

## Does biodiversity protect humans against infectious disease?

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**Abstract.** Control of human infectious disease has been promoted as a valuable ecosystem service arising from the conservation of biodiversity. There are two commonly discussed mechanisms by which biodiversity loss could increase rates of infectious disease in a landscape. First, loss of competitors or predators could facilitate an increase in the abundance of competent reservoir hosts. Second, biodiversity loss could disproportionately affect non-competent, or less competent reservoir hosts, which would otherwise interfere with pathogen transmission to human populations by, for example, wasting the bites of infected vectors. A negative association between biodiversity and disease risk, sometimes called the “dilution effect hypothesis,” has been supported for a few disease agents, suggests an exciting win–win outcome for the environment and society, and has become a pervasive topic in the disease ecology literature. Case studies have been assembled to argue that the dilution effect is general across disease agents. Less touted are examples in which elevated biodiversity does not affect or increases infectious disease risk for pathogens of public health concern. In order to assess the likely generality of the dilution effect, we review the association between biodiversity and public health across a broad variety of human disease agents. Overall, we hypothesize that conditions for the dilution effect are unlikely to be met for most important diseases of humans. Biodiversity probably has little net effect on most human infectious diseases but, when it does have an effect, observation and basic logic suggest that biodiversity will be more likely to increase than to decrease infectious disease risk.

*Key words:* biodiversity loss; conservation; dilution effect; disease; parasite; pathogen; zoonosis.

### INTRODUCTION

With accelerating biodiversity loss and increasing awareness of the global public health importance of zoonotic disease (e.g., Lloyd-Smith et al. 2009), a critical question in ecology is whether and how biodiversity can be managed for disease control. One existing hypothesis, the “dilution effect,” posits that high biodiversity communities can reduce disease risk for individual zoonotic disease agents. Mathematical models demon-

strate that this could be the case if anthropogenic biodiversity loss increases the abundance of competent hosts, decreases the abundance of non-competent hosts, or both (e.g., Schmidt and Ostfeld 2001, LoGiudice et al. 2003). If these conditions are frequently met, and the dilution effect is widespread across many disease agents, disease control might be a general ecosystem service of biodiversity (Ostfeld and LoGiudice 2003, Keesing et al. 2010, Keesing and Ostfeld 2012, Ostfeld and Keesing 2012, Vourc’h et al. 2012) and biodiversity conservation could provide an effective approach to zoonotic disease control (LoGiudice et al. 2003, Dobson et al. 2006, Keesing et al. 2006, Pongsiri et al. 2009). This exciting win–win outcome for the environment and society is

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being studied and cited at an increasing rate (Appendix A) and has gained traction in the national media (e.g., Robbins 2012).

But despite the attention devoted to it, numerous theoretical studies and empirical examples belie the generality of the dilution effect. These examples demonstrate that free-living species diversity can facilitate the diversity and abundance of infectious agents. Because hosts serve as habitats and resources for pathogens, if pathogens depend on hosts that decline as biodiversity loss proceeds, pathogens may decline alongside their hosts (Hudson et al. 2006). Mathematical models show how biodiversity loss can decrease the prevalence of an infectious disease, depending on the relative effects on host density, susceptibility, parasite mortality, and food web complexity (Lafferty and Holt 2003, Lafferty 2012). Some disease agents are predicted to be even more sensitive to biodiversity loss than are their hosts (Lloyd-Smith et al. 2005, Dunn et al. 2009, Colwell et al. 2012, Bush et al. 2013), particularly parasites with complex life cycles that require multiple host species to support their various life stages (Rudolf and Lafferty 2011, Lafferty 2012). Undisturbed ecosystems are also often problematic sources of infectious diseases, including leishmaniases (Lainson 1983, Lainson 1988), malaria (Sharma et al. 1991, Marrelli et al. 2007), onchocerciasis (Walsh et al. 1993), loaisis (Boussinesq and Gardon 1997), and brugian filariasis (Mak et al. 1982, Chang et al. 1991). In particular, several important human infectious diseases are more common in settlements near forests or other sources of wildlife than in settlements distant from undisturbed ecosystems (e.g., Llanos-Cuentas and Campos 1987, Walsh et al. 1993). The hypothesis that biodiversity begets infectious disease supports the use of clear-cutting, brush clearance, vector control, wetland draining, and wildlife culling as management strategies for some diseases (e.g., Mak et al. 1982, Esterre et al. 1986, Mott et al. 1990, Walsh et al. 1993, Gadelha 1994, Stafford and Kitron 2002): strategies that are antithetical to biodiversity conservation. Thus, despite increasing acceptance of the idea that the dilution effect governs the biodiversity–disease relationship (LoGiudice et al. 2003, Keesing et al. 2006, 2010, Keesing and Ostfeld 2012, Ostfeld and Keesing 2012), the abundance of examples in which undisturbed ecosystems serve as sources of pathogens to human settlements suggests that this phenomenon is not ubiquitous and that we should not expect consistent unidirectional responses.

Several recent efforts have critically examined the evidence for the dilution effect in the handful of disease agents in which the hypothesis has been tested (Randolph and Dobson 2012, Wood and Lafferty 2013) or used meta-analysis to screen for a dilution effect across well-studied disease agents of humans (Salkeld et al. 2013). But to date, no study has systematically addressed the potential generality of the dilution effect phenomenon. Given recent calls for the use of biodiversity

conservation as a management approach to disease control (Ostfeld and LoGiudice 2003, Keesing et al. 2010, Keesing and Ostfeld 2012, Ostfeld and Keesing 2012, Vourc'h et al. 2012), information on the conditions under which biodiversity is protective against disease is vitally needed: It spells the difference between successfully deploying conservation initiatives for disease control and inadvertently exacerbating human disease burdens with well-intentioned attempts to achieve conservation and public health synergy. For instance, recent efforts to protect forest in Brazil may increase malaria transmission (Valle and Clark 2013), suggesting that vector control and public health efforts might need to increase, not decrease, with conservation. Outside of a few intensively investigated diseases (e.g., Lyme disease, West Nile virus, hantavirus pulmonary syndrome; examples which are contentious in and of themselves [e.g., Randolph and Dobson 2012, Salkeld et al. 2013, Wood and Lafferty 2013]), data on the relationship between biodiversity and disease risk are sparse, making it difficult to draw conclusions about the potential generality of the dilution effect. Here, we discuss our concerns about the potential for error when assuming that the dilution effect applies across many diseases. We argue that, just as for free-living species, there are likely to be “winners and losers” among parasitic species in ecosystems subject to increasing anthropogenic biodiversity loss. We begin by briefly reviewing the theoretical underpinnings and prominent examples of the dilution effect (i.e., negative biodiversity–disease relationships). We review several examples of zoonotic disease agents that thrive in biodiverse environments (i.e., positive biodiversity–disease relationships). We then use ecologically relevant and operational criteria to hypothesize the proportion of epidemiologically important human protozoan and metazoan disease agents whose prevalence we expect will increase, decrease, or remain the same as biodiversity loss proceeds. Because the biodiversity–disease relationship is untested for many human disease agents, our tabulation is only a starting point for investigating the generality of the dilution effect. However, it provides a systematic, transparent, and reproducible set of predictions that can be a common foundation for discussion. Finally, we end by suggesting some potentially fruitful research directions. We hope that this paper lays the groundwork for empirical studies that will address the biodiversity–disease relationship rigorously and across a variety of disease agents: for example, by investigating the response to biodiversity loss of many disease agents within one ecosystem.

We use the terms “infectious disease agents,” “pathogens,” and “parasites” interchangeably, defining these as organisms with obligate, “intimate and durable” consumer associations with individuals of other species (Combes 2001). Although any animal, domestic or wild, could dilute or amplify disease transmission, we focus on wild biodiversity, as we are concerned with the impacts

of conserving or destroying native species and their habitats on human disease risk. We also focus on non-emerging infectious diseases, since (1) the vast majority of zoonotic disease cases are caused by disease agents that have a long evolutionary history with humans and (2) other processes are likely to operate in disease emergence. We express human disease risk as the instantaneous probability that an individual residing near a habitat containing a given level of biodiversity will be infected with a disease agent. Because this probability is difficult to measure, we rely on proxies (like prevalence in humans and density of infected vectors) to estimate it. We assume that in and around such human settlements are various degrees of native biodiversity. Under this scenario, if native biodiversity provides the ecosystem service of disease control, human exposure to infectious diseases should decline as native biodiversity increases near human settlements. Although human behavior (e.g., time allocated among different habitat types, efforts at personal protection against vector bites) can have a substantial influence on disease risk, we constrain our discussion to how *potential* disease risk is distributed across landscapes, acknowledging that interaction of this landscape with human behavior will determine *actual* disease risk. We also acknowledge that anthropogenic disturbance is not always negatively correlated with biodiversity, and in fact can cause increases in biodiversity (Sax and Gaines 2003), making it difficult for studies that compare disturbed and intact habitats to attribute differences in disease prevalence to biodiversity (Woolhouse et al. 2012). Thus, we focus on impacts such as habitat destruction and direct depletion of native mammals, which have clear negative effects on overall biodiversity.

We find that, while we can hypothesize negative, positive, and neutral relationships between biodiversity and different infectious agents, biodiversity seems likely to facilitate the abundance of more infectious disease agents than it reduces. If so, directives to maximize biodiversity as a strategy for disease control are unlikely to be effective for most infectious diseases.

#### NEGATIVE BIODIVERSITY–DISEASE RELATIONSHIPS

Biodiversity can reduce infectious disease prevalence through two primary mechanisms, *transmission interference* and *susceptible host regulation*, both of which have commonly been called *dilution effects* (Norman et al. 1999, Box 2 in Keesing et al. 2006, Johnson and Thieltges 2010, Johnson et al. 2012a). We refer to each term specifically because the two mechanisms are expected to operate under different conditions; for example, transmission interference is most likely to occur for vector-transmitted disease agents, whereas susceptible host regulation can occur for directly transmitted disease agents. Empirical examples of these effects come primarily from Lyme disease (*Borrelia burgdorferi*) in the northeastern USA (reviewed in Ostfeld 2011), West Nile virus in the continental USA

(e.g., Swaddle and Calos 2008), and hantavirus pulmonary syndrome throughout North and Central America (e.g., Clay et al. 2009a, b). Though numerous studies claim to demonstrate support for a dilution effect in each of these three diseases, the theoretical and empirical evidence has limitations, which are explored in other papers (e.g., Kilpatrick 2011, Randolph and Dobson 2012, Salkeld et al. 2013, Wood and Lafferty 2013) and in Appendices B and C. We constrain our discussion of the mechanics (Keesing et al. 2006) and the limitations (Randolph and Dobson 2012, Salkeld et al. 2013) of the dilution effect for individual disease agents, since both topics are thoroughly reviewed elsewhere.

Transmission interference invokes the possibility that some less competent host species can decrease human disease risk by intercepting pathogen transmission stages. Specifically, this hypothesis states that increasing the ratio of less competent host species density to competent host species density in a habitat should result in a greater number of vector bites (or other contact events) being “wasted” on hosts that do not transmit the pathogen and, thus, a reduction in pathogen prevalence in the vector, as long as the addition of less competent host species does not increase vector density (or the frequency of contact events; Norman et al. 1999, Rosà et al. 2003). It is hypothesized that the ratio of less competent host species density to competent host species density can be correlated with species richness, diversity, or either less competent or competent host species abundance, but the value of the *ratio* is the key metric mechanistically linking community composition to pathogen abundance. The process of transmission interference is simplest to envision for vector-transmitted diseases, because an infected vector that bites a species that is not a competent host for its pathogen has wasted the pathogen’s opportunity for transmission. The first empirical support for transmission interference came from Lyme disease (*Borrelia burgdorferi*) in northeastern USA forest ecosystems, where the low vertebrate biodiversity associated with small forest fragments results in the white-footed mouse (*Peromyscus leucopus*) comprising a greater proportion of tick blood meals in these communities. Because *P. leucopus* is a highly competent host for the Lyme disease spirochaete, such increases in its relative abundance increase the pathogen’s prevalence among nymphal tick vectors (reviewed in Ostfeld 2011). There are at least four conditions required for transmission interference to occur for a vector-transmitted disease (Appendix B; Ostfeld and Keesing 2000): (1) the vector must have low feeding specificity, (2) vectors must acquire infection primarily horizontally (i.e., from reservoir hosts, as opposed to transovarially from the adult female tick), (3) reservoir competence (the capacity of the host to pass an infection to the vector) must vary among host species, and (4) the most competent hosts must achieve higher relative abundance in species-poor compared to species-rich settings.

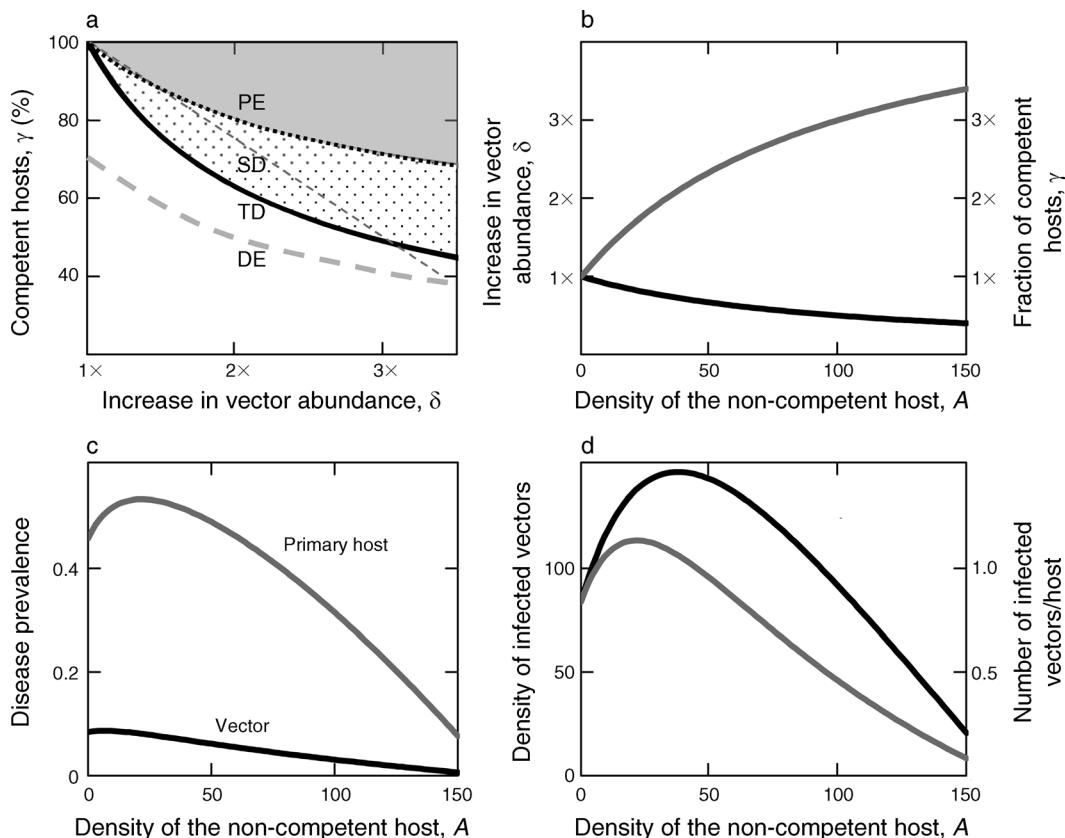


FIG. 1. Results of a simple mathematical model based on an extension of the Ross-McDonald model for a vector-borne disease (Appendix C). (a) Below the black solid line is the set of model parameters  $\gamma$  (the fraction of competent hosts among all hosts on which vectors feed) and  $\delta$  (the increase in vector density driven by the introduction of non-competent alternative hosts) where the introduction of the non-competent host leads to true dilution (TD; i.e., both prevalence and density of infected vectors are below the reference case  $A = 0$ , where  $\gamma = 1$  and  $\delta = 1$ ). Below the gray dashed line, the dilution effect is so strong that it leads to disease eradication (DE). The dotted area above the black line identifies the region of parameter space in which pathogen exacerberation occurs (i.e., the density of infected vectors increases relative to cases in which the non-competent alternative host  $A$  is absent, where  $\gamma = 1$  and  $\delta = 1$ ). Yet, in the area of spurious dilution (SD) between the black solid line and the black dotted line, prevalence of infection in the vector is below the reference case  $A = 0$ , and thus, SD could be erroneously inferred if assessment is based only on prevalence and not on density of infected vectors. In the gray area labeled PE (pathogen exacerberation) above the black dotted line, both prevalence and density of infected vectors are larger than the reference case. The straight dashed line represents a case in which  $\gamma$  and  $\delta$  jointly change as a function of the density of the non-competent host, as represented in panel (b), where the black line shows the fraction of competent hosts, and the gray lines shows the increase in vector abundance. Panel (c) reports the corresponding disease prevalence at equilibrium in the primary host and in the vector. In panel (d), the gray line indicates the mean number of infected vectors per host as a function of the density of the non-competent host. Number of vectors per host is the best measure of disease risk when humans are the primary host, such as in malaria. The black line indicates the density of infected vectors as a function of the density of the non-competent host, the best measure of disease risk to humans when humans are not the primary hosts, such as in Lyme disease.

Although less competent hosts can reduce the prevalence of a pathogen in a vector, they can also be food sources for the vector, leading to increases in vector density (a process called vector amplification; Appendices B and C). Because disease risk to humans will generally be more directly related to the density of infected vectors than to the prevalence of infection in a vector, the effect of a less competent host species on disease risk depends on the net balance between transmission interference and vector amplification (Norman et al. 1999, Rosà et al. 2003, Randolph and Dobson 2012, Roche et al. 2012). For instance, in one of the first papers on the dilution effect, a mathematical model

showed that a non-competent host could allow a pathogen to persist at low densities of the competent host if the non-competent host feeds many vectors (Norman et al. 1999). This effect has been demonstrated empirically for western fence lizards (*Sceloporus occidentalis*), which are non-competent hosts for *Borrelia burgdorferi* in California. Because lizards provide meals for ticks, experimental removal of lizards reduces infected tick density (Swei et al. 2011), which suggests that this non-competent host increases disease risk for humans.

The vector amplification effect is illustrated in Fig. 1, which displays the results of a simple mathematical

model based on an extension of the Ross-McDonald model for a vector-borne disease (Appendix C). Briefly, the density of infected vectors depends on the relative values of  $\gamma$  (the fraction of competent hosts among all hosts on which vectors feed) and  $\delta$  (the increase in vector density driven by the introduction of non-competent alternative hosts). Fig. 1a shows the regions of model parameters  $\gamma$  and  $\delta$  in which the density of infected vectors at equilibrium is higher (or lower) than in the absence of a non-competent alternative host (i.e., when  $A=0$  and, thus,  $\gamma=\delta=1$ ). Fig. 1a shows that, if the non-competent alternative host does not amplify vector abundance (i.e., if  $\delta=1$ ), its introduction would simply trigger a decrease in transmission efficiency, as the number of infected bites on the primary host would decline monotonically with the density of the alternative host. This will ultimately cause a reduction of disease prevalence in both the primary host and the vector and, in the extreme case, disease eradication for sufficiently low values of  $\gamma$ , consistent with the transmission interference mechanism of the dilution effect. Yet, if the non-competent alternative host also causes vector populations to increase in density, as represented in Fig. 1b and by the dashed line in Fig. 1a, a small or moderate addition of non-competent hosts leads to an increase in the density of infected vectors, even when disease prevalence in the vector remains stable or declines as shown in Fig. 1c. It is only for substantial additions of non-competent hosts that the reduction in transmission overrides the vector amplification effect and disease risk drops below its initial value. It is important to note that it is possible to observe simultaneous reductions in disease prevalence among vectors and increases in the density of infected vectors (compare Fig. 1c to 1d). The density of infected vectors is a more accurate metric of disease risk than is prevalence among vectors because the density metric reflects the rate at which hosts are bitten by infectious vectors, rather than the proportion of total bites by infectious vectors. While some experimental demonstrations of the dilution effect account for the effect of vector density (e.g., Allan et al. 2003), others do not (e.g., LoGiudice et al. 2003). This important caveat should be borne in mind when interpreting these studies as support for a net negative effect of less competent hosts on disease risk.

In contrast with transmission interference, susceptible host regulation occurs when the presence of non-competent competitors (Bowers and Turner 1997) or predators (Packer et al. 2003) keeps hosts below the threshold density for invasion of an infectious disease. Specifically, this hypothesis states that reservoir hosts should attain lower densities in high-biodiversity than in low-biodiversity environments due to interactions with other species (e.g., predators, competitors) that are themselves more abundant in high-biodiversity than in low-biodiversity environments. Consequently, this reduced density of the reservoir host should result in less intraspecific transmission of a pathogen, lower pathogen

abundance, and hence, a lower risk of interspecific transmission to humans. For example, in the western USA, diverse rodent assemblages contain lower densities of hantavirus-infected rodents, possibly because the density of the most competent host (*Peromyscus maniculatus*) is limited by competition with other rodent species, leading to susceptible host regulation (Clay et al. 2009a, b). The key distinction between transmission interference and susceptible host regulation is that, in transmission interference, non-competent hosts absorb pathogen infective stages, whereas in susceptible host regulation, non-competent hosts regulate competent host population density, reducing transmission among these susceptible hosts.

The relationship between biodiversity and disease risk in humans depends on how non-competent and competent hosts respond to biodiversity. If high biodiversity favors non-competent hosts that don't amplify vector populations, biodiversity conservation has the potential to reduce disease risk in humans through both transmission interference and susceptible host regulation. Some authors have suggested that the dilution effect should apply across a broad variety of disease agents if hosts that are likely to amplify pathogens (e.g., hosts with weak immune defenses) also tend to be resilient to human impacts (e.g., Keesing et al. 2010). This assumption is based on the reasoning that the "weedy" species that thrive in disturbed communities should have systematically different investments in immune function that make them particularly likely to amplify and transmit disease. Whether this relationship exists has only occasionally been tested, with mixed results. Negative relationships have been detected between vulnerability to human disturbance and competence for wildlife diseases (e.g., Johnson et al. 2012b), but other studies find no evidence for a relationship (e.g., Nunn 2002, Young et al. 2013). As we will indicate in the following section, there are other ways in which host communities might respond to biodiversity loss.

#### POSITIVE BIODIVERSITY–DISEASE RELATIONSHIPS

The examples of Lyme disease (reviewed in Ostfeld 2011), West Nile virus (e.g., Swaddle and Calos 2008), and hantavirus pulmonary syndrome (e.g., Clay et al. 2009a, b) provide the best support for predictions of the hypothesis that biodiversity can benefit human health. These cases are exciting in that they suggest common goals for conservation and human health, but the supporting evidence has significant limitations, including dependence on the assumptions that added biodiversity will not increase vector density and that competent hosts will be more common in low-biodiversity than in high-biodiversity assemblages. Perhaps the most important limitation is that study of the dilution effect has been confined primarily to the developed world. When we consider infectious diseases in developing countries, we find a number of examples of disease agents that increase with increasing biodiversity, in

direct contrast to the predictions of the dilution effect. This occurs primarily when competent host or vector species are sensitive to biodiversity loss.

We rarely think of vectors as sensitive species, but many have dependencies on biodiversity for food and habitat. For example, the *Kerteszia* subgenus of anopheline mosquitoes in the Atlantic rainforest of Brazil has, in the past, been an important vector of malaria to human populations; however, because the larvae of *Kerteszia* species develop only in water that accumulates in the leaf axils of bromeliads, extensive deforestation has reduced both *Kerteszia* abundance and malaria transmission in the Atlantic forest region (reviewed in Gadelha 1994, Marrelli et al. 2007). A global meta-analysis revealed that deforestation can drive increases or decreases in the density of anopheline mosquitoes and resultant malaria incidence among human populations, depending on the type of land-use impact and geographic location (Yasuoka and Levins 2007). However, a recent spatial analysis of a large malaria data set, including 1.3 million positive malaria tests arising from a region of 4.5 million km<sup>2</sup>, revealed that forest cover was the strongest positive predictor of malaria risk in the Brazilian Amazon (Valle and Clark 2013). Though land clearing also produced slight increases in the incidence of malaria cases, the effect of forest cover was 25 times greater than the effect of land clearing and, when the authors projected the effect on disease risk of avoiding 10% deforestation, their mathematical model predicted a two-fold increase in malaria incidence (Valle and Clark 2013). Deforestation has also been strongly linked to declines in the human burden of river blindness (caused by the filarial worm *Onchocerca volvulus*) in East Africa, where the parasite is transmitted by black flies of the *Simulium neavei* complex. Black flies feed on humans and forest animals, and their larvae develop as commensals on the carapaces of freshwater potamid crabs or atyid prawns in perennial streams (Raybould 1968, Raybould and White 1979, Muro and Mziray 1990; reviewed in Walsh et al. 1993). These associations demonstrate that vector populations can depend on hosts or habitats associated with high biodiversity within forests.

Similarly, and despite the fact that it is frequently cited as a key example of the dilution effect, human cases of Lyme disease appear to be driven by dependence of tick vectors on forest ecosystems. Epidemiological work suggests that human Lyme cases are spatially correlated with forested land, and that the prevalence of the disease decays with increasing distance from forests, because forested areas contain large mammals (like deer) that feed adult ticks and thereby increase overall tick density (reviewed in Wood and Lafferty 2013). Lyme disease's emergence in the USA in the late 1970s is thought to have resulted from extensive reforestation and restoration of native biodiversity in the northeastern USA, coupled with development of suburbs impinging on these forest tracts (Barbour and

Fish 1993). All studies demonstrating a dilution effect in Lyme disease have been conducted at small spatial scales within forest fragments (Ostfeld 2011). This suggests that, while the local composition of vertebrate assemblages may mediate the risk of Lyme within forests, it is the very presence of forest habitat that increases human Lyme risk on scales relevant to public health (Wood and Lafferty 2013). Consideration of scale dependency appears to resolve conflicting conclusions about the relationship of Lyme disease risk to biodiversity: across an urban to rural gradient, Lyme disease risk increases because the abundance of vectors increases with degree of forestation, while Lyme risk might be higher within high-biodiversity forests relative to low-biodiversity forests due to the dilution effect (Wood and Lafferty 2013). Because activity patterns determine a person's degree of exposure to sites that vary in entomological risk, human behavior (i.e., time spent in or near forests, time spent in forests with differing levels of biodiversity) is an important determinant of disease risk (e.g., Brownstein et al. 2005). It seems probable that scale- and behavior-dependencies might also be important for interpreting the biodiversity–disease risk relationship of other disease agents.

Certain groups of infectious diseases are geographically associated with undisturbed ecosystems because they depend on reservoir hosts that are sensitive to biodiversity loss. Cutaneous leishmaniasis are a suite of globally distributed diseases of many mammal species, including humans, which are vectored by phlebotomine sand flies and caused by a variety of flagellates in the genus *Leishmania*. These diseases are sometimes cited as a potential example of the dilution effect (e.g., Ostfeld and Keesing 2000, Schmidt and Ostfeld 2001, Chelbi et al. 2008). A few species of *Leishmania* (particularly those that can be vectored from human to human, like Old World *L. tropica*) do appear to thrive in urban rather than rural areas (e.g., Oliveira-Neto et al. 1988; reviewed in Mott et al. 1990, Ashford 2000, Desjeux 2001, Ashford and Crewe 2003). However, several *Leishmania* species show the opposite pattern (reviewed in Lainson 1983, Lainson 1988). For example, the risk of cutaneous leishmaniasis due to *Leishmania guyanensis* among households in Manaus, Brazil, declines with increasing distance from intact forest (Barrett and Senra 1989). In this system, two-toed sloths (*Choloepus didactylus*) are the primary reservoir host; because these large mammals are common only in intact forest (in other words, the competent hosts are not resilient to human impacts), infection of humans by sand fly vectors occurs only near biodiverse forest areas (Barrett and Senra 1989). Activity in intact forests has long been recognized as one of the most important risk factors for New World cutaneous leishmaniasis (see Plate 1; reviewed in Llanos-Cuentas and Campos 1987, Walsh et al. 1993) and the World Health Organization has, in the past, considered clearing native forests as a potential epidemiological intervention for the disease (Esterre et al. 1986, Mott et

al. 1990). Similarly, in Southeast Asia, subperiodic brugian filariasis, caused by a filarial worm (*Brugia malayi*), is vectored by mosquitoes of the genus *Mansonia* and persists in forest-dwelling reservoir hosts like macaques (*Macaca* spp.), leaf monkeys (*Presbytis* spp.), and other mammals. As attempts at disease control through chemotherapy and pesticide application have been ineffective due to the efficiency of the zoonotic cycle in maintaining *B. malayi* (Mak et al. 1982, Chang et al. 1991), destruction of wildlife (Mak et al. 1982) and deforestation (Walsh et al. 1993) were, at times, considered as alternative strategies for reducing the human filariasis burden. These examples demonstrate that intact ecosystems can facilitate the abundance and diversity of reservoir hosts and make it easier for infectious diseases to complete their life cycles.

Close contact of humans with the blood and body fluids (e.g., during hunting and butchering) of wild primates infected with simian immunodeficiency virus is thought to have caused the emergence of HIV (Hahn et al. 2000) and is probably still a source of viral spillover from wild reservoir hosts (Wolfe et al. 1998). Such spillover can happen only where there is intact forest to support the animals that are hunted (Wood et al. 2012). In Central Africa, Wolfe et al. (2004) studied the distribution among humans of simian foamy virus (SFV), a primate retrovirus thought to be nonpathogenic in humans, but nonetheless useful as an indicator of the potential spillover patterns of other, more pathogenic retroviruses. They found that humans living in regions of lowland tropical forest, particularly hunters and those who had butchered primate meat, were more likely to display serological evidence of SFV infection than were people living outside these regions. Only individuals living in dense forest (presumably with an abundant and diverse primate fauna) showed both polymerase chain reaction (PCR) and serological evidence of SFV infection, suggesting that transmission is greater in more intact forests (Wolfe et al. 2004). Intensive or sustained usage of areas of high biodiversity may also mediate the risk of other emerging and zoonotic diseases from a variety of reservoir hosts (Woolhouse and Gaunt 2007). For instance, the increased disease incidence documented where deforestation is occurring often cannot be ascribed directly to the loss of biodiversity that comes along with deforestation (and thus, to a dilution effect), but rather to the increase in human contact with forested habitat that deforestation entails (Wolfe et al. 2005). These examples illustrate how humans who enter areas of high biodiversity can be at heightened risk for some infectious diseases.

While these are case studies of a few relatively simple mechanisms by which biodiversity may increase the prevalence of infectious disease, Appendix D highlights the complexity of potential impacts of biodiversity on disease, and demonstrates that simple predictions can fail to account for influential ecological complexities. Although the relationship between biodiversity and disease is complex, one of the endpoints of the

relationship is certain: Extreme biodiversity loss will result in a reduction of zoonotic disease risk (Lafferty 2012). For some of the diseases expected to increase with biodiversity loss, transmission rates approach zero in urbanized areas where reservoir hosts can't survive; for example, 94% of those affected by the initial outbreak of Sin Nombre hantavirus pulmonary syndrome in the southwestern USA lived in rural areas, and the remaining 6% visited rural areas on weekends (Zeitl et al. 1995). Extreme biodiversity loss in the modern cities of the developed world has resulted in zoonotic disease becoming rare at these locations, with exceptions when wildlife biodiversity is imported into cities, as for severe acute respiratory syndrome (SARS; Li et al. 2005). We suggest that such scale-dependence might be a common feature of the relationship between biodiversity and disease risk (e.g., Wood and Lafferty 2013).

#### PREDICTING THE BIODIVERSITY–DISEASE RELATIONSHIP ACROSS MULTIPLE ZOOLOGICAL DISEASES

While biodiversity loss might cause disease risk to increase for a limited number of parasite species, ecosystems contain many infectious disease agents and “biodiversity” encompasses multiple hosts and non-hosts. This leads to several challenging questions. How many infectious disease agents increase in prevalence with increasing biodiversity? How many decrease? Is disease reduction a general ecosystem service of biodiversity?

An analysis that selects one or a few diseases in an ecosystem is unlikely to yield a general relationship for the association of biodiversity with infectious disease. Even when biodiversity reduces the prevalence of one infectious disease agent, if the overall richness of infectious diseases increases with biodiversity, there can be a net positive association between biodiversity and infectious disease risk. The relationship between parasite richness and human health is complicated by variability in exposure, pathogenicity, and relative abundance among parasite species (Johnson et al. 2013). However, tracking multiple diseases remains important because ecosystems contain more than one pathogenic or abundant disease agent. Without considering multiple disease agents, a selective interpretation of “biodiversity” and “infectious disease” can lead to erroneous conclusions about general disease risk.

We analyzed a database of human parasites to develop hypotheses on the proportion of disease agents that might increase, decrease, or remain unchanged as biodiversity loss proceeds. We used the database developed by Kuris (2012), who built on a comprehensive checklist of human parasites compiled by Ashford and Crewe (2003), to tabulate the human protozoan and metazoan parasites that are prevalent and cause substantial human morbidity or mortality (summarized in Tables 1–4). This list does not include viruses and bacteria, but does provide consistent evaluations of parasite abundance and pathogenicity in human hosts. We chose to focus on common, pathogenic species so as

TABLE 1. Human disease agents compiled by Kuris (2012).

Parasite species	Response to biodiversity	Rationale	Notes	Prev	Common hosts	Reservoirs	Path	Trans
<i>Armillifer armillatus</i>	positive	2	2	3	wild animal	snakes	1	DP
<i>Armillifer moniliformis</i>	positive	2	2	3	wild animal	pythons	1	DP
<i>Brugia malayi</i>	positive	2	3	4	wild animal/ human	primates, cat, pangolin	2	V
<i>Clonorchis</i> sp.	positive		5	4	human/animal	fish-eating mammals	1	TTP
<i>Cryptosporidium parvum</i>	positive	2	6	5	human/animal	mammals	1	DP
<i>Diphyllobothrium latum</i>	positive	2	7	3	human/wild animal	dogs, bears, seals	1	TTP
<i>Echinococcus granulosus</i>	positive	2	8	3	animal/human	ungulates, predators	2	TTP-int
<i>Fasciola gigantica</i>	positive	2	13	3	animal/human	ungulates	1	TTP-no BM
<i>Fasciola hepatica</i>	positive	2	13	3	animal/human	ungulates	2	TTP-no BM
<i>Giardia</i> sp.	positive	2	6	6	human/animal	primates, carnivores, ungulates, rodents	1	DP
<i>Leishmania braziliense</i>	positive	2	15	3	wild animal/ human	rodents	1	V
<i>Leishmania guayanensis</i>	positive	2	3	3	wild animal/ human	edentates	1	V
<i>Leishmania panamensis</i>	positive	2	3	3	wild animal/ human	edentates	1	V
<i>Leishmania tropica</i>	positive	2	20	4	human/domestic animal	dog, hyrax	1	V
<i>Nanophyetes salmincola</i>	positive	2	7	3	wild animal/ human	fish-eating mammals	1	TTP
<i>Onchocerca volvulus</i>	positive	3	21	5	wild animal/ human	none	2	V
<i>Opisthorchis viverrini</i>	positive	2	5	3	animal/human	fish-eating mammals	1	TTP
<i>Paracapillaria philippinensis</i>	positive	2	22	3	animal/human	fish-eating birds	1	TTP
<i>Paragonimus westermani</i>	positive	2	23	4	human/animal	crab-eating mammals	1	TTP
<i>Plasmodium knowlesi</i>	positive	2	25, 26	4	wild animal/ human	primates	1	V
<i>Schistosoma intercalatum</i>	positive	2	28	3	human	primates?	1	DA
<i>Schistosoma matheei</i>	positive	2	31	3	wild animal	ungulates, baboon, equids	1	DA
<i>Schistosoma mekongi</i>	positive	5	32	3	domestic animal/ human	dog	2	DA
<i>Strongyloides f. fuellerborni</i>	positive	2	33	3	human/wild animal	primates	1	DA
<i>Trichinella spiralis</i>	positive	2	35	3	animal	mammals	2	TTP
<i>Trypanosoma brucei gambiense</i>	positive	3	36	3	human	none	2	V
<i>Trypanosoma brucei rhodesiense</i>	positive	2	37	3	wild animal/ human	ungulates	2	DP
<i>Brugia timori</i>	neutral +	3	4	3	human	none	2	V
<i>Loa loa</i>	neutral +	3	4	4	human	none	1	V
<i>Plasmodium falciparum</i>	neutral +	3	24	5	human	none	2	V
<i>Plasmodium ovale</i>	neutral +	3	4	4	human	none	1	V
<i>Plasmodium vivax</i>	neutral +	3	4	5	human	none	1	V
<i>Ancylostoma duodenale</i>	neutral	1	1	3	human	none	2	DA
<i>Ascaris lumbricoides</i>	neutral	1	1	6	human	none	2	DP
<i>Cyclospora cayentanensis</i>	neutral	1	1	3	human/wild animal	none	1	DP
<i>Demodex brevis</i>	neutral	1	1	6	human	none	1	C
<i>Demodex follicularum</i>	neutral	1	1	6	human	none	1	C
<i>Dracunculus medenensis</i>	neutral	1	1	5	human	none	2	TTP-masked
<i>Echinostoma revolutum</i>	neutral	see Table 3	12	3	domestic animal/ human	rats, ducks, geese	1	TTP
<i>Entamoeba histolytica</i>	neutral	1	1	6	human	none	2	DP
<i>Fasciolopsis buski</i>	neutral	4	14	4	domestic animal/ human	dog, pig	1	TTP-no BM
<i>Leishmania peruviana</i>	neutral	see Table 3	19	3	animal/human	dog, possum, mouse	1	V
<i>Necator americanus</i>	neutral	1	1	6	human	none	2	DA
<i>Oesophagostomum bifurcum</i>	neutral	4	14	3	human/wild animal	domestic animals, primates	1	DP
<i>Opisthorchis filineus</i>	neutral	4	14	3	domestic animal/ human	cat, dog, pig	1	TTP
<i>Pediculus capitis</i>	neutral	1	1	6	human	none	1	C

TABLE 1. Continued.

Parasite species	Response to biodiversity	Rationale	Notes	Prev	Common hosts	Reservoirs	Path	Trans
<i>Pediculus humanus</i>	neutral	1	1	6	human	none	1	C
<i>Phthirus pubis</i>	neutral	1	1	6	human	none	1	C
<i>Plasmodium malariae</i>	neutral	1	1, 26	4	human	none	1	V
<i>Sarcoptes scabiei</i>	neutral	1	1	6	human	none	1	C
<i>Strongyloides fullerborni</i>	neutral	1	1	3	human	none	1	DA
<i>Strongyloides kellyi</i>								
<i>Strongyloides stercoralis</i>		1	1	5	human	none	1	DA
	neutral							
<i>Taenia asiatica</i>	neutral	1	1	3	human	none	1	DA
<i>Taenia solium</i>	neutral	1	1	4	human	none	2	TTP
<i>Trichomonas vaginalis</i>	neutral	1	1	6	human	none	1	TTP
<i>Trichuris trichiura</i>	neutral	1	1	6	human/wild animal	primates	1	DP
<i>Tunga penetrans</i>	neutral	see Table 3	39	5	human/animal	mammals	2	DA
<i>Schistosoma haematobium</i>	neutral –	5	27	5	human/wild animal	rarely primates	2	DA
<i>Wuchereria bancrofti</i>	neutral –	6	40	5	human	none	2	V
<i>Echinostoma lindoense</i>	negative	5	10	3	human/animal	none	1	TTP
<i>Echinostoma malayanum</i>	negative	5	11	3	domestic animal/human	rat, pig, shrew	1	TTP
<i>Leishmania infantum</i>	negative	5	17	3	animal/human	dogs, small forest mammals	2	V
<i>Leishmania major</i>	negative	see Table 3	18	4	human/domestic animal	rodents,	1	V
<i>Schistosoma mansoni</i>	negative	5	30	5	human/animal	primates, rodents	2	DA
<i>Toxoplasma gondii</i>	negative	5	34	6	animal	mammals, birds	1	TTP-int
<i>Trypanosoma cruzi</i>	negative	5, 6	38	5	human/domestic animal	mammals	2	V
<i>Echinococcus multilocularis</i>	?	see Table 3	9	3	animal	rodents, carnivores	2	TTP-int
<i>Leishmania donovani</i>	?	see Table 3	16	4	human/domestic animal	rodents, canines	2	V
<i>Schistosoma japonicum</i>	?	see Table 3	29	4	human/animal	mammals	2	DA

Notes: We hypothesized each disease agent’s response to biodiversity as positive, neutral, negative, neutral + (positively associated with forest habitat), and neutral – (negatively associated with forest habitat). The neutral + and neutral – categories imply that habitat, not biodiversity, drives the association (Appendix E). A rationale is provided for each hypothesis (see codes in Table 2). Notes pertaining to the rationale categorization of each parasite species are presented in Table 3. For prevalence (Prev), we used Ashford and Crewe’s (2003) evaluations of prevalence (where 1 is low and 6 is high), excluding rare diseases. We list the common categories of hosts (Common hosts) and, where applicable, common vertebrate reservoir species (Reservoirs). We include our own assessment of pathology (Path) to humans, where 1 is low pathogenicity and 2 is high pathogenicity. Transmission strategy (Trans) codes are listed in Table 4. From Kuris’ (2012) original list, we excluded *Echinostoma ilocanum* because it is presently rare, and we added *Plasmodium knowlesi* because it now makes up one-third of human malaria cases in Malaysia.

to draw conclusions about the parasitic diseases that cause the bulk of human suffering. The alternative, using a “complete” list (e.g., Cleaveland et al. 2001, Taylor et al. 2001, Guernier et al. 2004), obscures the role of prevalent diseases that cause substantial morbidity and mortality (Kuris 2012). Ashford and Crewe (2003) evaluated parasite abundance by dividing parasite species into six categories: (1) rare clinical case studies reported, (2) sporadic but nowhere common, (3) sometimes common but restricted in space or time, (4) common in at least one geographic area, (5) common worldwide or abundant but geographically restricted, (6) abundant worldwide. To focus exclusively on common human diseases, Kuris (2012) included all parasites in categories 3–6, adding those in category 2 that Ashford and Crewe noted as reaching at least 5% prevalence in at least one locality, and excluded the remainder of this category. This yielded 132 species of “prevalent” parasites. To further focus on pathogenic disease agents, Kuris (2012) excluded any parasite that is

nearly always nonlethal in humans and causes only mild or temporary pathology (e.g., *Leishmania infantum* is pathogenic, but *Entamoeba gingivalis* is not). We took a conservative approach, including parasites with limited potential to cause morbidity. Specifically, we excluded only those parasites that cause such low morbidity that

TABLE 2. Rationale for the hypothesized response to biodiversity for each human disease agent listed in Table 1.

No.	Rationale
1	Disease of humans, not wildlife associated.
2	Reservoir hosts are more abundant in undisturbed than in disturbed habitat.
3	Vector biting rates are higher in undisturbed than in disturbed habitat.
4	Transmission to humans primarily involves domestic animals.
5	Reservoir hosts are more abundant in disturbed than in undisturbed habitat.
6	Vector biting rates are higher in disturbed than in undisturbed habitat.

TABLE 3. Notes pertaining to the rationale categorization of each human disease agent listed in Table 1.

No.	Rationale
1	Disease of humans, not wildlife associated.
2	Infection is by contact with an infected snake, such as preparing snakes for food.
3	Forest animals are reservoirs. Might increase in areas where deforestation is occurring, but this is due to human contact with forest habitat, or creation of vector breeding sites, not reductions in biodiversity.
4	Associated with forest habitat. Might increase in areas where deforestation is occurring, but this is due to human contact with forest habitat, or creation of breeding sites, not reductions in biodiversity.
5	Transmission to humans mostly involves domestic animals. Life cycle also maintained in wild carnivores.
6	Commonly associated with water contaminated by wildlife feces in pristine areas.
7	Life cycle maintained in dogs and wild carnivores.
8	Transmission to humans mostly involves domestic animals. However, wild animals maintain a sylvatic zoonotic life cycle that probably increases exposure of domestic animals.
9	Rodents are common hosts; dogs and foxes (which are tolerant of humans) are important reservoirs. Public health concerns usually relate to the carnivore, not the rodent host. Foxes and their parasites have increased following rabies control.
10	Host snails increase in abundance in disturbed settings.
11	Associated with eating raw snails. Domestic pigs are the main reservoir. Generalist for first and second intermediate hosts, including snails found in eutrophic conditions.
12	Transmission to humans mostly involves domestic animals. Wild hosts are mainly ducks and geese, which we presume would increase with increasing biodiversity. Mammal and bird predators of snails would tend to complete the life cycle. Ectothermic predators of snails would decrease transmission.
13	Transmission to humans mostly involves domestic animals. Life cycle also maintained in wild ungulates.
14	Transmission to humans mostly involves domestic animals.
15	Forest rodents are common hosts. However, these are strongly associated with biodiverse forest habitat, suggesting important hosts increase with increasing biodiversity. Might increase in areas where deforestation is occurring, but this is due to contact with forest habitat, not reductions in biodiversity.
16	Disease of humans, and not wildlife associated. Might increase with wild rodents or canines, but most reservoirs are peridomestic.
17	Foxes, which may increase as biodiversity declines, can be an important reservoir.
18	Dogs and wild mammals are the main reservoirs. <i>L. major</i> is not a disease of forests. It is more common in rural areas. Association with rural areas suggests a negative association with biodiversity, perhaps due to vector biology.
19	Transmitted by sand flies in Peru, usually in pasture lands. The vector is described as anthropophilic. Not a disease of forests. Domestic animals serve as the primary reservoir hosts for human disease. Most other wild mammals can serve as hosts if they are bitten by sand flies. The effect of biodiversity is probably neutral, though it could be positive if wild mammals increase with biodiversity or negative if vectors decline with biodiversity.
20	Associated with forest habitat, especially where hyrax are common. Might increase in areas where deforestation is occurring, but this is due to contact with forest habitat, not reductions in biodiversity.
21	Associated with forest habitat. Vectors feed on forest animals and larval vectors are commensals with riverine crustaceans.
22	Humans exposed by eating fish from areas where many fish-eating birds are present.
23	Wild cats, minks, and some domestic animals serve as final hosts.
24	Often associated with forest habitat, but mixed responses depending on the vector.
25	Primates may be an important reservoir. Associated with forest habitats.
26	<i>Plasmodium malariae</i> and <i>P. knowlesi</i> are difficult to distinguish. Current thought is that <i>P. malariae</i> is primarily a pathogen of humans and its vector feeds mostly on humans and domestic species, while <i>P. knowlesi</i> is primarily a parasite of macaques.
27	Host snails are more abundant in brightly lit aquatic habitats.
28	Associated with forest habitat. Might increase in areas where deforestation is occurring, but this is due to human contact with forest habitat, or creation of breeding sites, not reductions in biodiversity. Possibly many wild hosts.
29	Wildlife associated.
30	Rodents are important reservoirs, and host snails are more abundant in disturbed settings with few predators.
31	Wild animals are important reservoirs.
32	Host snails are more abundant in disturbed settings with few predators.
33	Primarily a disease of nonhuman primates.
34	Infects all warm-blooded vertebrates. Depends on final host cats and their prey, which may be small mammals such as rodents.
35	Large carnivores are common hosts.
36	Vector (tse-tse fly) supported by forest wildlife. Associated with forest habitat. Might increase in areas where deforestation is occurring, but this is due to human contact with forest habitat, or creation of breeding sites, not reductions in biodiversity.
37	Wild ungulates are the main hosts.
38	Increases with the density of opossum, which may be released in areas of low forest biodiversity. Bug densities can increase in disturbed areas.
39	Transmission to humans mostly involves humans or domestic animals.
40	In Africa, prevalence can be lower in forests, presumably due to lower biting rates of mosquitoes. Examples of forest mosquitoes transmitting parasites are seen as unusual. Mosquitoes might waste bites on nonhuman hosts.

TABLE 4. Codes for transmission strategies listed in Table 1.

Code	Transmission strategy
DP	direct transmission, passive; spores, eggs, or larvae ingested
DA	direct active searching stage
C	contact
V	vectored
TTP	trophically transmitted, humans final host, behavioral modification possible
TTP-masked	trophically transmitted, humans final host, behavioral modification not possible, masked
TTP-no BM	trophically transmitted, humans final host, behavioral modification not possible because cysts external to prey
TTP-int	humans serve as intermediate host

they are only rarely treated therapeutically and, when treated, are primarily addressed for cosmetic or cultural reasons (e.g., *Enterobius vermicularis*). Kuris (2012) thereby narrowed the initial list of 447 species to 69 common, pathogenic species, and we used this operationally defined subset of prevalent and pathogenic human parasitic diseases for our analysis.

We projected the response to biodiversity of these 69 infectious disease agents based on their life cycles, the types of hosts they use, and expected effects of biodiversity on vectors and reservoir hosts. The projected response to biodiversity was determined independently of qualitative measures of pathology or prevalence (Table 1). We used the following logic to establish hypotheses for the association between diversity and disease risk. We assumed that biodiversity did not affect infectious diseases that occur exclusively in humans or infectious diseases using only human-associated species (domesticated and peridomestic animals) as reservoirs. For non-vectored species with wild reservoir/intermediate hosts, we assumed that the infectious disease would respond to biodiversity in the same direction as the reservoir/intermediate host. For example, increasing biodiversity should decrease the prevalence of diseases using rodent hosts (which frequently increase following biodiversity loss), but increase diseases using wild carnivores. Zoonotic diseases known to be associated with forests were assumed to increase with biodiversity (although, as discussed in Appendix E, this may not always be a direct causal relationship). These criteria could be applied to 49 non-vector-transmitted species. Because vector-transmitted diseases are most commonly proposed for transmission interference, we investigated their projected relationship with biodiversity in more detail. Some diseases have vectors associated with forest habitat, a few have wild reservoir hosts like rodents that might increase in abundance as biodiversity declines, and others have wild reservoir hosts that are likely to decline with biodiversity. Our projections are hypotheses and, by necessity, the approach used here is coarse and affected by the assumptions used. Other researchers might

generate different hypotheses (in both directions) for some of the species. We provide Table 1 so that readers can apply their own assumptions to the list of infectious diseases, and draw their own conclusions. However, for a large majority of species, the assumptions behind our hypotheses were straightforward and well-supported (Table 1). When this wasn't the case, we indicate our uncertainty in the results.

Six parasite species were directly transmitted by human-to-human contact and we assumed that these had neutral associations with biodiversity. Of the other 43 non-vectored disease agents, 18 species were projected to have positive associations with biodiversity and 17 species were projected to have neutral relationships with biodiversity. One species was associated with unforested habitat (not directly with biodiversity; neutral –; see Appendix E), and five species were projected to have negative associations with biodiversity (Table 1). There were two non-vectored species for which the information was too contradictory to predict an outcome. For the 20 vectored diseases, we projected that eight species would have positive associations with biodiversity, five were otherwise associated with forested habitat (neutral +; see Appendix E), two had a neutral relationship with biodiversity, one had a neutral – relationship with biodiversity, three species had negative associations with biodiversity, and one species' relationship to biodiversity was unknown. In sum, discounting the three species for which there was too much uncertainty, we projected that biodiversity would reduce the prevalence of 12% of infectious disease species, increase 38%, and would not affect 49% (having either a neutral, spurious, or unknown relationship; Fig. 2).

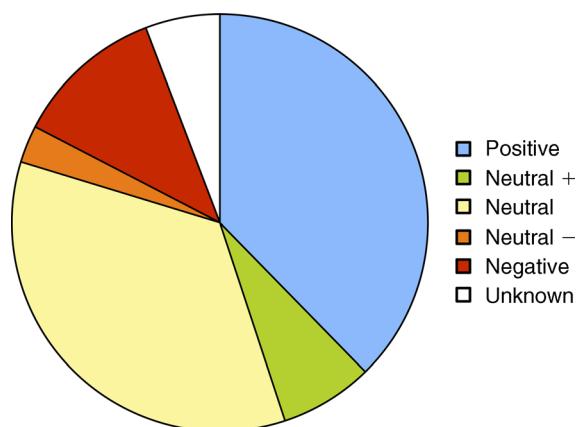


FIG. 2. Projected effects of biodiversity on 69 common and pathogenic human parasite species. Wedges indicate the relative frequency of positive, negative (the “dilution effect”), neutral, and unknown responses of disease to biodiversity. Neutral relationships include those positively (neutral +) or negatively (neutral –) associated with biodiverse communities but not directly affected by biodiversity (see Appendix E). Outcomes were assessed based on the hypothesized response of reservoir or intermediate hosts to biodiversity loss (Table 1).



PLATE 1. In the Yucatan Peninsula, Belize, and Guatemala, cutaneous leishmaniasis (caused by *Leishmana mexicana* and vectored by sand flies) has long had the nickname, “chiclero’s ulcer.” Chicle is the latex produced by sapodilla trees, and chicleros are the men who venture into the forest for months at a time to collect it. Several other species of *Leishmania* have the same positive association with biodiversity: they primarily infect those humans who have close associations with intact forests. Photo credits: forest image, P. J. Hudson; inset image © Copyright 1997, 2004 by Current Medicine LLC. All rights reserved. Image reproduced here with kind permission from Springer Science+Business Media B.V.

This tabulation of parasites suggests that (1) diseases may have positive, negative, or neutral relationships with biodiversity and (2) negative relationships with biodiversity (i.e., the dilution effect) may be relatively uncommon. As a result, our overall hypothesis is that biodiversity probably has little effect on most infectious diseases of humans and, when it does, the effect seems more likely to be positive than negative, indicating that biodiversity conservation will probably not be an effective general approach to disease control.

#### WHERE DO WE GO FROM HERE?

The dilution effect hypothesis has generated a substantial amount of research attention in past years. But uncertainty remains regarding its applicability to individual diseases (Randolph and Dobson 2012, Salkeld et al. 2013, Wood and Lafferty 2013) and its generality across diseases. What are the most productive research directions moving forward? We suggest that two broad research areas must be addressed: (1) better experimental tests for dilution in individual disease agents, and (2) systematic assessments for biodiversity–disease patterns across a diversity of pathogens, hosts, and environmental contexts. Both approaches must be

undertaken with recognition that the relationship between biodiversity and disease is likely to be nonlinear and, across a given range of diversity, could be primarily negative or positive.

Most studies on human infectious disease risk and biodiversity are correlational (e.g., Allan et al. 2003, LoGiudice et al. 2003, Swaddle and Calos 2008, Clay et al. 2009a, b), but some manipulative experiments have been performed to test for dilution effects in human disease agents. For example, Suzán et al. (2009) removed rodent species not competent for Choclo and Calabazo hantaviruses from experimental forest edge plots in Panama, and found that higher hantavirus seroprevalence resulted in manipulated plots relative to control plots. However, no analysis is given in their paper to suggest whether manipulated rodent communities resemble rodent communities in naturally occurring low-biodiversity habitats. Perkins et al. (2006) experimentally excluded deer from two <1-ha plots in the Italian Alps, and found higher abundance of ticks and prevalence of tick-borne encephalitis (TBE) in deer exclosures relative to matched control areas. The authors proposed that this effect was observed because, without deer hosts to provide blood meals, questing

ticks were concentrated on rodent hosts, amplifying transmission of TBE. This was, in effect, a scale issue and a larger exclusion area would no doubt have resulted in the loss of disease in mice. In other cases, host removal leads to a decrease in infectious disease. Laurenson et al. (2003) removed mountain hares from experimental areas in heather moorlands of Scotland and documented reduced abundance of ticks and prevalence of louping ill in red grouse of treatment relative to control areas, demonstrating that mountain hares are important hosts for tick vectors. An important component of this study was that the authors applied the model developed by Norman et al. (1999) and fitted the model to the data to assess the proportion of the decline in louping ill virus that was due to tick removal vs. removal of the competent host.

It is our opinion that the key test of the dilution effect hypothesis has not yet been performed for any of the human disease agents in which the hypothesis has been well studied. For disease agents in which biodiversity is hypothesized to dilute disease risk, we suggest an experiment in which the abundances of the hypothesized competent reservoir and dilution hosts are independently manipulated. Dilution will be supported if the following conditions are met: (1) A reduction in disease risk (e.g., the density of infected vectors) is observed when hypothesized reservoir hosts are reduced in abundance relative to non-competent hosts, (2) an increase in disease risk is observed when hypothesized dilution hosts are reduced in abundance, and (3) surveys of the environment indicate that high-biodiversity communities contain a greater relative abundance of dilution hosts to reservoir hosts than do low-biodiversity communities, at densities and relative abundances similar to those generated experimentally. This experiment would not be especially difficult to conduct for some diseases (e.g., Lyme disease, hantavirus), and could be complemented with mathematical modeling efforts. Some especially important considerations in experimental design will include the choice of a meaningful yet tractable spatial scale for analysis, as well as appropriate controls. However, even a clear demonstration of dilution in one disease agent will not shed light on the generality of the dilution effect across disease agents.

Moving forward, we believe the most profitable lines of research will be: (1) Assessing the shape and direction of the biodiversity–disease relationship across a diverse and unbiased sample of disease agents to determine whether the dilution effect is common or rare across disease agents, (2) assessing whether the shape and direction of the biodiversity–disease relationship can be determined by context (e.g., environmental factors, type of host, type of pathogen, type of disturbance), and (3) assessing the generality across ecological communities of conditions required to produce a dilution effect (e.g., nested host community patterns such that species least likely to serve as

reservoirs are most vulnerable to biodiversity loss). One option for testing the generality of the dilution effect (research priority 1) within an ecosystem would be experimental simulation of biodiversity loss (e.g., large-vertebrate exclusions), with sampling to measure the change in abundance of various human disease agents. A key consideration in this type of experiment will be the choice of a large, diverse, and unbiased sample of disease agents to measure. Meta-analysis might also be a profitable approach, and has already been used to test the effects of habitat disturbance on the abundance of primate parasites (Young et al. 2013). For research priority 2, disease agent traits might be especially influential determinants of sensitivity to biodiversity loss. For example, parasites with complex life cycles and multiple obligate host species might be especially likely to decline with biodiversity loss, while generalist disease agents might benefit from a biodiversity loss-driven increase of one of their many host species. Host traits could also be important. For example, we might expect, given that many rodent species are tolerant of human impacts, that rodent-borne diseases might be more likely to exhibit a dilution effect than are diseases transmitted by more sensitive animal species (Young et al. 2013). We strongly encourage disease ecologists to elucidate the biodiversity–disease relationship in multi-host, multi-pathogen systems. By investigating the response of pathogen abundance to biodiversity loss across a broad and unbiased sample of disease agents, we will develop a fuller understanding of the contexts in which dilution should occur.

#### CONCLUSION

Although there is logical and empirical support for some cases where human disease risk might increase with biodiversity loss, the conditions for this outcome are restrictive. Biodiversity seems unlikely to reduce the threat of most disease agents. Infectious disease outcomes will not be simple or consistent responses; instead, for infectious disease agents, just as for free-living species, there will be winners and losers in environments subject to anthropogenic change. This is a perspective that is increasingly embraced by ecologists (e.g., Begon 2008, Cardinale et al. 2012, Randolph and Dobson 2012, Salkeld et al. 2013, Young et al. 2013). Despite the fact that biodiversity can sometimes exacerbate infectious disease, we regard biodiversity destruction as a coarse and ultimately counterproductive approach to improving human health because the ecosystems that produce disease spillover are often also rich sources of services critical to human well-being (Wood et al. 2012). A key challenge moving forward will be to identify opportunities for effective deployment of biodiversity conservation in the service of disease control, while recognizing that this approach may work only in a restricted subset of environments, and for a small proportion of all diseases. It is imperative that

public health practitioners, epidemiologists, and ecologists recognize that the relationship between biodiversity and infectious disease is complex, and that disease control is probably not a general ecosystem service of biodiversity.

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#### SUPPLEMENTAL MATERIAL

##### Appendix A

Representation of the dilution effect in the disease ecology literature ([Ecological Archives E095-069-A1](#)).

##### Appendix B

Criteria for negative biodiversity–disease relationships ([Ecological Archives E095-069-A2](#)).

##### Appendix C

Mathematical models of diversity and disease ([Ecological Archives E095-069-A3](#)).

##### Appendix D

Hypothesized mechanisms by which biodiversity may affect the prevalence of human disease agents ([Ecological Archives E095-069-A4](#)).

##### Appendix E

Incidental relationships between biodiversity and disease ([Ecological Archives E095-069-A5](#)).