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REVIEW ARTICLE

Primate Disease Ecology in Comparative and Theoretical Perspective

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Infectious disease plays a major role in the lives of wild primates, and the past decade has witnessed significant strides in our understanding of primate disease ecology. In this review, I briefly describe some key findings from phylogenetic comparative approaches, focusing on analyses of parasite richness that use the *Global Mammal Parasite Database*. While these studies have provided new answers to fundamental questions, new questions have arisen, including questions about the underlying epidemiological mechanisms that produce the broader phylogenetic patterns. I discuss two examples in which theoretical models have given us new traction on these comparative questions. First, drawing on findings of a positive association between range use intensity and the richness of helminth parasites, we developed a spatially explicit agent-based model to investigate the underlying drivers of this pattern. From this model, we are gaining deeper understanding of how range use intensity results in greater exposure to parasites, thus producing higher prevalence in the simulated populations—and, plausibly, higher parasite richness in comparative analyses. Second, I show how a model of disease spread on social networks provides solid theoretical foundations for understanding the effects of sociality and group size on parasitism across primate species. This study further revealed that larger social groups are more subdivided, which should slow the spread of infectious diseases. This effect could offset the increased disease risk expected in larger social groups, which has yet to receive strong empirical support in our comparative analyses. In addition to these examples, I discuss the need for more meta-analyses of individual-level phenomena documented in the field, and for greater linkage between theoretical modeling and field research. Am. J. Primatol. 74:497–509, 2012.

Key words: parasitism; disease ecology; comparative study; epidemiology; theoretical modeling

INTRODUCTION

Wild primates harbor an incredible diversity of parasites and pathogens, including many that also infect humans [Davies & Pedersen, 2008; Gillespie et al., 2008; Huffman & Chapman, 2009; Nunn & Altizer, 2005, 2006; Wolfe et al., 2005]. For example, diverse protozoa, viruses, and nematodes are found in the blood of wild primates, including the yellow fever virus, *Plasmodium*, and filarial nematodes. Similarly, a wide variety of parasitic organisms are found in primate guts, including many helminths that attach to the gut wall, such as tapeworms (cestodes), and also protozoa such as *Giardia* and bacteria such as *Campylobacter* [reviewed in Nunn & Altizer, 2006]. Viruses and bacteria also infect tissues of the respiratory tract of wild primates; less well appreciated are lung mites that live in the respiratory passages of some primate species, such as baboons [Kuntz & Myers, 1967]. Collectively, a typical individual primate host in the wild experiences multiple simultaneous infections [e.g., Goldberg et al., 2009; Leendertz et al., 2010; Muller-Graf et al., 1996], and at the population or species level, more than 60 different parasites or pathogens have been documented to infect some well-studied host species (e.g., *Pan troglodytes*, *Gorilla gorilla*, and several species of *Papio*) [Nunn & Altizer, 2005].

The majority of research on primate socioecology has focused on predation, competition for resources, and infanticide as factors that influence primate behavior [Campbell et al., 2007; Smuts et al., 1987; van Schaik, 1989; van Schaik & Janson, 2000]. This attention to predation, competition, and infanticide makes sense, as these factors clearly influence primate behavior, and their effects are readily observable. In addition to these more standard foci, researchers increasingly appreciate the important role

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that parasites play in the lives of wild primates [Janson, 2000; Nunn & Altizer, 2006; Thierry, 2008], with often impressive effects on survival and reproduction. For example, multiple studies have provided compelling evidence that disease-related mortality has produced striking effects on the demography and behavior of wild primate hosts [e.g., Carpenter, 1964; Milton, 1996; Sapolsky & Share, 2004]. Similarly, a number of authors have called attention to the conservation implications of disease-related population declines in wild primates [Bermejo et al., 2006; Chapman et al., 2005], further suggesting that parasites could represent a significant selective force in primate evolution. Finally, evidence is growing for the role of infectious organisms in the evolution of primate immune defenses. One recent study found, for example, that evolutionary transitions in promiscuity and group size are associated with selection on immune-related genes [Wlasiuk & Nachman, 2010]; another study found that the richness of nematode parasites covaries with rates of molecular evolution in the major histocompatibility complex (MHC) [Garamszegi & Nunn, 2011].

Consistent with parasites acting as a selective pressure on primates, parasitism has likely favored behaviors to reduce contact with parasites [Huffman, 2007; Nunn & Altizer, 2006]. For example, primates may avoid gastrointestinal parasites through a variety of behaviors involving movement patterns [Freeland, 1980], alternating sleeping sites [Hausfater & Meade, 1982], and use of defecation sites that reduce subsequent exposure to parasites when traveling on arboreal pathways [Gilbert, 1997]. Similarly, primates have been observed to use millipede secretions and other substances as insect repellents [Huffman, 2007; Valderrama et al., 2000]. Parasitism has probably also favored behaviors aimed at eliminating parasitic infections, including leaf swallowing and bitter pith consumption [Huffman, 1997, 2007] and other forms of dietary selection [MacIntosh & Huffman, 2010], while "sickness behaviors" probably facilitate recovery from infection [Hart, 1990]. Less well studied is the intriguing possibility that parasitic organisms could shape social contact patterns in primates, including grouping tendencies, territoriality, mating behavior, and dispersal [Freeland, 1976; Kokko et al., 2002; Loehle, 1995; Nunn & Altizer, 2006].

The past 12 years have witnessed a rapid increase in research on primate disease ecology (Fig. 1). This growth represents many exciting advances in the collection of noninvasive samples [Gillespie, 2006; Liu et al., 2008], thousands of hours of hard work by innovative young scientists to investigate disease ecology in wild primates [e.g., Clough et al., 2010; Gillespie et al., 2005; Leendertz et al., 2004, 2006; Muehlenbein, 2005], a growing literature that models the spread of infectious agents in primate populations [Bonnell et al., 2010; Kennedy et al., 2009; Nunn et al., 2008], and two books that integrate the findings of these diverse research approaches [Huffman & Chapman, 2009; Nunn & Altizer, 2006]. Primate disease ecology research has been further strengthened through interest in the public health and conservation implications of infectious diseases in wildlife [Daszak et al., 2000; Wolfe et al., 2007]. In addition, the field of disease ecology has matured in its own right to become a sophisticated, dynamic, and productive area of research, particularly with regard to the modeling of infectious disease dynamics [Hudson et al., 2002; Keeling & Rohani, 2008; Sattenspiel, 2009].

Given the rapid growth of research, the time is right to take stock of where research in primate disease ecology stands, and to consider some future productive directions for research. My research is largely comparative in its focus and approach, meaning that I examine variation across populations or species to assess support for particular hypotheses in a macroevolutionary framework [Nunn, 2011]. With this broad focus, comparative research synthesizes data from many different empirical and theoretical perspectives, including by making use of raw data collected through exceptional hard work and numerous logistical field challenges. Thus, a summary of comparative research—and the theoretical and empirical foundations upon which it stands—can serve as a barometer for the state of the field itself, including future field research. Similarly, we desperately need greater integration of theoretical and empirical research. Again, the use of theoretical models to make novel predictions and better understand comparative patterns serves, I hope, as a valuable example of the power of this integrative approach for field and comparative primatologists [Altizer et al., 2003; Gillespie et al., 2008; Nunn, 2009; Nunn & Altizer, 2004].

In what follows, I provide an overview of key comparative findings, focusing on research on parasite species richness. I then discuss ways that my colleagues and I are integrating theoretical models with comparative research to deepen our understanding of primate disease ecology. I use two examples. The first involves a comparative study that documented an association between ranging behavior and parasitism [Nunn & Dokey, 2006] and a theoretical model [Nunn et al., 2011] that aimed to assess whether the proposed mechanism—namely, that more intensive use of the home range increases exposure to parasites in the soil—could plausibly account for the comparative pattern that we discovered.

The second example [Griffin & Nunn, in press] involves the spread of infections on social networks, and whether understanding phylogenetic variation in social networks can provide insights to proposed hypotheses linking group size and parasitism, i.e. the "group size hypothesis" [Altizer et al., 2003; Côté & Poulin, 1995]. Surprisingly, the group size

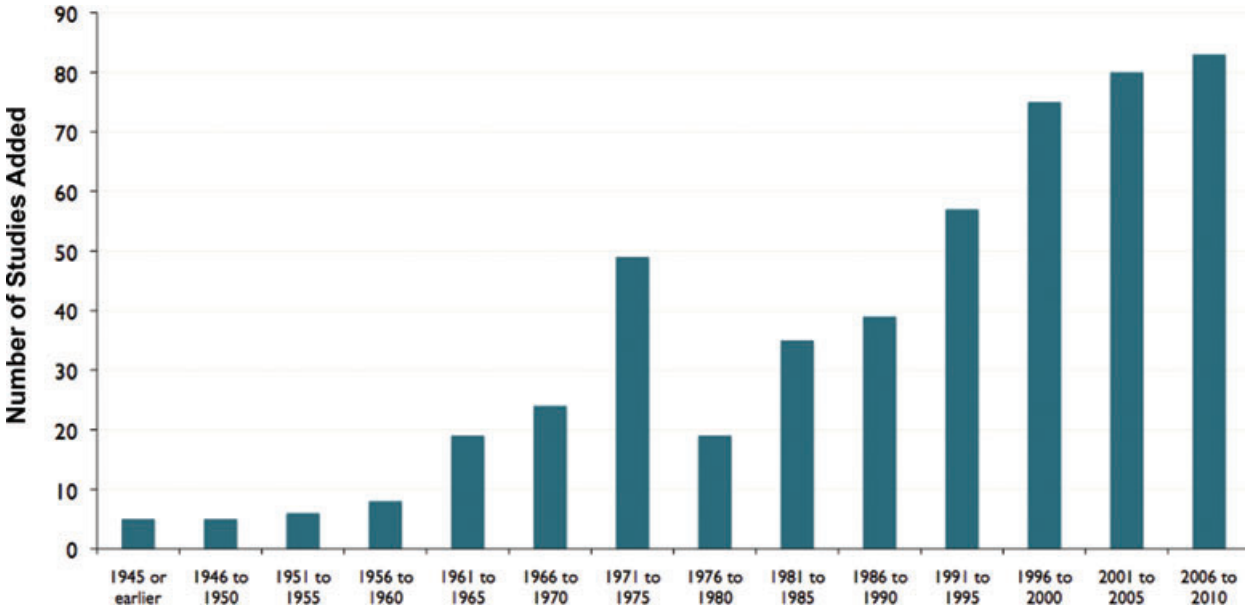

Fig. 1. Studies on primate parasites in the *Global Mammal Parasite Database*. New studies of wild primates are added to the database as soon as possible after they are published (and available online after they have been double checked, typically within 6 months). The number of studies has increased over time, and based on known papers in the publication pipeline, this trend appears on track to continue upward in coming years.

hypothesis is largely unsupported in comparative studies on primates. The question is: could understanding social networks give insights to the *absence* of an association between group size and parasitism? In particular, perhaps larger social groups are more subdivided, which might slow the spread of disease, and thus weaken an underlying positive association between group size and parasitism.

Finally, by way of conclusion, I turn my attention to field research. Given the large number of ecological factors that have the potential to account for variation in parasitism within and among social groups, we rarely have the statistical power to fully assess all the possible predictor variables. More sophisticated statistical techniques are sorely needed, as are approaches that enable researchers to combine statistical results from multiple studies in a more rigorous and synthetic way. I discuss some possibilities, and particularly the use of meta-analytical techniques to more directly combine the statistical findings of individual field studies, rather than simply combining the raw or summary data from the field (as is typical of most comparative research, including my own).

COMPARATIVE RESEARCH ON PRIMATE PARASITISM

Over the past decade, my research has focused on a very basic question: which host traits and environmental factors influence primate disease risk? This is a comparative question, which thus requires investigation of multiple populations or species. Here, I focus on interspecific comparisons across primate phylogeny. In many cases, a comparative study stands on the shoulders of numerous, painstaking studies of individual populations or species; a single scientist would find it difficult—even impossible—to collect data at such a broad scale. Recent advances in comparative methods make explicit use of phylogenetic information and statistical modeling, with the aim to assess how evolutionary changes in one trait covary with changes in other traits [Nunn, 2011; Nunn & Barton, 2001].

In the case of comparative research on parasitism, we might be interested in how some host trait, such as group size, correlates with measures of parasitism [Alexander, 1974; Altizer et al., 2003; Côté & Poulin, 1995; Møller et al., 1993]. For example, do animals living in larger groups have higher prevalence of malaria, as might occur if mosquito vectors can more easily locate hosts living in larger groups [Davies et al., 1991; Nunn & Heymann, 2005]? We also might expect that species that live on the ground, such as patas monkeys (*Erythrocebus patas*) or mountain gorillas (*Gorilla beringei*), are exposed to a larger number of parasites than a primate that is strictly arboreal, such as a white-handed gibbon (*Hylobates lar*). Similarly, a more promiscuous primate might be expected to have more sexually transmitted infections, those infections should exist at higher prevalence, and we might reasonably expect to find selection on genes related to immunity [e.g., Wlasiuk & Nachman, 2010]. Does parasite richness covary with body mass, possibly because larger bodied primates consume more resources (and thus incidentally ingest parasites), or because they offer more distinct niches for parasite colonization [Kuris et al.,

1980; Morand, 2000; Poulin & Morand, 2004]? From applied perspectives, do threatened primates have more or fewer parasites [Altizer et al., 2007], and are host shifts—including the emergence of many new infectious diseases in humans—more likely among more closely related host species [Davies & Pedersen, 2008; Pedersen & Davies, 2009]? Thus, in comparisons among species, we might investigate host traits, such as group size, body mass or promiscuity, or environmental traits, such as rainfall, temperature, or variability in these measures over space and time [Guernier et al., 2004; Morand, 2000; Nunn & Altizer, 2006; Poulin, 1995; Poulin & Morand, 2004].

Conducting a comparative test on the drivers of disease ecology requires information on parasitism in different primate species, typically measured as parasite richness (number of parasites infecting a host) or parasite prevalence (percentage of individuals in a group or population who are infected) [see Nunn & Altizer, 2006]. When using prevalence or richness as a metric of disease risk, the researcher assumes that higher values of these measures indicate that hosts have social or ecological characteristics that make parasite spread and establishment more likely, that the organisms cause negative effects on hosts, and that sampling has been consistent across species or, if not, that sampling biases can be controlled for statistically. It is worth noting that each group of parasites poses different risks to hosts, and even within groups of parasites considerable variation in host-related effects exists; for example, measures of parasitism based on intestinal worms may have very different fitness-related impacts than measures based on vector-transmitted parasites. In addition, the effects of a parasite may have variable effects in different primate species, or even among individuals of the same species in a primate social group. From an ecological point of view, variation in these indices of infection is interesting, regardless of the impacts they may or may not have on their primate hosts.

When I started research on primate disease ecology in 1999, there had been some excellent descriptive studies of parasites in natural populations, and in some of these studies, the authors investigated specific ecological hypotheses [e.g., Milton, 1996; Muller-Graf et al., 1996; Stoner, 1996]. However, there were only a handful of comparative studies that aimed to discover the correlates of parasitism across primates, typically in a small number of species [e.g., Davies et al., 1991; Freeland, 1979]. Moreover, systematically collected and comparable data on parasitism for a wide range of primate hosts were not available.

To deal with this shortage of data, Sonia Altizer and I initiated a systematic collection of data on the parasites of primates, which was then expanded to include carnivores, terrestrial ungulates (i.e., Artiodactyla and Perissodactyla), and other mammals. We also worked closely with a number of parasitologists to include essential details on parasite transmission mode, host specificity, and parasite taxonomy, and also to ensure that the organisms were indeed likely to be parasitic rather than commensals, and thus likely to have negative effects on hosts. We call this database the *Global Mammal Parasite Database* [Nunn & Altizer, 2005], and the primate portion of the database continues to be updated as new papers are published. In the most recent version of the primate database, we have 5,980 records of host-parasite relationships (including some multiple records of the same host–parasite combination), obtained from 517 references. This is a large data set by the standards of comparative biology, representing 145 primate host species and 623 parasite species. Importantly, we restrict our data collation to studies of free-living primate populations; zoo animals and those in other captive settings are excluded from the database. We have been extremely broad in our data collection, including data on macroparasites (i.e., helminths and arthropods) and microparasites (protozoa, viruses, bacteria, and fungi). This is a major strength of the database because it allows us to examine patterns among all parasites, and also to investigate variation among major taxonomic components of parasite communities. An important goal is to share these data with others, who may have different uses or interests (www.mammalparasites.org).

We summarized the taxonomic distribution and transmission characteristics of the primate parasites in an earlier version of the database [Pedersen et al., 2005]. The most commonly reported parasites of primates are helminths (43%), and most of these are nematodes. The helminths of primates are transmitted through a wide range of mechanisms; some, such as filarial nematodes, are even transmitted by arthropod vectors. The protozoa and viruses are approximately equally represented, at about 22% of the database records for each of these groups of parasites [Pedersen et al., 2005]. Many of the protozoa are transmitted by arthropod vectors or through fecal contamination of the environment; the viruses also exhibit variation in transmission mode, with several examples of sexually transmitted infections. The database contains fewer records of bacteria and fungi in primates, accounting for a combined 13% of the database. We also have surprisingly few records of parasitic arthropods in primates. Thus, despite the great attention that primatologists give to studying grooming, we know remarkably little about the ectoparasites of primates [Graczyk et al., 2001; Leo, 2009; Milton, 1996]. As noted, these statistics refer to an earlier version of the database, and the database continues to grow as new studies are published on primate parasites—and the rate of new papers has been increasing (Fig. 1), which means that the database is perpetually incomplete.

Once the data are compiled, many interesting questions can be addressed using a comparative approach, including those questions raised above. Questions involving parasite richness pose a special problem, however, because the more intensively a species is studied, the more infectious agents are typically discovered; as mentioned above, this is a form of sampling bias. Humans, for example, have 1,415 documented parasites and pathogens [Cleaveland et al., 2001; Taylor et al., 2001], compared to only 22 documented in *Cebus capucinus* (*Global Mammal Parasite Database*, accessed in May 2011). As we continue to study humans, we identify new parasites, and if we studied *C. capucinus* to the same degree that we have already studied humans, we might plausibly discover that *C. capucinus* has several hundred different parasites and pathogens. Whether the number would reach the number found in humans is doubtful, however, given that we likely acquired many of our parasites and pathogens from our close contact with domesticated animals, and because we have a substantially larger geographic range size that potentially exposes us as a species to more parasites [Gregory, 1990; Nunn et al., 2003; Poulin & Morand, 2004]. The point is that the intensity of effort devoted to studying parasites varies greatly among primate hosts, and we need to take this into account when we investigate the drivers of parasite richness.

My collaborators and I have investigated a number of options to control for sampling effort, including counts of the number of animals actually sampled (when this is known) and the use of citation counts [Nunn et al., 2003]. The option that we have used most commonly is to count the number of citations in bibliographic databases for a particular host species, and include that number as a covariate in the analysis (Fig. 2). This approach assumes that effort devoted to parasite sampling is represented to the same degree in the citation counts for the different primate species. The database has grown to the point that other options are becoming available, including use of species richness estimators [Poulin, 1998; Walther & Morand, 1998]; we are using these and other approaches in our current analyses.

A final methodological issue involves phylogeny. In any comparative study, we expect that more closely related species have more similar trait values [Blomberg et al., 2003; Freckleton et al., 2002; Nunn, 2011]. This nonindependence might occur for parasites that coevolve with hosts, and thus are shared among closely related species, or if parasite host shifts are more likely among closely related host species (because of similar immunological defenses, or if they share similar ecological niches). Thus, it is important to assess the degree to which phylogeny accounts for variation in parasitism and other host traits, and to take phylogeny into account when necessary [Garland et al., 2005; Nunn, 2011]. In the

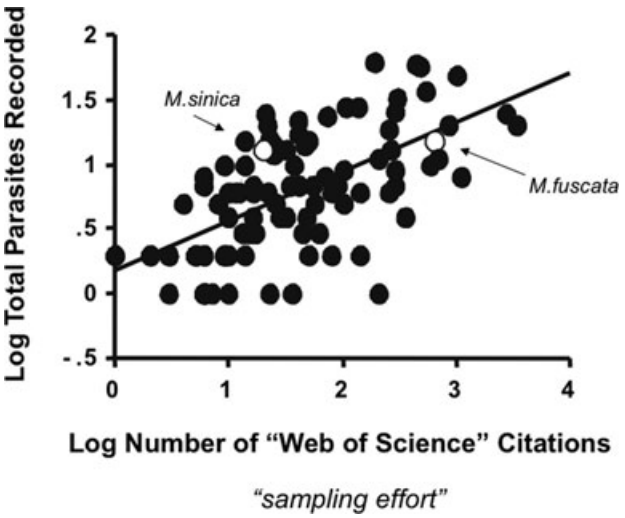

Fig. 2. Sampling effort and parasite richness. As a host species is studied for parasites in greater depth, more parasites are documented. In comparative tests, we control for sampling effort by including in the statistical model information on citation counts or the number of animals sampled for parasites for each host species [Nunn et al., 2003]. In this particular case, both *Macaca sinica* and *M. fuscata* have similar total numbers of parasites. Relative to sampling effort, however, *M. sinica* has more parasites, which is quantified as a positive residual. This figure was constructed using the first version of the database [see also Nunn et al., 2003]; the database is now more than twice as large.

results that follow, we used methods to assess phylogenetic signal and to incorporate phylogeny into the analyses, and I focus on results that were tested using phylogenetic methods.

In our comparative analyses of the first set of data (approximately half the size of the current database described above), we found that six major variables influence parasite richness in primates. First, measures of population density predicted parasite richness, and this was true for the three major groups of parasites—helminths, protozoa, and viruses [Nunn et al., 2003]. Second, we found that geography plays a role, with parasite richness increasing with geographic range size [for viruses, Nunn et al., 2003] and for species closer to the equator [for protozoa, Nunn et al., 2005]. Third, host species characterized by having larger body mass harbor more parasites [although this appeared to be sensitive to whether phylogeny was taken into account, Nunn et al., 2003]. Fourth, species in which individuals range further per day showed higher parasite richness [for helminths, holding home range size constant, Nunn & Dokey, 2006]. Fifth, we found an intriguing pattern in which more rapid rates of host diversification covary with higher parasite richness; this finding raises questions about whether parasites might influence host speciation, or vice versa, or whether something else entirely influences the diversity of both parasites and their primate hosts [Nunn et al., 2004]. Finally, we find in all analyses that sampling effort is the best predictor of parasite

richness. In subsequent analyses that examined sampling localities more directly, we documented major geographic sampling gaps in our knowledge of primate parasites [Hopkins & Nunn, 2007, 2010].

Of course, it is often the hypotheses that are not supported that are most interesting to pursue, especially when we have solid theoretical reasons to expect a pattern and it is not found. One such example involves group size. While we had clear a priori expectations for an effect of group size on parasitism under the group size hypothesis [Alexander, 1974], we failed to find any compelling support for this prediction, including in another set of phylogenetic comparisons that used white blood cell counts as a measure of investment in immune defenses [Nunn, 2002; Nunn et al., 2000]. These negative findings are puzzling, given that epidemiological models of spatially structured populations have revealed positive effects of group size on parasitism [Nunn et al., 2008, 2011]. I will return to the group size hypothesis below, as it has motivated much of the modeling and subsequent comparative research that we are conducting. In addition to probing the effects of group size, members of my research group are reexamining all these hypotheses, with the goal to assess whether the patterns that we initially found continue to be supported with our significantly larger database and when using newer methods to investigate patterns statistically and phylogenetically.

Integrating Theoretical Models and Comparative Research

Comparative research using the *Global Mammal Parasite Database* has provided some answers to many questions about variation in primate parasitism, particularly involving the drivers of parasite species richness [Altizer et al., 2007; Davies & Pedersen, 2008; Nunn et al., 2003, 2004, 2005; Nunn & Dokey, 2006; Pedersen & Davies, 2009]. As just noted with regard to group size, however, many new questions have emerged, and it is fair to say that some of our comparative analyses have raised more questions than answers, for example regarding the underlying mechanisms that generated the observed patterns. In addition, multiple mechanisms could account for some of the patterns that we discovered.

These emerging questions call for new analyses, and as our understanding of primate parasitism increases and phylogenetic methods improve, additional comparative studies are likely to shed important light on these outstanding questions. However, we need more than just additional analyses. We also need a deeper understanding of disease dynamics in socially structured populations, for example, by building epidemiological models that are appropriate for spatially distributed social groups where the groups are linked through individual dispersal, home range overlap, and interactions at territorial boundaries [Nunn et al., 2008, 2009, 2011]. These conditions characterize primate populations, yet the interactions among these variables and other epidemiological parameters are too complex to understand from simply pondering them without formal theoretical investigation. By developing spatially explicit models, we can gain a richer understanding of the multitude of interacting mechanisms that drive parasitism in primate populations [Nunn, 2009]. And from this, we can generate new, theoretically grounded predictions that link those mechanisms to real data on parasites in the field and comparative research.

One example of how theory informs comparative analysis of parasitism comes from a model of the dynamics of sexually transmitted diseases (STDs) by Thrall et al. [2000]. These authors used an individual-based model to investigate whether the spread of an STD in a socially living, polygynous host was influenced by variance in male mating success, longevity, and migration of females among mating groups. Thrall et al. [2000] showed that prevalence of the STD is predicted to be higher in females than in males, and that this predicted sex difference increases with increasing variance in male mating success. Drawing on this model, Sonia Altizer and I predicted that the prevalence of STDs would be greater in female than male primates—which was supported [Nunn & Altizer, 2004]—and that sex differences in prevalence increase with increasing skew toward one or a few males doing most of the mating [Nunn et al., unpublished data]. Thus, we drew upon Thrall et al.'s [2000] modeling study to generate predictions, and then we tested those predictions with comparative data [Nunn & Altizer, 2004].

These studies revealed the power of combining models with empirical data, both as a way of generating predictions and gaining a richer understanding of the drivers of disease dynamics. Following this comparative research aimed at testing specific predictions, I built a spatially explicit version of the model to investigate the spread of pathogenic infections in socially structured primate populations [Nunn et al., 2008], and I used that modeling framework to address two questions that had puzzled me from my previous comparative research. First, to what extent does host ranging behavior influence parasite risk? Second, why does group size show such weak associations with parasitism? I discuss each of these in turn.

Ranging Behavior and Fecal-Oral Transmission

Recently, my colleagues and I developed a spatially explicit model to investigate the links between ranging behavior and parasitism, focusing in particular on whether species that use their ranges more intensively have higher levels of parasitism

[Nunn et al., 2011]. This modeling effort arose from a comparative study noted above, in which Adrian Dokey and I examined the relationship between ranging intensity and parasitism [Nunn & Dokey, 2006]. Ranging intensity simply refers to how intensively a group of animals uses their home range, which can be operationalized as day range relative to the home range and is familiar to primatologists as Mitani & Rodman's [1979] defensibility index (or D-index). While it is widely known that the D-index covaries positively with territoriality, could it be that the index also reflects exposure to infectious stages of parasites in the soil, and thus covaries with infection with fecally transmitted parasites? In comparative research, that is what we found: helminth richness covaried positively with ranging intensity, as measured by the D-index [Nunn & Dokey, 2006].

Dokey and I originally assumed that the association between parasitism and the D-index reflects exposure to parasites. However, new questions arose. Could it be, for example, that the pattern is generated by contact among groups at territorial boundaries? In other words, could the infectious disease spread among groups through aggressive contact among groups, which is likely to also covary with the D-index? Another question about underlying mechanisms concerns susceptibility to parasites. Rather than greater exposure to larvae in the soil, could it be that animals that range more intensively—and possibly engage in higher rates of intergroup conflict—are more stressed, and thus more susceptible to infectious diseases, including gastrointestinal parasites? It is worth noting that other researchers have investigated the links between territoriality, range use, and parasitism. For example, Ezenwa [2004] found that territorial ungulate species exhibit higher prevalence of parasitic nematodes than nonterritorial species, and among two groups of mantled howler monkeys (*Alouatta palliata*), Stoner [1996] found that parasitism was higher in a group that used a narrow forest corridor between two blocks of forest (rather than a more cohesive block of forest for the other group). As with our comparative study, questions about the actual mechanisms for these patterns also remained in these field studies, which further motivated our desire to develop a theoretical model.

Thus, to further investigate the links between parasitism and ranging behavior, Pete Thrall, Christophe Boesch, Fabian Leendertz, and I developed a spatially explicit, agent-based model [Nunn et al., 2011]. Our primary goal was to assess whether greater range use intensity can plausibly generate the patterns that we discovered in the comparative data. In other words, does simply having a higher D-index lead to higher levels of infection at the population level, driven by greater individual exposure to parasites in the soil? Along similar lines, does having a larger D-index lead to greater penetration of a gastrointestinal parasite into a spatially and socially structured population, and to greater population losses due to disease? Importantly, how does the effect of ranging behavior compare to the effects of other, more familiar epidemiological parameters, such as disease-related mortality and per-contact probability of transmission? These are questions of fundamental importance in the context of primate conservation and emerging infectious diseases.

In our model, we investigated how range use intensity impacts the spread of fecally transmitted micro- and macroparasites in a population that was spatially structured into social groups (i.e., a metapopulation, see Fig. 2). Animals ranged as a cohesive social group within a core area, with biased movement toward the range center when they moved outside the core area. For comparison, we also systematically varied parameters that represent more standard epidemiological factors involving rates of host mortality, rates at which infectious stages of parasites develop and die in the soil, per-contact probability of acquiring parasites, group size, and disease-related mortality rate. Disease-related mortality was expressed as a multiplier of the baseline mortality, and depended on infection status rather than parasite load. The parasite was introduced through spillover from a reservoir population along the edge of the spatial lattice of social groups, which was designed to mimic a reserve and the emergence of new pathogens in primate populations that inhabit protected areas. Thus, we used the model to investigate the conservation implications of infectious disease spillover from humans or domesticated animals. While the model ignored variation in the number of infectious organisms in individual hosts, infectious material accumulated in the ranging matrix in a quantitative fashion, such that risk of infection was greater in more heavily used areas.

We ran 1,000 simulations in which we systematically varied 12 parameters reflecting ranging behavior, social behavior, and parasitological parameters. At the end of each simulation, we recorded output variables including prevalence, population decline, and spatial patterns of infection [Nunn et al., 2011]. From these simulations, we found a strong effect of ranging intensity: as the social groups used their ranges more intensively, the prevalence of infection rose (Fig. 3). This effect was comparable in magnitude to some epidemiological parameters, such as disease-related mortality, but somewhat weaker than others, such as group size (a measure of local density), parasite lifespan in the soil, and per-contact probability of transmission [see Nunn et al., 2011]. In addition, the model output revealed that gastrointestinal parasites have the potential to cause substantial population declines (Fig. 4), suggesting that understanding threats of spillover from domesticated animals and humans has important conservation implications.

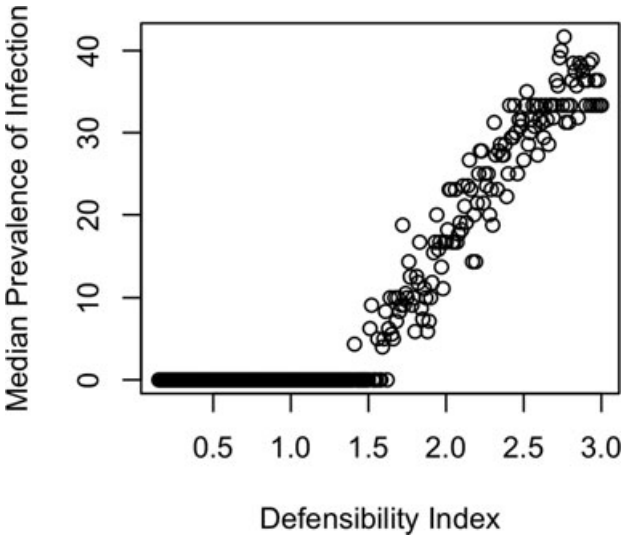

Fig. 3. Median prevalence of a gastrointestinal parasite relative to the defensibility index. In this simulation, the other 11 parameters were held constant at their midpoint values [Nunn et al., 2011]. A social group moves on its home range, which is embedded in a 9 × 9 social lattice of 80 other groups (and their ranges). A group can overlap with other groups (i.e., move to another group's range), but two groups cannot occupy the same grid cell, and individuals disperse between adjacent groups. Under these conditions, the parasite appears unable to persist unless the agents move at least 1.5 home range diameters per time step (in temporal units of 1 day).

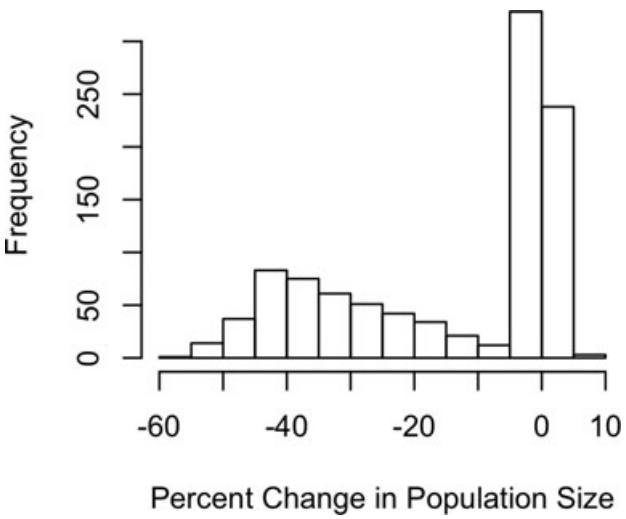

Fig. 4. Change in population size due to introduction of a fecally transmitted infectious organism. In the majority of the simulations, population size remained stable, with stochastic fluctuations around the starting population size (tall bars to right of plot). In a substantial number of cases, however, the population declined significantly, in some cases by more than 50%.

Let us return to the original motivation for the study. Across species, we found that the D-index covaried positively with parasite richness, but the effect could be driven by multiple mechanisms, including greater exposure to parasites in the soil, greater exposure to parasites during territorial interactions, and greater susceptibility to parasites due to possible stress of longer day ranges and risks involving territorial defense. The model revealed that ranging behavior on its own has the potential to increase disease risk through greater exposure to infectious stages of parasites in the soil. Intergroup contact at territorial boundaries may further increase transmission rates, and the stress of territoriality and greater ranging may increase susceptibility. The main point, however, is that the model clearly shows that ranging behavior on its own is likely to be a significant source of infectious disease risk; moreover, the effects of ranging behavior are on par with other major epidemiological parameters. As with any theoretical model, these conclusions may be sensitive to a number of assumptions used to build the model, and thus will require further investigation—and, ideally, parameterization with actual ranging behavior for different populations or species.

Social Networks, Group Size, and Disease Risk

As discussed already, our comparative research also failed to uncover a strong link between group size and disease risk, as predicted by the group size hypothesis. One possible explanation for the lack of a group size effect involves the possibility that social networks within groups are also important to disease dynamics, perhaps even more so than overall group size. Could it be, for example, that larger groups have more social substructure, and this substructure hinders the spread of infectious agents? In other words, do larger groups have more cliques that might slow infectious disease spread? To investigate this question, we need two kinds of approaches: one rooted in understanding how infectious agents spread on social networks, and the other focused on understanding the links between group size and network properties in real primate social groups.

Randi Griffin and I investigated these questions by combining approaches based on social network analysis, agent-based modeling, and phylogenetic comparisons [Griffin & Nunn, in press]. Specifically, the modeling portion of the project generated 10,000 random social networks for a hypothetical group of 25 primates. These networks might reflect, for example, patterns of association or grooming, and thus indicate potential transmission routes for a socially transmitted infection. Because the networks were generated randomly, the network characteristics differed across the networks. One of these characteristics involved *community modularity* that captures the degree to which a group is subdivided into smaller communities of more closely interacting individuals [see also Jacobs & Petit, 2011; Kasper & Voelkl, 2009; Sueur et al., 2011].

With these networks, we then randomly selected an individual to be initially infected (i.e., the index case), and we examined how effectively the infectious agent spread on the network, which we measured as

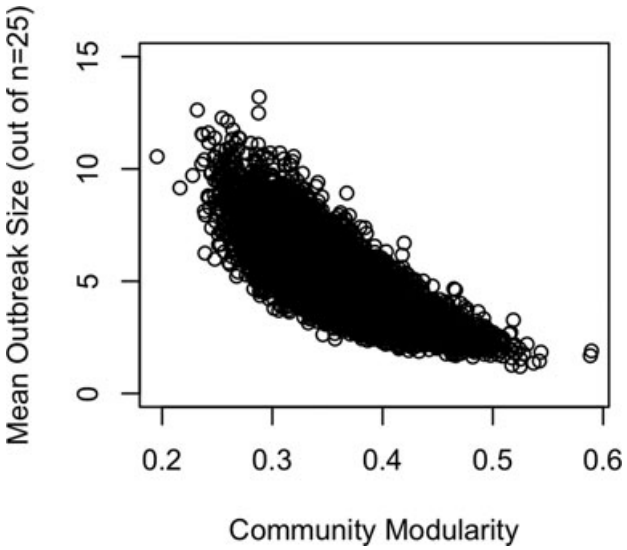

Fig. 5. Community modularity and outbreak size from the simulation model of Griffin and Nunn [in press]. Plot shows results with per-contact probability of transmission set to 0.2. Mean outbreak size ignores the initial infection, and has a maximum of 25 because the network contained only 25 nodes (individuals). Results are based on simulations across 10,000 random networks.

the number of individuals infected over the course of a simulation run ("outbreak size"). This process was repeated 1,000 times on each of the 10,000 random networks, giving us a mean outbreak size for each of the networks. We then examined how outbreak size covaried with network properties of the random networks. For example, the outbreak size covaried negatively with community modularity (Fig. 5), as might be expected if greater subgrouping (or "cliqueishness") results in smaller outbreak sizes [Salathe & Jones, 2010; Watve & Jog, 1997; Wilson et al., 2003]. In effect, tighter communities of more closely interacting individuals act to slow the spread of infections at the group level, much as a quarantine works in the context of public health to slow the spread of infectious agents in human or animal populations.

These are interesting findings, but not necessarily surprising. Importantly, however, they provide a strong theoretical basis to examine how parasitism covaries with network properties—particularly community modularity—in different species of primates. In other words, the model generates a novel prediction and shows that some network properties are more predictive of parasitism than other properties. Thus, we next collected data on 19 different primate social networks, drawing both on published papers and original data collected by R. Griffin [see also Kasper & Voelkl, 2009]. The networks were mainly from wild groups and based on grooming data, but in a minority of cases, other kinds of data, such as proximity, were used, and some data came from captive animals, subject to the requirement that group size and composition were typical of wild primates.

As predicted by the model, we found that increases in community modularity on real primate networks covaried with lower richness of parasites that spread through close transmission [Griffin & Nunn, in press], as might be expected on a social network. As with the other comparative tests, sampling effort also explained much of the variation in parasite richness; more parasites are documented in hosts that are studied more intensively. The statistical model explained 68% of the variation in the richness of the socially transmitted infectious organisms.

Importantly, we also found that primate species characterized by larger social groups have higher community modularity; larger groups show more subgrouping, and this should depress the number of parasites that can establish in larger groups [Griffin & Nunn, in press]. This finding is therefore relevant to previous studies of parasite richness and group size. It could be, for example, that parasite success increases with group size—a finding documented in other simulation models that I developed—but that in real primate groups, the increasing modularity (subdivision) of larger groups depresses this effect. Collectively, these findings highlight the importance of considering network structure within social groups when investigating disease dynamics, rather than focusing only on group size as a measure of the potential for parasite transmission.

CONCLUSIONS AND FUTURE DIRECTIONS

Using two examples from my recent research, this paper makes the case for greater integration of theoretical modeling and empirical research in studies of primate disease ecology. The complexity of disease dynamics in socially and spatially structured populations requires that we develop rigorous, spatially explicit models to understand infectious disease dynamics. In some cases, the models confirm intuition, as in the case of greater modularity reducing outbreak size, yet they provide more quantitative assessment of how two or more variables relate to one another (Fig. 5), and they can help to pinpoint which host traits make the strongest predictions for variation in parasitism [Griffin & Nunn, in press]. In other cases, the models generate new predictions that can be tested [Thrall et al., 2000]; in such cases, the models lead directly to new discoveries [Nunn & Altizer, 2004], and that is an exciting outcome. And in yet other cases, the models help to assess possible mechanisms, and to place these effects in line with other epidemiological drivers of infection dynamics, such as mortality rates or per-contact probability of transmission [Nunn et al., 2011].

In addition to informing comparative research, these spatially explicit models can be used to generate predictions for field research. For example, just as we might predict that community modularity

influences variation in infection risk across species, we might also predict that this network property (and others) influences risk among different groups. Ideally, such a prediction would be tested among groups in the same population at the same time, so that environmental and other factors are held constant. Conversely, field data can be used to parameterize the agent-based models, and that is a valuable direction that some primatologists are already taking [Bonnell et al., 2010; Kennedy et al., 2009]. Developing a greater linkage between field conditions and models will be essential for future advances in primate disease ecology.

Comparative approaches are useful for understanding broad patterns of variation, ideally in light of a priori hypotheses, but a major challenge arises when attempting to understand variation at the individual level [Nunn & Altizer, 2006]. For example, do we expect to see that dominance rank covaries with parasitism? Or, does variation in parasite risk covary with age, reproductive status, or sex? In addition to using theoretical models focused on the group level, these questions can be fruitfully addressed with field research, where data are collected on individuals of known dominance rank, age, and other characteristics [e.g., Hausfater & Watson, 1976; Muehlenbein & Watts, 2010; Muller-Graf et al., 1996]. In actual publications of field research, however, the summary statistics are rarely provided at the level needed for comparison, i.e., in terms of variation in parasitism among individuals.

Another approach to addressing these group-level questions is through meta-analysis. As more statistical tests of individual variation accrue from field studies (see Fig. 1), it is becoming possible to use meta-analytical techniques [Adams, 2008; Arnqvist & Wooster, 1995; Lajeunesse, 2009] to assess whether patterns hold more generally across studies, and to investigate which factors influence variation in effects across studies. For example, Joanna Rifkin, Laszlo Garamszegi, and I used meta-analytical approaches to investigate the association between group size and parasitism measured across different social units and parasite transmission modes [Rifkin et al., in press]; our study is a significant expansion of a previous meta-analysis [Côté & Poulin, 1995]. Similar approaches could be used to investigate whether parasitism covaries with dominance rank [Hausfater & Watson, 1976; Muehlenbein & Watts, 2010], or whether parasitism differs between sex or age groups [Muller-Graf et al., 1996, 1997], keeping in mind that covariates, such as transmission mode, can and should be taken into account in a meta-analysis. It is important to realize that the meta-analytical approach uses the actual statistical tests from the different individual field studies to assess an overall effect (e.g., a *t*-statistic or correlation coefficient reflecting association), rather than summarizing the data into the form of a typical comparative analysis data set using simple summary statistics of individual data from those same studies (e.g., a mean or median prevalence, or presence or absence of a parasite).

As a related issue, how might we improve statistical analyses of field-collected data? As a gross generalization, many field studies collect data, identify the parasites, and then attempt to assess different hypotheses for variation in prevalence or richness at the group and population levels. Rarely do the researchers attempt to control for multiple testing, for example when data on different parasites are examined in separate tests. It is often impossible to assess the mechanisms at play, or there may even be too many hypotheses to test given the number of samples collected. And, of course, many additional methodological issues arise, such as estimating prevalence based on the proportion of individuals examined, rather than proportion of samples [Gillespie, 2006]. As many of the studies collect data on gastrointestinal parasites in fecal samples, a fruitful option for the future may be to use the fecal sample itself as the unit of analysis, and control for individual identity as a random effect in linear mixed models—as some researchers are doing [e.g., Clough et al., 2010; MacIntosh et al., 2010; Muehlenbein, 2006; Muehlenbein & Watts, 2010]. Importantly, with more compelling statistical tests of hypotheses within species, we will have higher power to assess patterns synthetically in cross-species meta-analyses.

This has been an exciting decade for primate disease ecology, and the next decade looks to be just as promising. As we improve our understanding of primate disease ecology, we will gain deeper insights to primate socioecology. In addition, primate disease ecology research is proving critical for addressing pressing conservation concerns in wild primates, and for improving public health in the context of new infectious diseases. While progress is likely to come from multiple directions, including continued improvements in noninvasive sampling of parasites, I also see many improvements ahead for quantitative approaches to understand disease ecology, specifically in terms of spatially explicit agent-based models, advances in phylogenetic comparative methods, greater use of meta-analysis approaches, and improved statistical rigor in analyses of field-collected data.

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