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REVIEW AND SYNTHESIS

The macroecology of infectious diseases: a new perspective on global-scale drivers of pathogen distributions and impacts

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Abstract

Identifying drivers of infectious disease patterns and impacts at the broadest scales of organisation is one of the most crucial challenges for modern science, yet answers to many fundamental questions remain elusive. These include what factors commonly facilitate transmission of pathogens to novel host species, what drives variation in immune investment among host species, and more generally what drives global patterns of parasite diversity and distribution? Here we consider how the perspectives and tools of macroecology, a field that investigates patterns and processes at broad spatial, temporal and taxonomic scales, are expanding scientific understanding of global infectious disease ecology. In particular, emerging approaches are providing new insights about scaling properties across all living taxa, and new strategies for mapping pathogen biodiversity and infection risk. Ultimately, macroecology is establishing a framework to more accurately predict global patterns of infectious disease distribution and emergence.

Keywords

Biodiversity, conservation, disease ecology, infectious diseases, macroecology, pathogens.

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INTRODUCTION

Each year infectious diseases cause 9.6 million human deaths globally (Lozano *et al*. 2013) and cost about $120 billion in the U.S. alone (US Centers for Disease Control and Prevention 2008). Most of these diseases have a long history of infecting humans, but growing population size, global connectivity and habitat disruptions collectively boost the chances that a novel infectious disease will emerge in humans (Morse *et al*. 2012). At the same time, infectious diseases have caused die-offs among terrestrial and marine biota ranging from bats and birds to frogs and sea stars (Pedersen *et al*. 2007; Frick *et al*. 2010; Heard *et al*. 2013). The problem of identifying high-risk pathogens ranks among the greatest challenges facing modern science; critical to this effort is the need to predict geographic locations where disease outbreaks are likely to occur, identify the reservoir hosts from which pathogens will emerge, and predict host species at greatest risk of pathogen-mediated declines. A new perspective is needed to develop integrative, broad-scale models that examine determinants and constraints on pathogen distributions and predict their responses to environmental change. Macroecology can provide this perspective.

Macroecologists search for statistical relationships explaining species, abundance, and trait distributions at broad scales of organisation and from both historical and geographical perspectives (Brown 1995). In contrast to traditional experimental and mechanistic approaches in ecological disciplines such as population and community ecology (Johnson *et al*. 2016), macroecological studies generally use existing data to investigate and generate hypotheses. The emergence of macroecology roughly 25 years ago coincided with the new age of informatics that has fostered studies at broad spatial and temporal scales, where localised ecological phenomena transition into the global processes of biogeography, paleobiology and evolutionary diversification (Brown 1995; Burnside

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et al. 2012; Smith *et al*. 2014). As a field, macroecology offers a framework for investigating questions across diverse areas of research. In conservation, for example, macroecological approaches have revealed complex suites of biological and environmental factors that drive mammal extinction risk (Cardillo *et al*. 2005; Davidson *et al*. 2012); thus providing a new basis for predicting species most vulnerable to future declines. Macroecology has provided equally important advances in climate science (e.g., Kerr *et al*. 2007; Algar *et al*. 2009), animal behaviour (e.g., Viscido *et al*. 2004; Carbone *et al*. 2005), and evolution (e.g., Taylor & Gotelli 1994; Clauset & Erwin 2008).

Macroecology complements the science of infectious disease ecology by identifying broad-scale patterns of relationships between parasites and hosts, and evaluating support for underlying causes that apply generally across taxa and geography. To date, however, studies of host–parasite interactions remain on the fringes of macroecology, in part because of data limitations (but see, e.g., Nunn *et al*. 2003; Guernier *et al*. 2004; Jones *et al*. 2008; Dunn *et al*. 2010; Murray *et al*. 2015). We define parasites broadly as disease-causing organisms ranging from viruses and bacteria to helminths and arthropods, including all pathogens. Compared to free-living organisms, taxonomic and distributional information is less complete for parasites. Most parasitic species are still unknown to science (Dobson *et al*. 2008; Poulin 2014), existing data are spatially and temporally sparse, and taxonomic confusion or lack of resolution is common. Early attempts to explore broad scale patterns of parasite biodiversity indicated that the diversity of helminth species infecting vertebrates globally greatly exceeds that of their hosts (Poulin & Morand 2000; Dobson *et al*. 2008) and that host species traits might predict variation in parasite species richness (e.g., Guégan *et al*. 1992; Feliu *et al*. 1997; Morand & Poulin 1998; Nunn *et al*. 2003; Ezenwa *et al*. 2006). New global data sets on parasites (e.g., Nunn & Altizer 2005; Dallas 2016) coupled with more flexible computational tools (e.g., Elith *et al*. 2008) offer opportunities to expand on previous work and make new discoveries.

Greater synthesis of infectious disease ecology and macroecology has advantages for both disciplines. Because parasites often have unique life history traits that affect their energetics and distribution, incorporating parasites into macroecology could provide new insights into scaling properties across all living taxa (Hechinger *et al*. 2011; Lagrue *et al*. 2015). Macroecology can benefit understanding of parasites as a hyper-diverse component of the earth's biota by investigating whether parasites conform to the macroecological paradigms discovered in free-living species (e.g., Table 1). Macroecological data sets and approaches can also advance basic questions in the ecology and evolution of infectious diseases, such as how anthropogenic drivers and global environmental change are altering parasite distributions. Typical studies of disease biogeography focus on understanding the distributions of individual diseases or vectors (e.g., Blackburn *et al*. 2007; Simoonga *et al*. 2009). Macroecology contributes to this understanding by illuminating additional principles that drive global variation in parasite biodiversity (Fig. 1).

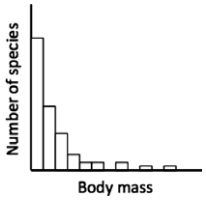
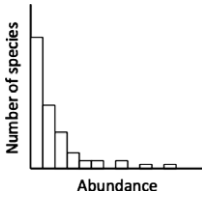
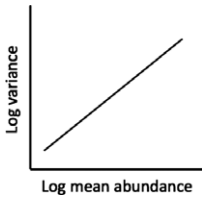
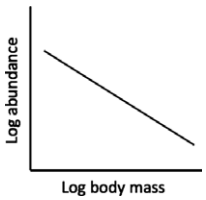
Here, we outline how the perspectives and tools of macroecology advance our understanding of infectious disease ecology. We first discuss common macroecological patterns in free-living species and the extent to which parasitic species conform to similar rules. We next turn to broad scale patterns of host defense, and examine what macro-scale approaches can tell us about taxonomic and geographic variation in susceptibility to infection. We also review recent computational advances, including machine-learning approaches, that allow researchers to use heterogeneous data sets and accommodate imperfect sampling regimes that often characterize macroecological and broad-scale disease datasets. We go on to consider how insights from infectious disease macroecology can inform efforts to protect human health and conserve biodiversity. Finally, we examine crucial needs for future work including better prediction of disease emergence and spread and overcoming the analytical and data challenges inherent in macroscale disease research.

MACROECOLOGICAL PATTERNS IN FREE-LIVING AND PARASITIC SPECIES

Numerous studies have revealed consistent patterns of species abundance, distribution and diversity that occur with such frequency in free-living organisms that they can be thought of as macroecological 'rules' (Table 1; Brown 1995; Witman & Roy 2009; Smith *et al*. 2014). Some of these rules concern patterns of trait relationships among species. For example, body size and abundance distributions are strongly right skewed for most taxa, with a higher number of small and rare species than large and abundant species. Other rules concern species distribution and diversity. For example, species richness tends to decrease with latitude, whereas the range area of species tends to increase with latitude (Rapoport's rule). Each pattern or rule hints at the ecological and evolutionary forces that shape patterns of biodiversity. Compared to studies of free-living organisms, relatively few studies have considered analogous patterns in parasites (Poulin & Morand 2004). However, studies conducted on parasites to-date reveal intriguing similarities between parasitic and free-living organisms in some cases (Table 1). This implies that much of the theory developed to explain diversity patterns in free-living organisms might also apply to parasites, such that insights from macroecology could advance knowledge of parasite diversity (e.g., Fig. 1).

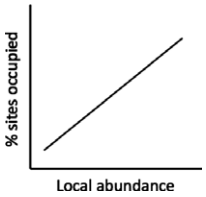
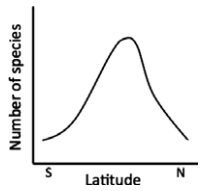
Biodiversity is the product of current environmental conditions and biogeographic history, and differences between regional faunas and floras often reflect differential constraints stemming from these two factors (Mittelbach *et al*. 2007). Parasite biodiversity is known to increase with host biological traits such as body mass, range area, longevity and population density (Kamiya *et al*. 2014a) and further depends on host evolutionary history, with host species lacking close relatives tending to have fewer parasite species compared to species in rapidly diversifying clades (Nunn *et al*. 2004; Huang *et al*. 2015). More recently, quantitative studies on the effects of allometric scaling in host demographic parameters suggest that transmission thresholds for parasite establishment, parasite biodiversity, and the tendency for parasites to induce host population cycles scale allometrically among host species (e.g., Hechinger 2013; Han *et al*. 2015a). Further work should

Table 1 Macroecological rules for free-living and parasitic species. A number of important macroecological patterns have been described for free-living organisms, and in some cases, key examples of animal parasites conforming to similar rules

Macroecological rule	Summary of trend	Visual pattern	Pathogen (pathogen) examples
Body size distributions	More small-bodied species have been described relative to large-bodied species		Right-skewed body size or genome size distributions in many groups of helminths, arthropods, and viruses (Poulin & Morand 1997; Claverie & Abergel 2013)
Species abundance distributions	More low-abundance species exist compared to highly abundant species		Right-skewed abundance distributions of helminth species in their fish hosts (Poulin *et al*. 2008)
Taylor's power law	Variance in abundance is a power function of mean abundance across species populations		Log variance scales with log mean number of pathogens per host and the log mean number of clinical cases per outbreak for human pathogens (Keeling & Grenfell 1999; Woolhouse 2002; Morand & Krasnov 2008)
Abundance–body size relationships	Abundance generally decreases with body mass across species within any large taxon		Mean number of pathogens per host decreases with pathogen body size across metazoan pathogens of vertebrates (Krasnov *et al*. 2013)
Abundance–distribution relationships	Local abundance increases with regional occupancy or distribution		Locally abundant pathogen species occur in more populations of fish or invertebrates on a regional scale, than locally rare species (Poulin *et al*. 2012; Thieltges *et al*. 2013)
Species–area relationships	The number of species in an area is a power function (or some similar function) of the size of that area		The richness of pathogens and pathogens in humans and wildlife scales with the size of the geographic area sampled (Smith *et al*. 2007; Dunn *et al*. 2010; Guilhaumon *et al*. 2012)

(continued)

Table 1. (continued)

Macroecological rule	Summary of trend	Visual pattern	Pathogen (pathogen) examples
Rapoport's rule	The geographical range size of species generally increases towards higher latitudes		The geographical range size of Palaearctic fleas parasitic on mammals correlates positively with latitude (Krasnov *et al.* 2008)
Latitudinal gradients in diversity	The number of species (in comparable habitat patches) increases towards lower latitudes		Human and primate pathogen species richness peaks at low latitudes (Guernier *et al.* 2004a; Jones *et al.* 2008; Kamiya *et al.* 2014b). Note: this pattern is overall uncommon in parasites (Poulin 2007)
Distance decay of similarity	Similarity in species composition decreases exponentially with increasing distance between sites		Similarity of helminth or arthropod assemblages decreases exponentially with increasing distance between host populations (Krasnov *et al.* 2005)
Nested species subsets	Within a larger region, species in depauperate assemblages are subsets of those in richer assemblages		Human pathogens exhibit a nested species distribution, such that higher latitude assemblages are of often subsets of tropical assemblages (Guernier *et al.* 2004a). Note: this pattern is uncommon in non-human parasites (Poulin 2007)

determine whether this represents a general scaling relationship (similar to the relationship between body mass and metabolic rate) or only occurs in certain taxa. In addition to advancing understanding of parasite distributions in natural systems, macroecological perspectives can also be applied to illuminate infectious disease patterns in human populations. For example, human infectious diseases exhibit a latitudinal gradient in diversity similar to the richness of free-living organisms (Guernier *et al.* 2004), which appears to be strongly influenced by underlying vertebrate biodiversity (mammals and birds), human population size, and disease control efforts (Dunn *et al.* 2010). This pattern highlights the dual importance of ecological and socio-economic factors in determining patterns of disease diversity.

Studying the broad-scale diversity and distribution of parasites also promises to advance the field of macroecology and ecological theory in general. Owing to their obligate and intimate associations with hosts, parasites often exhibit different life histories and metabolic demands compared to free-living organisms, which in some cases leads to scaling patterns that differ from those of non-parasitic species. In cases where parasites diverge from the macroecological patterns of free-living species, knowing why and how parasites deviate can help illuminate why a pattern holds true for other taxa. For example, Hechinger *et al.* (2011) found that metabolic theory could explain observed variation in the abundance of parasite species in estuarine food webs only after including the dynamics of energy flow among trophic levels. This led to discovery of the principle of production equivalence, where species within a given trophic level tend to produce biomass at the same rate across all body sizes and functional groups.

Parasites also offer distinct advantages as study systems for advancing macroecological theory. Their degree of resource specialisation (i.e., the number of host species used and/or the phylogenetic diversity of their hosts) can be readily quantified, potentially with less subjectivity than free-living species (Poulin & Mouillot 2003), which enables stronger tests of macroecological theories. For example, by comparing the abundance and host breadth of fleas on small mammals, Krasnov *et al.* (2004) obtained clear empirical support for the resource breadth hypothesis, which states that the same attributes that allow some species to exploit many resources also allow them

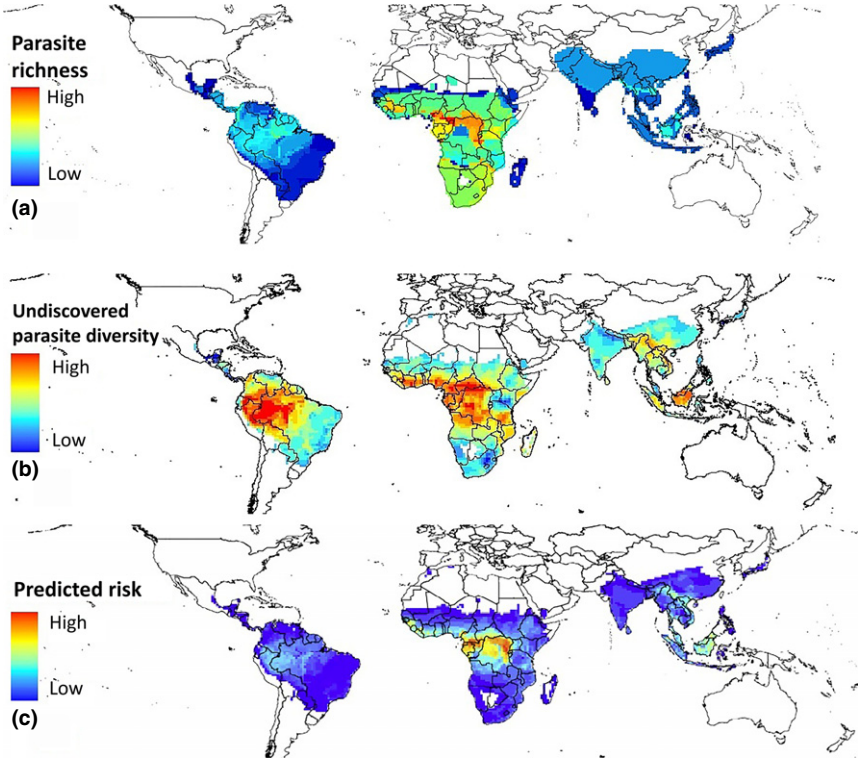


Figure 1 Three different views of parasite diversity in free-living primates: (a) predicted global patterns of known parasite species richness in wild primates based on the geographic ranges and known pathogen diversity (ranging from viruses to helminths) of over 100 wild primate host species, (b) areas likely to contain large numbers of undiscovered parasite species based on the geographic distribution of understudied primate species, and (c) areas of high zoonotic disease risk for humans based on the geographic distribution and phylogenetic similarity to humans of wild primate species. Host-parasite diversity was estimated based on records in the Global Mammal Parasite Database (http://www.mammalparasites.org/). See (Cooper & Nunn 2013; Pedersen & Davies 2009) for additional details on how maps were generated.

to reach high local abundance. For further discussion of 'rules' in parasite ecology see Poulin (2007).

GLOBAL BIOGEOGRAPHY OF HOST DEFENSE

Macroecology offers tools to understand the otherwise perplexing variation in defense strategies against parasites among host species, a significant unanswered evolutionary puzzle (White & Perkins 2012; Graham 2013). The nature and extent of these defenses are to a large part the product of host-parasite co-evolution, which encompasses the constraints of history and adaptation inherent to any particular host-parasite association. With its use of phylogenetically-based comparative approaches, macroecology allows different co-evolutionary histories to be taken into account in investigations of broad-scale variation in defense strategies among host taxa (Hadfield *et al.* 2014). For example, macroecologists have examined the cost of immune defenses trade-off against other components of host life-history and discovered that short-lived species with rapid reproductive cycles often forgo or reduce investment in immune defense, whereas longer-lived species with slower rates of reproduction tend to invest more in defense (Lee 2006; Previtali *et al.* 2012). Moreover, host life history strategy, combined with metabolic traits, explains significant variation in the presence and intensity of infections tolerated by species (Johnson *et al.* 2012). Notably, variation in host defense strategies might have crucial consequences for the global distribution of parasites and spillover risk to human populations. For example, bats have been identified as the source of a disproportionate number of emerging zoonotic viruses, including SARS, Ebola, Nipah, Hendra and rabies (Dobson 2005). Macroecological studies show that the uniqueness of bats cannot be explained by their life history and ecological traits (Luis *et al.* 2013), spurring new investigations of bat immune defenses relative to other vertebrate hosts (Zhang *et al.* 2013; Brook & Dobson 2015). As genetic tools increase our ability to screen for multiple parasite infections and assess immunity in wild hosts, the potential for macroecological approaches to facilitate novel insights into the variation and implications of host defense strategies will continue to grow.

In humans, macroecological studies have shown that there is great variation in parasite occurrence among populations (Burnside *et al.* 2012). In addition, different human parasite assemblages tend to form nested subsets, with the pathogens that occur at higher latitudes consisting of subsets of pathogens that occur close to the equator (Guernier *et al.* 2004). Macroecological approaches allow us to investigate whether immune defense investment and immunogenetic variation differ among human populations, as might be predicted by heterogeneity in the diversity or composition of parasite assemblages. The availability and quality of food resources also vary considerably among human populations, and nutritional deficiencies can lead to decreased immunity due to trade-offs between immune response and growth rates

(reviewed in Viney & Riley 2014). Comparative studies of diet, immune response and growth rates among human populations could identify which nutritional supplements are the most efficacious and cost effective at alleviating such trade-offs. A macro-scale perspective could also ask how modern changes in lifestyle interact with human immunology and the frequency of immune system errors such as allergies (Maizels 2005). More generally, studies of macro-scale variation across human populations could provide an important perspective that complements existing experimental and cohort based approaches to problems in human health.

COMPUTATIONAL APPROACHES AND DATA CHALLENGES

The non-experimental nature of macroecological approaches complicates the ultimate goal of inferring causal mechanisms. One challenge of macroecological data involves statistical non-independence, which can be phylogenetic, with some species sharing characteristics by descent (Felsenstein 1985), or spatial, with adjacent sampling locations having more similar environmental conditions (Beale *et al.* 2010). Consequently, methods for assessing and controlling for non-independence are critical and under continued development (e.g., Freckleton & Jetz 2009; Garamszegi 2014). Controlling for phylogenetic non-independence in studies of parasites and host–parasite interactions is complicated by the relative dearth of parasite phylogenies of the resolution and breadth available for free-living taxa. This highlights the need for additional resources devoted to elucidating evolutionary relationships among parasites.

Another major set of challenges concerns correcting for variation in sampling effort. For example, in comparative studies of parasite richness better-studied host species almost always have more parasites recorded (Gregory 1990; Walther *et al.* 1995). Indeed, the best predictor of known parasite species richness per host species or location is often the number of studies conducted or individuals sampled (Nunn *et al.* 2003). Biases also exist in which host species are studied. For example, a primate host is more likely to be sampled for parasites if it is large-bodied and has a wide geographic distribution (Cooper & Nunn 2013). Similarly, there appears to be a mismatch between countries where primates are better studied and locations likely to harbour the greatest parasite richness (Hopkins & Nunn 2007; Cooper & Nunn 2013). Sampling biases thus present a significant hurdle for understanding drivers of parasite diversity and distributions across host taxa (Davies & Pedersen 2008; Cooper *et al.* 2012; Gómez *et al.* 2013).

A macroecological perspective demands large data sets, often compiled from multiple sources, with information on many species and biogeographic variables. This need for breadth presents unique challenges in the collection and curation of data. For instance, the Global Mammal Parasite Database includes data on the biology and distribution of mammalian parasites from more than 2400 primary literature sources (Nunn & Altizer 2005). Effective use of such data requires wide accessibility, cohesive data integration, and a detailed understanding of the strengths and limitations of the data available. Existing tools for promoting access and cross-reference include the ecological metadata language (Fegraus *et al.* 2005), Darwin Core (Wieczorek *et al.* 2012), the Knowledge Network for Biocomplexity (Jones *et al.* 2001), and the Dryad Digital Repository (Vision 2010). More sophisticated tools are needed, especially for exploring and suggesting connections that can be made among heterogeneous databases. For example, a centralised Amazon™ (North Seattle, WA, USA) style rating system for potentially useful datasets – coupled with relational maps of existing databases – would be invaluable to advance disease macroecology and bioinformatics in general.

Recent developments in data science would also advance disease macroecology, where data science is defined as the integrated practices of data curation, visualisation, and analysis (Kelling *et al.* 2009; Michener & Jones 2012). In terms of analysis, the process of data interrogation can be conceptualised as a repeating cycle (Fig. 2) involving the formation of research questions, the acquisition of data, and the choice or

Box 1 A case study in applying data science to macroecology

Science is an iterative process. Many research problems can be characterised as a cycle (Fig. 2) involving (a) the construction of tractable research questions, (b) data acquisition, and (c) analysis and visualisation. This workflow produces both (d) candidate solutions to the focal research question, and (e) new hypotheses and ultimately (f) generates new questions for future work. In macroecology, the data used in step (b) are often constructed from existing data products and the methods used in (c) are often custom-built for the focal analysis. As one example of how this approach has been applied to broad-scale data sets in infectious disease ecology, Han *et al.* (2015b) investigated the traits that predict whether rodent species are reservoirs of zoonotic diseases. They followed this by collating comparative trait data, such as adult body size, average number of litters per year, and age to sexual maturity, across 2200 + rodent species worldwide. Next, the authors performed analyses using generalised boosted regression trees (Elith *et al.* 2008), an ensemble machine learning method for fitting statistical models that can incorporate predictor variables with non-parametric distributions and incomplete data. Their results showed that a fast life history strategy (short lifespan, rapid development to maturity) predicted zoonotic reservoir status with over 90% accuracy. The authors then developed new visualisation techniques to depict model outcomes, identify especially high-risk reservoir hosts, and predict rodent species that might be likely zoonotic disease reservoirs but have not yet been sampled for parasites. Finally, this study identified a new question that might be pursued in future empirical work, namely asking whether physiological trade-offs between immunity and reproductive output underlie the observed biogeographical and life history patterns found in the most permissive rodent reservoirs hosts.

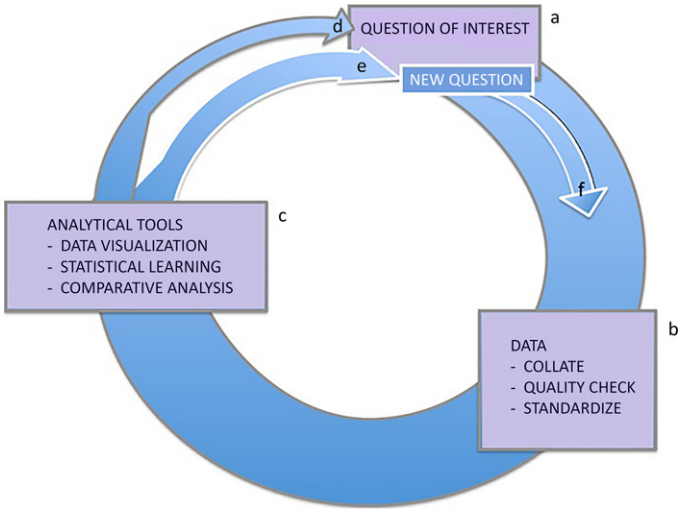


Figure 2 The process of data interrogation conceptualised as a repeating cycle (see Box 1 for full description).

construction of analytic tools that further refine research questions (e.g., Box 1). Modern analytical tools – many of which are derived from decades of research in machine learning and computational statistics - range from widely used off the shelf methods for well-defined problems (e.g., Elith *et al.* 2008) to custom-built algorithms that require methodological innovations. Data visualisation is also critically important. Creating insightful representations of macroecological data, which can be high-dimensional and exhibit complex geometry, often requires novel approaches to visualize patterns. For example, Gómez *et al.* (2013) used a network to represent how primate hosts are connected through the parasites that they share. Future advances in the macroecology of infectious disease will in many cases rely on increased use of rapidly evolving computational tools at multiple points along the data interrogation continuum.

INSIGHTS FOR PUBLIC HEALTH AND WILDLIFE CONSERVATION

Human-driven environmental change and globalisation of travel and trade have increased the probability of parasite spillover into human and animal populations and facilitated parasite spread at regional and global scales (Morse *et al.* 2012; Gottdenker *et al.* 2014). Some researchers have suggested that the odds of an infectious disease pandemic have never been higher (Smith & Guégan 2010; Daszak 2012; Morse *et al.* 2012). Macroecological approaches are already increasing our understanding of emerging infectious diseases (EIDs). For example, based in a global database of 335 human EID events, more than 60% of human EIDs were determined to be of animal (i.e., zoonotic) origin (Jones *et al.* 2008). A recent review also showed that RNA viruses that infect a wider variety of animal hosts are much more likely to infect and be transmitted among humans, and have a greater potential to cause pandemics (Woolhouse *et al.* 2014).

The study of zoonotic EIDs highlights a pressing need to integrate human, animal and environmental health within a common framework, as underscored by the 'One Health' movement (Zinsstag *et al.* 2011). Macroecology informs One Health approaches by providing crucial information on how the elements of human and natural systems are linked. For example, by exploring which traits make different host species likely to share parasites (Fig. 3, Davies & Pedersen 2008; Huang *et al.* 2014), and by determining which parasite traits influence whether they are specialists or generalists (e.g., Agosta *et al.* 2010), macroecology can help identify likely origins of future zoonotic outbreaks. Pedersen & Davies (2009) applied this approach to map areas of high zoonotic disease risk for humans based on the geographic distribution and phylogenetic affinity to humans of wild primate species (Fig. 1c), assuming that areas that contain many primate species closely related to humans are more likely sources of zoonoses than areas containing fewer and more distantly related species (see also Cooper *et al.* 2012). They concluded that the forests of central and western Africa represent areas where zoonotic outbreaks are likely to occur. Similar macroecological studies in the future could help focus on-the-ground efforts for parasite surveillance and detection (Farrell *et al.* 2013).

Macroecological studies have proved critical to biodiversity conservation by revealing the complex suite of biological and environmental factors that threaten wildlife, thus helping to predict which species are most vulnerable to future declines (Cardillo *et al.* 2005; Davidson *et al.* 2012). In some cases, infectious diseases are a primary driver of species declines, such as chytridiomycosis in amphibians (Skerratt *et al.* 2007) and white-nose syndrome in North American bats (Frick *et al.* 2010). Macroecological studies have also shown that being threatened by any other factor (e.g. land-use change, invasive species, pollution) increases the risk of a host species also being threatened by disease, and that parasite-related problems increase with host threat status (i.e., threatened, endangered or critically endangered, Heard *et al.* 2013). Other work has shown that wildlife species phylogenetically closely related to domesticated animals are more likely to be threatened by parasites, and that parasites transmitted by close contact are more likely to cause extinction risk than those transmitted by other routes (Pedersen *et al.* 2007). Appling macroecological approaches can provide crucial insights towards predicting the parasite impacts on animal populations in light of environmental change and other anthropogenic forces.

Parasites themselves are also undergoing a biodiversity crisis that mirrors the biodiversity crisis of free-living animals (Koh *et al.* 2004; Dunn *et al.* 2009). Somewhat counterintuitively, even though the chances that the parasites that remain negatively impact host populations often increase with host threat status (Suzán *et al.* 2012; Heard *et al.* 2013), more threatened species also tend to be infected by fewer parasite species overall (e.g., Altizer *et al.* 2007; Farrell *et al.* 2015). Loss of parasites may thus provide a 'canary in the coal mine' indicator of increased host threat status, and of habitat degradation more generally (Huspeni & Lafferty 2004). The consequences of the loss of hosts and their parasites go beyond simply pruning more biodiversity from the tree of life. Parasites are critically important in ecosystem services, such as mediating interspecific competition (Hudson *et al.* 2006; Dobson *et al.* 2008); they

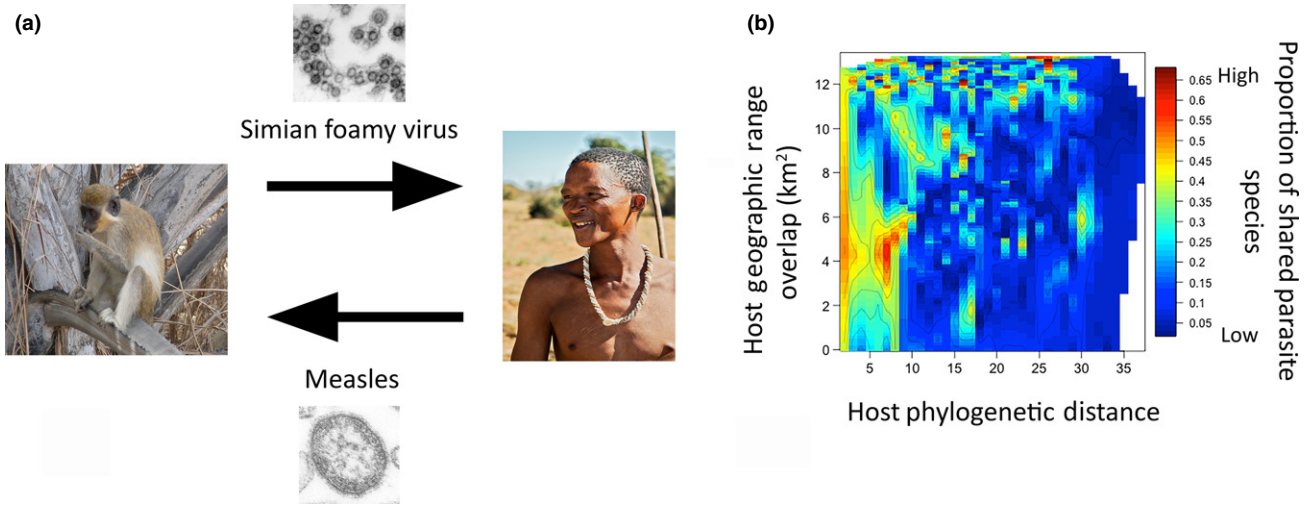


Figure 3 Studies of parasite sharing have implications for conservation biology and human health. For example (a), contact between humans and wild mammals provides opportunities for cross species transmission both to and from humans. Macroecological studies of parasite sharing among wild mammals can reveal what factors that make it more likely for cross species transmission to occur. For example (b), in wild carnivores host species with moderate-to-large range overlap and high phylogenetic affinity tend to share the largest proportion of parasite species. See (Huang *et al.* 2014) for further details.

can also promote genetic diversity in their hosts (e.g., by favoring sexual reproduction in their hosts or altering reproductive compatibility; Nunn *et al.* 2004; Karvonen & Seehausen 2012), facilitate species coexistence within communities (e.g., by frequency-dependent infection; Gilbert 2002), and provide natural biological control of weeds and pest species (Viterbo *et al.* 2007; Abdul-Ghani *et al.* 2012). Macroecological perspectives have already contributed to knowledge of the implications of parasite loss for ecosystems and individual hosts (e.g., Torchin *et al.* 2003; Koh *et al.* 2004; Dunn *et al.* 2009). With new data on animal health and physiology from comparative work, macroecological studies can help scientists develop a clearer picture of the double-edged sword of infectious disease costs and benefits, for ecosystems, biodiversity and human health.

FURTHER DIRECTIONS FOR FUTURE WORK

One of the primary goals of infectious disease macroecology is to help forecast future disease outbreaks or emergence, for humans, domestic species, and wildlife. While no approach can predict exactly where and when specific outbreaks will occur, macroecological research can reveal circumstances in which new parasites are most likely to emerge, and thus can act as a valuable guide for future allocation of research funds and monitoring efforts. Methods for modelling the distribution and transmission risk of individual parasites are fairly well established (e.g., Blackburn *et al.* 2007; Simoonga *et al.* 2009; Alexander *et al.* 2012). These methods are invaluable for predicting the dynamics and even potential future outbreaks of parasites that are already being monitored (e.g., Fischer *et al.* 2014), but provide little insight into where new parasites might be expected to emerge. Comparative macroecological studies can in some cases provide such insight. For example, Cooper & Nunn (2013) generated maps of areas likely to harbour undiscovered parasite diversity based on primate species richness and the number of studies of primate parasites in various countries. They predicted that Central America, along with parts of Africa and Asia, harbour the largest numbers of undiscovered primate parasite species (Fig. 1b); these regions could represent targets for future parasite surveys. Similarly, Han *et al.* (2015b) investigated the traits of rodent species known to harbour zoonotic diseases. By comparing these to the traits of rodent species not yet sampled for infectious diseases, they identified a set of host species and geographic locations likely to pose future risk of rodent borne zoonotic disease. As a final example, Morse *et al.* (2012) used a database of the localities of all past disease emergence events since 1940 to generate models that predicted areas of likely future disease emergence. Areas of high disease emergence risk were identified on nearly every continent, though by far the greatest number of hotspots occurred in southeast Asia. The application of macroecological approaches to guide the discovery of novel parasites and future threats is still a relatively recent development, and we suggest that it represents a fruitful avenue of research for both basic and applied science.

Disease macroecology is also well suited to investigating why some parasites remain local threats while others achieve pandemic status. For example, Zika virus, which has been linked to macrocephaly and other neurologic disorders, is already infecting humans in South, Central, and North America after being introduced in Brazil roughly a year ago (Petersen *et al.* 2016), while Middle Eastern Respiratory Syndrome remains largely limited to the Middle East despite more than 4 years of spread (Zumla *et al.* 2015). Today, many infectious diseases appear to be a product of anthropogenic environmental changes and thus represent a hidden cost of human development (Jones *et al.* 2008; Bonds *et al.* 2012). Changes of particular concern include land-use change, climate change

and globalisation through trade and travel (Lafferty 2009; Smith *et al*. 2009; Jones *et al*. 2013). Climate-induced shifts in phenology and species movements will certainly affect disease dynamics, but it is unclear whether parasite range shifts, contractions, or expansions are most likely (Altizer *et al*. 2013). Many animal species are already shifting towards higher latitudes or altitudes in response to climate change (Hickling *et al*. 2006), and a key question is whether these shifts will bring novel groups of hosts and parasites together. Macroecological studies could do much to clarify this issue. Niche modelling and related methods can be used to predict shifts in host or parasite geographic ranges in response to climate change (e.g., Morin & Thuiller 2009; Elith *et al*. 2010), and thus potential novel patterns of co-occurrence. Macroecological studies of the traits that make it likely for host species to share parasites (e.g., Cooper *et al*. 2012; Huang *et al*. 2014) would then provide key information on which potential climate induced patterns of future sympatry would be likely to lead to interspecific disease transmission and emergence events. We suggest that further work wedding predictive species range modelling with models of interspecific disease transmission risk represents a pressing area for future research (see also Peterson 2006).

Macroecology has generally been viewed as an observational discipline that can be used to investigate hypotheses about systems that are too large to be manipulated experimentally. While it has great success in providing novel insights about diverse systems (e.g., Clauset & Erwin 2008; Algar *et al*. 2009; Burger *et al*. 2012; Burnside *et al*. 2012), macroecology is sometimes criticised for its seeming lack of ability to isolate the mechanisms that produce observed patterns (Gaston & Blackburn 1999; McGill 2003; McGill & Nekola 2010). For example, numerous mechanisms have been proposed to explain species abundance distributions but there is little consensus on which are most important (McGill *et al*. 2007). This perceived weakness of macroecology in general would presumably apply to disease macroecology as well. However, like other observational sciences (e.g., cosmology) macroecology can refute mechanisms that make predictions about patterns in nature different from those observed. For example, the once widely held idea that scaling of metabolic rates with body size across animal species is driven by geometric scaling of surface area and internal volume was rejected when the 2/3 scaling constant predicted by this mechanism was not observed empirically (reveiwed in Whitfield 2006). Further, a number of newer statistical approaches for discerning mechanism are coming online that may hold particular promise for investigating parasite diversity and distributions. For example, state-space models that separate observation processes from generation processes are often used to infer mechanism in population biology (e.g., Jonsen *et al*. 2005; Patterson *et al*. 2008; Breed *et al*. 2009) but have not yet been applied in macroecology. The use of instrumental variables (Angrist *et al*. 1996) and greater use of tools from the statistical sub-discipline of causal inference (Rothman & Greenland 2005; Van der Laan & Rose 2011) also hold great promise. Some of these methods are already starting to be applied in macroecology (e.g., Harte *et al*. 2008).

Finally, a major challenge facing disease macroecology is the problem of incomplete data: very few natural systems have been thoroughly sampled at scales relevant to macroecological studies. This problem can be at least partially ameliorated by applying newer statistical approaches designed to deal with incomplete data and variation in sampling effort. For example, to mitigate the effects of variable sampling effort, parasite-host association lists could be analysed using network methods in which some edges (links) have been sampled and others have not. Markov networks and path-occupancy models can be used to investigate species interactions and network structure in such partially observed systems (Harris 2015; Mihaljevic *et al*. 2015), but so far these approaches have rarely been applied to disease ecology. Values for other kinds of missing data (e.g. host or parasite traits) can be imputed (Royston 2004; Little & Rubin 2014; Swenson 2014), or estimated via surrogate splits in classification and regression tree analyses (Feelders 1999; Hapfelmeier *et al*. 2012). The pattern of which data are missing from a database can also itself in some cases be used to improve prediction (Murphy 2012). In conjunction with ongoing efforts to collect additional primary macroecological data on disease occurrence, applying the latest analytical tools to effectively work within the limitations of currently available data is critical to advancing scientific understanding of broad scale infectious disease dynamics.

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STATEMENT OF AUTHORSHIP

All authors contributed to the conceptualisation (outline and general design) and revision of the manuscript. PRS, SA, KFS, JMD, JHB, JLG, VE, CN and RP wrote first drafts of the main text. JB and RP drafted Table 1. Figures were assembled by PRS using materials provided by SH, CN, TJD, and MJF. Box 1 was initially drafted by JMD and BAH. PRS was responsible for synthesising feedback from co-authors for the final text.

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