time, we show that parasite interactions may represent another driver of variation in parasite species richness across host taxa. Specifically, our results indicate that changes in total helminth prevalence are tied to increases in the richness of intracellular microparasites across species of wild primate hosts. In contrast, support for a relationship between helminth prevalence and extracellular microparasite richness was weaker although still indicative of a possible effect that will require more sensitive tests in the field or laboratory. Overall, however, we interpret these findings as support for the macro-micro facilitation hypothesis, namely, that strong effects of helminths on susceptibility to intracellular

Table 4: Intracellular richness in relation to sampling effort and helminth prevalence

		Sampling effort		Prevalence		λ	
Parasite	R^2	Mean β	% support	Mean β	% support	Mean	95% CI
Strongyloides	.22	.36	99.9	.085	61	.33	.03–.68
Trichuris	.29	.39	100	.21	77	.38	.08–.72
Oesophagostomum	.40	.41	99.9	.20	77	.28	.01–.73
Ascaris	.28	.44	99.8	−.086	43	.41	.04–.79
Enterobius	.05	.08	65	.70	79	.45	.05–.84
Necator	.55	.53	100	−.22	35	.63	.18–.95

Note: λ is a measure of phylogenetic signal, and CI refers to the 95% Bayesian credible interval.

microparasites within individual hosts can drive patterns of parasite establishment across host species.

In our simple analyses examining only the effects of sampling effort and helminth prevalence on intracellular parasite richness, support for a correlation between prevalence and intracellular richness reached 91%, just above our 90% a priori cutoff for support. When we reran this analysis including a suite of additional traits, we found that body mass and geographic range size were also strong predictors of richness. Importantly, controlling for these host-related variables raised the level of support for a helminth prevalence effect to 95% and helped to reduce the likelihood that these patterns are driven by some confounding variable. Moreover, the strength of support for a helminth effect approached levels of support for body mass and geographic range size—two variables widely considered to be important predictors of parasite richness across a range of vertebrates (Poulin 1995; Morand 2000; Nunn and Altizer 2006). The effect sizes for host ecological traits ranged from $r = 0.11$ to 0.31, compared to $r = 0.20$ for the effect of helminth prevalence on intracellular parasite richness. These findings therefore suggest that parasite interactions are as important as some host traits in accounting for parasite richness.

We hypothesized that the effects of helminths on microparasite richness observed in our study would be driven predominantly by immunological changes within the host. As detailed in the "Introduction," suppression of host immunity by helminths can occur in multiple ways. Host Th1 responses, directed against intracellular microparasites, can be suppressed as a result of upregulation of antihelminth immunity (Th2 responses) by the host (Flynn et al. 2009; McSorley et al. 2011). Furthermore, helminths can modulate host immunity in ways that result in suppression of Th1, Th2, and Th17 responses, with implications for both intracellular and extracellular microparasites (Curtis and Way 2009; Walsh et al 2009; Wammes et al. 2010; Maizels et al. 2011). Because, on balance, helminths may facilitate the establishment of intracellular microparasites in more ways than they influence extracellular microparasite establishment, we made the prediction that broad-scale effects of helminth prevalence on microparasites should be stronger for intracellular compared to extracellular microparasites.

Our results support this prediction, although we did pick up some weaker signals of helminth effects on extracellular microparasites. Specifically, we found that support for an effect of helminth prevalence on extracellular microparasite richness was lower than for intracellular richness, falling below our 90% a priori cutoff for support in most tests but still possibly indicative of real effects. The size of the effect of helminth prevalence on intracellular richness was 67% higher ($r = 0.20$) than the effect size for the equivalent analysis involving extracellular richness ($r = 0.12$; table 3), supporting the idea that helminth effects on intracellular microparasite establishment should be stronger. Many unknowns remain concerning the ways in which helminths interact with the host immune system (Khan and Fallon 2013), but as new paradigms emerge the approach outlined in this article can be refined to explore more subtle interaction effects.

While our predictions were supported for analyses using the prevalence of all helminths combined (all-helminth prevalence), we found little support for effects of particular helminth genera on either intracellular or extracellular microparasite richness (generic-helminth prevalence). These more focused genera-level tests examined the six most prevalent helminths reported to infect primates in our database, as described in table 1. In contrast to analyses in which helminth prevalence was aggregated, results were mixed and unsupportive of the hypothesis for the genera-level analyses. These findings suggest that combined effects of many helminths—rather than individual helminth species—may be the primary drivers of broad-scale helminth-microparasite interactions in the wild. In addition, the smaller sample sizes in analyses of generic-helminth prevalence may have weakened our ability to detect effects.

Our macro-micro facilitation hypothesis was formulated on the basis of well-described immune mechanisms. However, the positive prevalence-richness pattern that we observed might conceivably be caused by other factors, and causation is difficult to assess in comparative studies

Table 5: Extracellular microparasite richness in relation to sampling effort and helminth prevalence

		Sampling effort		Prevalence		λ	
Parasite	R^2	Mean β	% support	Mean β	% support	Mean	95% CI
Strongyloides	.13	.19	99.3	−.062	38	.35	.02–.77
Trichuris	.24	.22	99.9	−.65	36	.29	.02–.69
Oesophagostomum	.25	.18	98.5	.20	87	.34	.02–.80
Ascaris	.37	.28	99.9	.32	86	.32	.02–.75
Enterobius	.19	.22	98.6	−.14	36	.40	.05–.82
Necator	.38	.28	99.9	−.10	42	.44	.04–.91

Note: λ is a measure of phylogenetic signal, and CI refers to the 95% Bayesian credible interval.

(Nunn 2011). In terms of exposure, for example, species with high total helminth prevalence might also experience greater exposure to intracellular parasites—a possibility that could be investigated with more details on transmission mode and in field studies, as most studies of helminths in our database did not collect corresponding data on microparasite richness. In terms of susceptibility, species with high helminth prevalence might allocate fewer resources to immunity in general—possibly through correlated life history or other factors—which might also enable a greater number of different microparasites to establish. While overall immune investment is difficult to measure, differential allocation to immune defenses appears insufficient to explain our results. First, in primates, a previous study found that micro- and macroparasite richness was not significantly associated with investment in immunity, as measured by total white blood cell counts (Cooper et al. 2012). Second, a recent comparative analysis of immune investment in mammals showed that host species with more helminth species tend to invest more (rather than less) in immunity, measured as total and differential white blood cell counts (Bordes and Morand 2009). Finally, we might expect larger-bodied hosts with slower life histories to invest more in immune defenses, which is supported by a positive association between body mass and white blood cell counts in mammals (Cooper et al. 2012). Yet larger-bodied primates and ungulates tend to have higher microparasite richness (Cooper et al. 2012), reducing the plausibility of the argument that the prevalence-richness association observed in our data set might be simply due to interspecific variation in overall immune investment. In addition, none of the host traits we investigated (e.g., group size, geographic range size) provide a good explanation for the observed differences in analyses of intra- and extracellular parasites.

Perhaps the most helpful information for more rigorous testing of hypotheses about the role of immunologic mechanisms in generating variation in parasite richness and community structure among host species would be comparable immunological data collected from a diverse range of host species. While considerable knowledge of immunity exists for laboratory rodents and humans, very little immunological information is available for other species, and this lack of comparative immunologic data limits our ability to understand the evolutionary roots of interspecific variation in immunity and its consequences for parasite communities (Maizels and Nussey 2013). Most broad-scale comparative analyses of species immune responses have examined white blood cell populations (e.g., Nunn 2002), but this is a crude representation of the functional complexity of vertebrate immune systems. Measuring meaningful variation in immunity in nonmodel species is challenging, but current work in ecological immunity is providing methods that can be applied to a broad range of nonmodel species (Boughton et al. 2011; Demas et al. 2011). Some studies in birds (Matson et al. 2006; Lee et al. 2008) and mammals (Martin et al. 2007; Previtali et al. 2012) are beginning to characterize variation in immunity in relation to species' life histories, but to our knowledge, no comprehensive survey including multiple functional measures of immunity has yet been conducted for any taxon that would allow comparative analysis of the role of immune-mediated parasite interactions in shaping parasite communities.

In conclusion, our results suggest that the consequences of coinfection span multiple scales of biological organization. An increasing number of studies show that within-individual interactions among parasites can influence patterns of infection at both the individual and population levels (Jolles et al. 2008; Ezenwa et al. 2010; Telfer et al. 2010; Johnson and Hoverman 2012; Pathak et al. 2012; Pedersen and Antonovics 2013). We extended this perspective and found that helminth coinfection may shape patterns of parasitism across species. Identifying general ecological principles that shape patterns of biodiversity is a central problem in ecology, and understanding parasite diversity has lagged behind our understanding of the factors that affect diversity of free-living species. Our study confirms that standard host ecological factors are important, including those related to exposure to parasites, while

highlighting the role of differential susceptibility driven by interactions among parasites and the immune system, which reflects ecological factors occurring within the host. Future studies in additional mammalian taxa will help evaluate the generality of this phenomenon, and better data on comparative immunology will be central to discovering the mechanistic basis for the stronger association between helminth prevalence and microparasite richness.

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