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Towards common ground in the biodiversity–disease debate

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The disease ecology community has struggled to come to consensus on whether biodiversity reduces or increases infectious disease risk, a question that directly affects policy decisions for biodiversity conservation and public health. Here, we summarize the primary points of contention regarding biodiversity–disease relationships and suggest that vector-borne, generalist wildlife and zoonotic pathogens are the types of parasites most likely to be affected by changes to biodiversity. One synthesis on this topic revealed a positive correlation between biodiversity and human disease burden across countries, but as biodiversity changed over time within these countries, this correlation became weaker and more variable. Another synthesis—a meta-analysis of generally smaller-scale experimental and field studies—revealed a negative correlation between biodiversity and infectious diseases (a dilution effect) in various host taxa. These results raise the question of whether biodiversity–disease relationships are more negative at smaller spatial scales. If so, biodiversity conservation at the appropriate scales might prevent wildlife and zoonotic diseases from increasing in prevalence or becoming problematic (general proactive approaches). Further, protecting natural areas from human incursion should reduce zoonotic disease spillover. By contrast, for some infectious diseases, managing particular species or habitats and targeted biomedical approaches (targeted reactive approaches) might outperform biodiversity conservation as a tool for disease control. Importantly, biodiversity conservation and management need to be considered alongside other disease management options. These suggested guiding principles should provide common ground that can enhance scientific and policy clarity for those interested in simultaneously improving wildlife and human health.

Humans alter biodiversity in complex ways; sometimes, human impacts add biodiversity to ecosystems through species introductions or restoration efforts, but in many cases they cause local biotic homogenization and loss of native biodiversity[1–3]. These changes to biodiversity have the potential to affect human and wildlife infectious diseases through a variety of mechanisms, and understanding when, where and how this might happen could be important for predicting and mitigating disease outbreaks. Biodiversity–infectious disease interactions have roots as far back as the classic work of Charles Elton[4] and have influenced the fields of integrated pest management of crops[5]. More recently, this topic has generated intense debate in the literature and media, and the question of its generality has become a subject of lively discussion in the discipline of infectious disease ecology[6–19]. Much published research supports the dilution effect hypothesis, which proposes that biodiversity can reduce the abundance of a particular parasite species per host and thus reduce the risk of infectious disease caused by that parasite[20–23]. The dilution effect therefore predicts that biodiversity loss should increase infectious disease burden (with caveats noted below in 'Points of agreement and contention'). Other studies support alternatives to the dilution effect, such as no relationship, a context-dependent relationship or an amplification effect[6,11–14,24–26]—defined by Keesing et al.[27] as the opposite of the dilution effect, or a positive relationship between biodiversity and risk of a particular infectious disease. Debate has also centred on whether managing species composition or biodiversity in general is more effective at reducing risk and whether human diseases are exceptions to general rules about biodiversity–infectious disease associations[6,9,13,14,16,17,28–30]. Hypotheses regarding biodiversity–disease relationships have potentially important public health, management and policy implications, because they imply that changes to biodiversity could increase or decrease disease, thus suggesting that biodiversity conservation could have unaccounted costs or benefits, respectively[1,6,11–14,20,24–26,31]. Despite this, there are few examples where biodiversity–disease relationships have been used to set policy or reduce disease burdens. We define biodiversity conservation as preserving functioning ecosystems with predominantly native species and note that this is distinct from single-species conservation or restoration (see Supplementary Information for discussion of restoration and biodiversity augmentation versus biodiversity conservation), which might also affect parasite transmission. The policy and management implications of this debate are real, given that there is a precedent for wildlife management to be used to control disease. For example, based on guidance from ecological models and theory, estate owners in Scotland have culled mountain hares in an attempt to reduce nematode infections in grouse[32], and the British government has culled European badgers in an attempt to limit the spread of *Mycobacterium bovis*, the causative agent of bovine tuberculosis[33].

An improved understanding of biodiversity–disease relationships could lead to considerable progress towards disease control.

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As individuals with a diversity of perspectives on biodiversity–disease relationships, we joined together to summarize the primary points of contention underlying the debate and to identify potential common ground, building upon several recent reviews of biodiversity–disease relationships[13,15,20,31,34,35]. We first describe the host–parasite systems that are most likely to be affected by changes to biodiversity. Throughout this Review, 'biodiversity' is generally used to refer to species richness, whereas 'species composition' accounts for the identity or relative frequencies of species in a community. Next, we summarize the points of disagreement in the biodiversity–disease literature. We then describe the state of the science by comparing the results of two recent synthetic statistical analyses of biodiversity–disease relationships. If biodiversity management as a tool for disease control is considered in the broader context of other disease management options, we contend that it could have two primary benefits. First, it might prevent zoonotic and wildlife diseases from becoming problematic where they currently are not. Second, it might provide a means for managing existing diseases where no or few conventional interventions are available. If researchers can agree on this common ground, the resulting scientific and policy clarity could simultaneously improve ecosystem and human health.

How can biodiversity affect infectious disease?

Many pathogens might not interact with biodiversity (Fig. 1) or are well controlled in some settings by sanitation, drugs, pesticides or vaccines[28]. Other pathogens are likely to interact with biodiversity, including zoonotic diseases, which are caused by parasites that can be transmitted from animals to humans, and vector-borne diseases, which are transmitted by biting arthropods[36–38]. Hence, it is critical to identify the types of host–parasite systems most likely to be affected by biodiversity before asking whether positive, negative or neutral biodiversity–disease relationships predominate.

Biodiversity is unlikely to increase or decrease directly transmitted, specialist parasites without free-living stages, intermediate hosts or vectors (Figs. 1 and 2). Examples include sexually transmitted diseases of wild vertebrate and human hosts, such as simian and human immunodeficiency viruses, and the causative agents of human tuberculosis, measles, non-pandemic influenza and pneumonia, all of which have few interactions with species other than their host[13,14,28] (Fig. 1). By contrast, parasites such as West Nile virus, which can infect humans and numerous species of birds[29], the causative agent of Chagas disease, which can infect humans and various wild and domestic animals[39,40], the bacterium causing leptospirosis, which is typically transmitted from rat excreta to humans[41], and hantavirus, which can infect humans and numerous mammals[42–44], might be more likely to be influenced by biodiversity[31,45]. The sensitivity of these parasites to biodiversity also depends on the number and distribution of infectious stages and how they are transmitted (Fig. 1). For example, systems in which potential host contacts are limited—such as vectors that take a limited number of blood meals in their lifetime—are more likely to be affected by host and non-host biodiversity than are parasites that spread billions of infective stages into the environment (but see ref. [46]) (Fig. 1). Hence, multi-host parasites, wildlife parasites, parasites with complex life cycles or free-living infectious stages, parasites with generalist vectors, and zoonotic parasites would be predicted to respond most readily to changes to biodiversity (that is, to be biodiversity-responsive parasites; Fig. 1). However, to the extent that biodiversity (1) regulates the density of susceptible wildlife hosts that might then pass directly transmitted parasites amongst themselves[27] or (2) influences microbiota that protect against infectious diseases (for example, refs. [20,34,47]), some of these expectations will need re-evaluation. Among these diversity-responsive parasites, negative effects of biodiversity on disease risk (that is, prevalence or per-capita parasite abundance) support the dilution effect, positive effects support the amplification effect, and unimodal relationships support both dilution and amplification under different circumstances. Finally, all of these patterns could be sensitive to the biodiversity and disease metrics used and the scale at which they are observed[14,48,49].

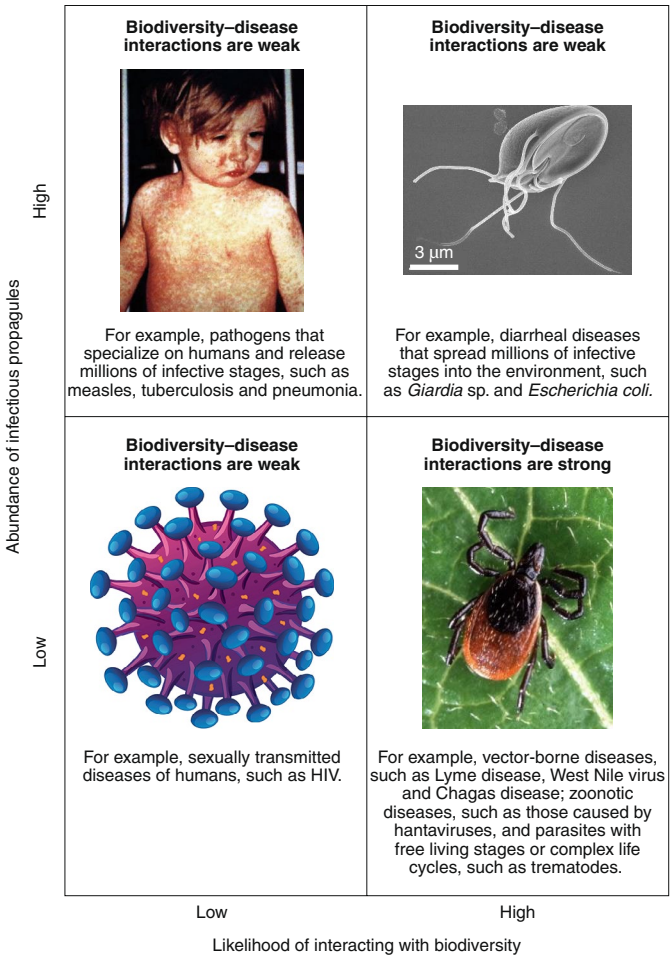

Fig. 1 | The frequency of interactions with biodiversity and transmission potential are likely to influence whether a parasite will be weakly or strongly affected by biodiversity. Transmission potential can be a product of releasing millions of infectious stages into the environment (high), or the number of blood meals a vector can take in its lifetime, or the number of sexual partners humans generally have in monogamous societies (low). When transmission potential is low, lost transmission events have a higher potential of reducing disease risk. However, to the extent that biodiversity regulates susceptible hosts[27] and diverse microbiomes protect against infectious diseases (for example, refs. [20,34,47]), some of these expectations will need re-evaluation. Credit: Measles photo, CDC/NIP/Barbara Rice; *Giardia lamblia*, CDC/Janice Haney Carr; HIV image, Matthew Cole / Alamy Stock Vector; tick photo, Scott Bauer, USDA Agricultural Research Service.

To facilitate policy and management decision making, it is important to (1) identify which diseases are likely to respond to biodiversity, (2) understand the relationships between biodiversity and disease risk, (3) link biodiversity change to change in both disease burden (that is, loss of fitness due to disease) and metrics of disease risk, such as infection prevalence, (4) consider the ecological and medical importance of a disease to a particular system or to humans, and (5) understand the trade-offs between biodiversity management and other land-use and public health options[28,34] (see 'Research frontiers' section). Indeed, different response variables, such as disease burden, prevalence, intensity and force of infection, might respond differently to biodiversity.

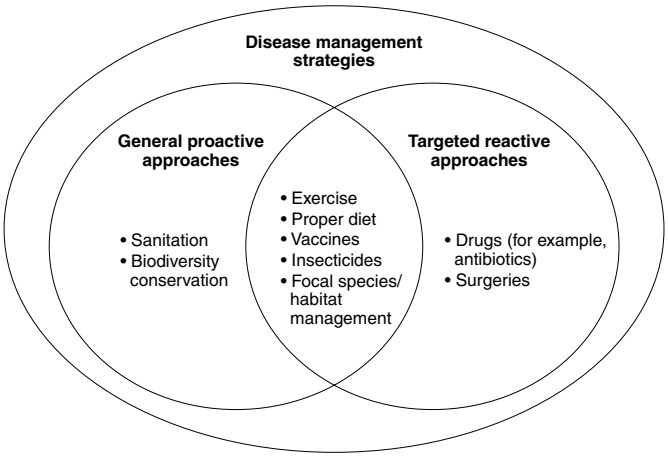

Fig. 2 | Venn diagram depicting two primary disease management strategies, general proactive and targeted reactive approaches, and examples of each. Most disease management strategies are either proactive or reactive but some can be both. If dilution occurs more frequently than amplification, we postulate that the value of general biodiversity conservation might be to prevent: (1) multi-host, zoonotic and wildlife diseases from becoming problematic; (2) diseases where specific key hosts are hard to manage; and (3) diseases where little is known about their ecology, because too little is known to hone any intervention to specific species. In contrast, when the key hosts are manageable, interventions might be targeted to specific species or habitats that are known to amplify or dilute disease, which might make the intervention more effective than general biodiversity conservation. To the extent that biodiversity regulates the density of susceptible hosts that might then pass directly transmitted pathogens amongst themselves[27] or influences microbiota that protect against infectious diseases (for example, refs. [20,34,47]), some of these hypotheses will need re-evaluation. Although this figure is presented as a dichotomy, it does not imply that each option is equally probable.

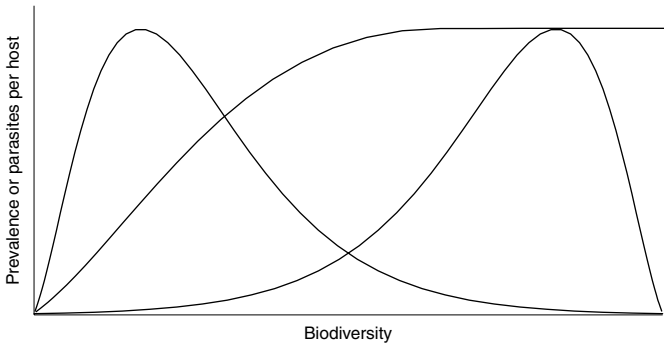

Fig. 3 | Hypothetical relationships between biodiversity and disease risk. The right-skewed distribution suggests that dilution might occur more frequently, but less intensely than amplification because the relationship is moderately negative over a greater portion of the biodiversity gradient than it is strongly positive. The left-skewed distribution suggests that amplification might occur more frequently but less intensely than dilution, because the relationship is moderately positive over a greater portion of the biodiversity gradient than it is strongly negative. An asymptotic distribution suggests that amplification becomes increasingly moderate with biodiversity. In addition to the shape of biodiversity–disease relationships, the frequency with which each biodiversity level occurs in the environment will also affect the likelihood and intensity of dilution and amplification. These hypothetical curves underscore the importance of documenting the shape of biodiversity–disease relationships, which has rarely been accomplished empirically.

Biologists generally agree that biodiversity affects some parasites and not others, so the measured effect of diversity on disease risk depends on whether all parasites or just diversity-responsive parasites are considered. This leaves two questions: (1) what fraction of infectious diseases interact with biodiversity (and through what mechanisms)? and (2) for those diseases that interact with biodiversity, how often is the outcome positive, negative, neutral or nonlinear? By analogy, because we would not expect an antibacterial compound to be effective against all pathogens, we would not ask how effective it is against pathogens other than bacteria. By this rationale, because we only expect biodiversity to interact with a subset of infectious diseases, when assessing whether biodiversity results in dilution or amplification, it is most relevant to consider only those pathogens that are likely to respond to biodiversity.

Points of agreement and contention

This section reviews the points of agreement and contention in biodiversity–infectious disease research.

What is the shape of the biodiversity–disease relationship? For diversity-responsive parasites, the relationship between diversity and disease risk might be nonlinear. No parasites can exist where host richness equals zero[11,12,35,50,51]. For this reason, most dilution effect research has focused on how biodiversity reductions in intact communities affect some metric of disease given that a parasite can complete its entire life cycle in that community[7,23,27,31,52].

Given the likelihood that biodiversity–disease relationships will be nonlinear, it is crucial to know the relevant ranges over which to evaluate diversity and over which diversity is related to conservation action. If unimodal biodiversity–disease relationships are often left-skewed or asymptotic, amplification effects should dominate, whereas if they are right-skewed, dilution should dominate[14] (Fig. 3). Where the diversity of a community falls on these curves is also important, because if most communities fall in the right or left portions of unimodal diversity–disease curves, then dilution or amplification, respectively, will be most common, regardless of the direction of the skew (Fig. 3). We therefore must focus research on assessing the shape of diversity–disease risk relationships and identifying where systems generally fall along the x axis of diversity encompassed by these curves[13,34,35,50] (see 'Research frontiers' section).

What is the influence of habitat transformation or species composition on pathogen transmission, relative to the direct influence of biodiversity? Deforestation and urbanization can affect disease risk both directly and indirectly, via impacts on biodiversity, temperature, sanitation, access to health care, human population density, area of impervious surfaces, contact with biodiversity or other factors[28,53]. These multivariate relationships can make it difficult to disentangle the effects of biodiversity per se (see ref. [54] for a discussion of parasitism within the context of biodiversity–function relationships) on disease risk in changing landscapes[9,28,35]. Hence, it is crucial to control for these potentially confounding factors when testing for relationships between biodiversity and disease (for example, ref. [28]). If these demographic, economic and environmental factors have stronger impacts on disease burden than does changing biodiversity per se, then management of biodiversity could have a relatively small effect on disease.

In contrast to direct biodiversity–disease relationships, changing species composition, rather than diversity per se, can affect disease risk. This hypothesis states that the presence of certain host species increases or decreases disease, and because many experimental studies manipulate species composition in conjunction with biodiversity, the effects of these factors are difficult to disentangle[51,52,55].

Species vary in their diluting and amplifying capacity based on their abundance, susceptibility and transmission potential, and thus certain species can disproportionately affect disease risk[56]. However, there is also support for biodiversity in general affecting disease, particularly when changes in diversity are substitutive—that is, adding new species to a community reduces the abundance of existing species (for example, refs. [57–60]). If species composition rather than diversity per se has a large effect on disease, then managing particular species might be more effective than managing overall biodiversity. Some species, including many rodents, thrive in communities with few predatory species and thus low overall diversity: communities in which many zoonotic diseases can be amplified[10]. However, adding or sustaining top predator species in a community without increasing or maintaining biodiversity, respectively, could be difficult for predators that require an ample abundance and diversity of prey species. This observation that low-diversity communities contain a nested subset of their higher-diversity counterparts[57] is an example of how diversity and species composition can be correlated[20] (see 'Research frontiers' section). This correlation makes it challenging to disentangle composition from diversity in nature and to manage composition independent of biodiversity. Importantly, however, this correlation can make it easier to manage diseases than if diversity and composition were related to one another idiosyncratically, because managing diversity will de facto result in management of composition[20] (see 'Research frontiers' section).

What are the mechanisms underlying biodiversity–disease relationships? Some have suggested that the biodiversity–disease literature lacks evidence for convincing causal mechanisms for a relationship between biodiversity and disease (for example, refs. [61,62]). However, decades of literature on the dilution effect hypothesized explicit mechanisms[23,50,52], and empirical support is growing for several of these. For example, communities with greater biodiversity might have greater densities of non-competent hosts, which can dilute disease by reducing encounters with vectors (for example, wasted bites)[27], competing with competent hosts and reducing their densities[44,49], or consuming free-living parasites or infected hosts (if the parasites are not trophically transmitted) (for example, refs. [58,59]). When controlling for parasite exposure, traits of individual species may be predictive of whether they are likely to be a competent (amplifying) or non-competent (diluting) host for a focal parasite, including phylogenetic relatedness to focal hosts[36,63–65], life history and immunity or other defence strategies[66–70], numerical abundance[63,64,71], predilection to consume parasites relative to hosts[58,59], and contact rates or connectedness within communities[72]. Alternatively, increasing biodiversity might theoretically increase the density of competent hosts, which amplify parasite burden by increasing rates of parasite or vector reproduction, by serving as long-lived reservoirs of infection, or by having high contact rates with other hosts[73].

The extent to which mechanisms that are affected by species composition relate to biodiversity depends on community (dis) assembly—how species are added to (or lost from) a community—which can be affected by the previously mentioned species traits[55,74,75]. Community assembly can range from substitutive, in which individuals of a new species replace individuals of existing species in a community, to additive, in which adding new species adds more individuals to a community. Often, both substitutive and additive assembly occur within a community, because systems typically start assembling additively and shift to substitutive assembly as niches become more fully occupied and competition increases[76].

Some community assembly mechanisms could produce amplification. For example, when community (dis)assembly is additive, amplification is expected because host densities increase as new host species are added to a community. When community (dis) assembly is substitutive, amplification can occur when the addition of individuals of new, competent host species reduce the density of less competent host species[27,50,52]. Amplification or dilution can occur when competent hosts or non-competent hosts, respectively, are added to or subtracted from communities via the sampling effect (that is, more diverse communities are more likely to contain a host species that either strongly increases or decreases disease) (for example, ref. [77]). Additionally, the overall burden of multiple diseases might increase through the cumulative effect of greater pathogen diversity[78]. If considering the cumulative effects of all pathogen species on a host population, host diversity could decrease the disease burden of individual pathogens (dilution) while simultaneously increasing the combined burden of all pathogens (see 'Extrapolations beyond collected data' section for further discussion and counter examples). Although this mechanism for an increase in disease is important for individual health, it would not meet the traditional definition of amplification[27], which focuses on the prevalence or abundance of individual pathogen species in hosts, not the combined effects of all pathogens or an increase in pathogen richness.

Dilution should predominate when community disassembly is substitutive and competent hosts are abundant or are resilient to biodiversity loss. We focus on community disassembly because most of the literature on the dilution effect assumes biodiversity loss and thus disassembly. A commonly hypothesized mechanism for dilution assumes that: (1) parasites experience greater selection to infect abundant rather than rare hosts; (2) abundant hosts make considerable investments into reproduction, growth, and/or dispersal that might come at the expense of defences against parasites; (3) abundant hosts are more likely to colonize and less likely to be extirpated from ecosystems; and (4) adding rare hosts reduces the abundance of common host species in high-diversity communities[50,70]. When these assumptions are met, a right-skewed biodiversity–disease relationship should result (Fig. 3), and abundant and widespread hosts might be amplifying hosts, while hosts with greater diluting potential would be added to communities as biodiversity increases, or would be lost from communities when they become fragmented or disturbed[7,34,76,79]. A combination of mesocosm experiments and field surveys demonstrates that the most abundant and widespread amphibian hosts are also the most competent hosts for a parasitic trematode species, supporting the notion that community disassembly processes function in a manner consistent with the dilution effect for this parasite[57]. Similarly, community disassembly processes support dilution effects documented for Lyme disease[20,45,55,74]. In a recent study, when plant communities were (dis)assembled randomly, dilution was not observed, but when they (dis)assembled naturally, biodiversity significantly reduced disease, again highlighting the potential importance of natural assembly processes[80]. Nevertheless, the generality of this dilution mechanism remains unclear, in part because the frequency with which natural communities assemble and disassemble in a substitutive versus additive manner is not well characterized. Although we call for additional work, we emphasize that substantial progress has been made on mechanisms underlying biodiversity–disease relationships.

Extrapolations beyond collected data. Even when evidence supports a positive or negative biodiversity–disease relationship, there are often several links in the causal pathway between change in biodiversity and change in disease. Few studies have tracked all the links in this causal chain and links in the causal chain can act in opposite directions. For example, there are several links in the hypothesized causal chain connecting high vertebrate diversity to a high probability of zoonotic disease establishment and transmission in humans[20], but not all of these pathways have strong scientific support[10]. There is considerable support for the argument that host diversity begets parasite diversity[26,81–84]. However, there is not consistent support for the hypothesis that increasing parasite diversity

increases disease burden[10]. In fact, recent experimental work on wildlife and plants diseases[57,78,85] showed that higher pathogen diversity can be associated with lower disease severity of individual pathogens in both plants[85] and animals[78]. Ultimately, the impact of parasite species diversity on the health of hosts will depend on how the additional parasite species affect disease burden and severity (see 'Research frontiers' section).

Do biodiversity–disease relationships depend on scale? The dependence of dilution and amplification on spatial scale has been a common thread throughout the biodiversity–disease debate[11,12,35]. There are two main ways in which scale might influence the relationship between biodiversity and disease. First, Johnson et al.[34] proposed that any relationship between biodiversity and infectious disease should be strongest at local scales and weaken at larger scales. This prediction arises because species interactions affecting dilution and amplification occur at relatively small spatial scales, whereas abiotic factors like climate tend to dominate as drivers of biological pattern at larger spatial scales. Cohen et al.[48] found support for this hypothesis in the amphibian chytrid fungus, West Nile virus and the bacterium that causes Lyme disease: at small spatial scales, host richness was a significant predictor of disease prevalence, whereas at larger spatial scales, the distribution of pathogens was more strongly influenced by climate and human population density[48]. Second, it is possible that the diluting capacity of a non-competent host might be most observable at small scales, where encounter reduction can occur, whereas the amplifying effect of a competent host might be most observable at larger temporal and spatial scales[73]. For example, for vector-transmitted diseases, removing a competent host can initially increase vector abundance on alternative hosts, suggesting a dilution effect, while over longer time and larger spatial scales, the removal of the competent host can ultimately cause decreases in the vector population[73]. Importantly, these results suggest that at least some of the variation in outcomes across biodiversity–disease studies could be a product of variation in the scales at which studies were conducted and at which mechanisms operate (see 'Synthesizing the evidence' and 'Research frontiers' sections). Indeed, biodiversity–disease studies have occurred from global to local scales[6,81,86], while conservation actions and public health interventions generally occur at intermediate scales within countries[6,28,86]. In general, the most relevant studies are those conducted at temporal scales long enough to encompass pathogen life cycles and at spatial scales that are most relevant to both biodiversity–disease interactions and conservation, which are generally at the local to regional scales[35].

Synthesizing the evidence

Two recent quantitative syntheses have examined the biodiversity–disease relationship; each has different strengths, limitations and foci. These two syntheses attempted to assess the relative frequencies of positive versus negative biodiversity–disease relationships, whether such relationships are detectable for human diseases despite the influence of other forces on disease burden (for example, wealth and disease control efforts), and whether these relationships depend on scale[17,28].

In a systematic meta-analysis of the published literature on biodiversity–disease studies, which included 202 effect sizes for 61 parasite species, negative biodiversity–disease associations were common[17] (see ref. [87] for similar findings among plant diseases). Negative diversity–disease associations were equally strong for zoonotic and wildlife diseases, and the meta-analysis did not reveal any significant context dependencies[17], nor evidence of publication bias for zoonotic diseases[18], though it is possible that null and amplification effects are underrepresented in the literature (that is, system selection rather than publication bias) (Table 1). Additionally, although Civitello et al.[17] did not explicitly quantify the scale of the studies in their meta-analysis, there were no significant differences in effect sizes between smaller-scale experimental and larger-scale correlative field studies, indicating that, within the range of scales at which the studies were conducted, scale was unlikely to affect the nature or strength of dilution effects[17,18]. These results suggest that, among the diseases for which relationships with biodiversity have been tested, a negative association (1) is frequently reported for wildlife and human diseases, (2) is robust across ecological contexts, and (3) is consistent across the spatial scales studied and between experimental and observational studies. However, many important human parasites have not been studied under these conditions and therefore could not be included in this meta-analysis, and many of the studies in the meta-analysis quantified infection prevalence or parasite abundance rather than disease burden (Table 1). Finally, in a meta-analytic framework, it is difficult to separate effects of species composition (for example, sampling effects) from effects of biodiversity per se, although the meta-analysis included several studies that did separate these effects.

A second synthesis tested for associations between environmental, demographic, economic and social factors and disease burden for the 24 most important human infectious diseases tracked by the World Health Organization, of which 11 were potentially affected by biodiversity[28]. To do so, Wood et al.[28] conducted a global analysis investigating across-country associations between disease burden (disability adjusted life years; DALYs) and biodiversity (country-level bird and mammal species densities), while controlling for other potential drivers of disease burden, such as wealth, forestation and urbanization. All vector-borne or zoonotic diseases (that

Table 1 | Characteristics that differ between the Civitello et al. and Wood et al. studies

Studies within the Civitello et al.[17] meta-analysis	Wood et al.[28] within-country through time analysis	Wood et al.[28] across-country analysis
Typically, include only relevant diversity.	Includes diversity that is of questionable relevance to hosts.	Includes diversity that is of questionable relevance to hosts.
Typically, do not homogenize patterns across communities.	Homogenizes patterns across communities.	Homogenizes patterns across communities.
Typically, compare same ecosystems and species.	Compares same ecosystems and species.	Compares different ecosystems and species.
Diversity varies mostly because of non-biogeographic differences, such as anthropogenic influences.	Diversity varies mostly because of non-biogeographic differences, such as anthropogenic influences.	Diversity varies mostly because of biogeographic differences.
Motivated by mechanism.	Motivated by mechanism.	Mechanism not necessarily clear.
Mix of manipulative and observational studies.	Only observational studies.	Only observational studies.
Generally small scale with some spatiotemporal scales smaller than what is relevant in nature.	Medium scale.	Largest scale.
Could have system selection bias.	No system selection bias.	No system selection bias.
Dilution	Ambiguous	Amplification

is, biodiversity-responsive) examined in this study were positively associated with biodiversity at the across-country scale, though only five of the associations were statistically significant. By contrast, when considering changes in biodiversity and disease burden over time within each country, coefficients for seven diseases were negative (one significantly), and four were positive (one significantly). Thus, biodiversity effects were less positive at the within-country scale, relative to comparisons among countries[28]. Because the study is global, it relies on country-scale estimates of biodiversity, which include species not directly relevant to each disease (for example, total bird diversity in disease systems for which only mammals can become infected) (Table 1). Additionally, the spatial scale of analysis (intermediate-size countries) is larger than the scale at which species interactions occur, but is a scale at which some policy decisions are made.

How can two synthetic analyses published two years apart come to such divergent conclusions? We hypothesize that the discrepancies arise in part from differences in the spatial scales and methods of the studies (Table 1). Civitello et al.[17] used published studies that experimentally investigated diversity–disease associations at logistically feasible scales that were substantially smaller than the within- and across-country spatial extents and grains included in Wood et al.[28] (see Source Data Fig. 4). In fact, the median replicate size for studies on zoonotic parasites in Civitello et al.[17], as compiled by Halliday and Rohr[88] (for studies with ≥3 biodiversity levels and rounding all replicate sizes to the nearest order of magnitude), was 1.5 km^2, whereas the median replicate size for the analyses in Wood et al.[28] was 321,489 km^2. As discussed above, the association between biodiversity and chytrid, West Nile, and Lyme disease declined with spatial scale in multiple regression analyses[48], consistent with the notion that mechanisms for dilution might operate at smaller scales than mechanisms for amplification. Clearly, the role of spatial scale in affecting the net effect of diversity on disease requires more attention.

We re-analysed data from Wood et al.[28] to ask whether effect sizes in a single country through time differed from effect sizes across countries at a given time. Any disease designated as biodiversity-responsive by Wood et al.[28] was considered biodiversity-responsive for this re-analysis. We conducted a general mixed-effects linear model in which we treated as the response variable their 11 pairs of regression coefficients (one for the across-space comparison and one for the across-time comparison) for the effect of biodiversity on human disease burden of biodiversity-responsive diseases, with time versus space as the predictors, and the disease identity as a random effect (coefficients taken from the full model; see Fig. 1 of ref. [28]). The positive coefficient between biodiversity and disease decreased significantly when transitioning from the across-country global comparison to the within-country, across-time comparison ($F_{1,10} = 13.59$, $P = 0.0042$, Fig. 4), from significantly positive at the cross-country global scale to non-significant at the within-country scale over time. This re-analysis of the Wood et al.[28] study suggests that when spatial scale is reduced from across to within countries (by considering a single country over time), biodiversity–disease relationships become less positive (Fig. 4). However, numerous other important factors differ between the Wood et al.[28] and Civitello et al.[17] studies (Table 1). For example, most studies in Civitello et al.[17] assessed parasite prevalence or abundance, whereas Wood et al.[28] analysed DALYs, which represent the burden of infection rather than parasite presence or abundance. Thus, for several reasons, we cannot definitively attribute differences in effect size and magnitude to differences in scale (Table 1).

It is important that we determine whether the relationship between biodiversity and disease does vary with spatial scale and, if so, that we identify the mechanisms that drive this relationship. Another key research frontier is evaluating the scale at which diversity can be feasibly managed to reduce the burden of disease. When diversity at the scale of nations or continents predicts disease patterns, information on the diversity–disease association seems most useful in assessing general risk at large scales. Biogeographic patterns of diversity, however, are rarely if ever amenable to direct management for disease reduction. When diversity at local and regional scales predicts disease patterns, management of diversity will sometimes be feasible as a means of managing disease.

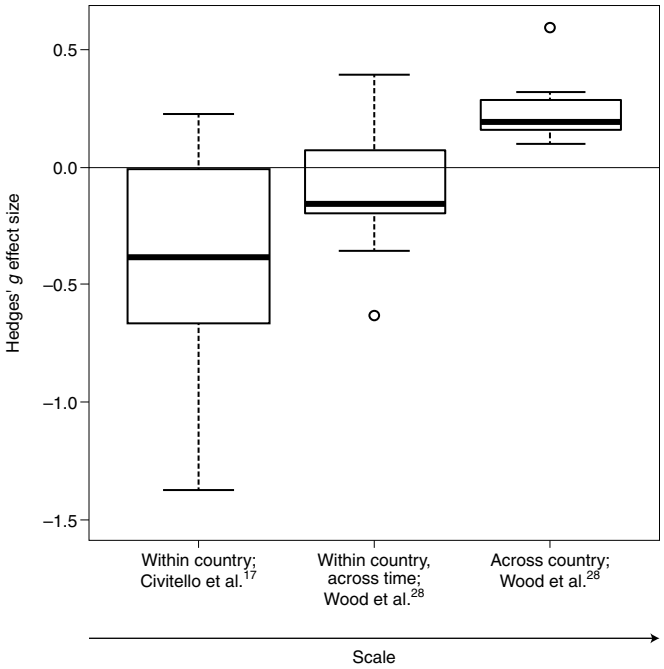

Fig. 4 | Hedges' *g* effect sizes. Effect sizes are shown for the association between biodiversity and zoonotic parasites (plus typhoid, because Wood et al.[28] suggest it is biodiversity-responsive) at the cross-country and within-country (through time) scales (median replicate size: 321,489 km^2; $n = 11$) from Wood et al.[28] and various smaller-scale studies (median replicate size: 1.5 km^2; $n = 12$) compiled by Civitello et al.[17]. Hedges' *g* was provided by Civitello et al.[17], whereas Wood et al.[28] provided standardized regression coefficients. We converted the standardized regression coefficients to the Hedges' *g* used in Civitello et al.[17] by multiplying these coefficients by the sample size bias adjustment, $\frac{N-3}{N-2.25} \times \left(\frac{N-2}{N}\right)^{0.5}$. To properly account for the lack of independence among multiple effect sizes within studies and for the same diseases in Civitello et al.[17], we calculated a mean effect size for each study weighting by the inverse of the variance, and then used inverse variance weighting on those study-wise means to obtain a weighted mean for each disease (see Source Data Fig. 4 for data used to generate this figure). In the Wood et al.[28] study, the cross-country coefficient is significantly greater than zero ($z = 5.82$, $P < 0.001$), whereas the within-country (over time) coefficient is negative but not significantly different from zero ($z = -1.20$, $P = 0.116$). However, the relationship between these mean coefficients and scale is significantly positive ($F_{1,10} = 13.59$, $P = 0.0042$), indicating that positive diversity–disease associations are more likely for among-country comparisons than for comparisons within a country, over time. Relative to Wood et al.[28], smaller-scale studies compiled in Civitello et al.[17] were more likely to find negative diversity–disease associations. However, other factors also differ between the Wood et al.[28] and Civitello et al.[17] studies so we cannot confidently attribute all of this difference to the effect of scale. The midline of each boxplot is the median, the lower and upper limits of the box are first and third quartiles, respectively, the whiskers extend to 1.5 times the interquartile range, and the circles are extreme data points. Note that one extreme Hedges' *g* value from Civitello et al.[17] at −4.92 (*Leptospira* spp.) is not shown but was used to calculate the median, quartiles and whiskers of the boxplot.

Towards common ground

Given that scientists struggle to predict which, when and where infectious diseases will become problematic, general preventative approaches that produce net reductions in disease could have considerable value (Fig. 2). Ecosystems regularly pose a threat of disease to humans and wildlife, but ecosystems vary in these threats. Thus, targeting conservation toward protecting ecosystems that are not currently posing a major threat of problematic disease to humans or wildlife might prevent increases in disease (Fig. 2). In contrast, when the goal is to manage a specific disease whose ecology is reasonably well understood, it may be simpler and more effective to manage the particular species (vectors or amplifying or diluting hosts) or habitats that are known to decrease or increase disease (for example, through vaccination, culling, predator supplementation and habitat manipulation) than to conserve biodiversity in general (Fig. 2). However, management of particular species or habitats might only be effective against a focal pathogen. By contrast, preservation of intact, functioning ecosystems and finding sustainable, equitable interventions that discourage human incursions into those ecosystems (for example, for logging and bush-meat hunting), could reduce the risk of transmission of multiple pathogens, even if these interventions are not the single most efficient control method for individual diseases. Thus, they could represent win–win scenarios for conservation and disease control.

When considering disease management strategies, the costs and benefits of each tactic and their alternatives must be evaluated thoroughly before implementation. For example, it is possible that the land needed for biodiversity conservation might have greater value to humans if it is used differently, such as for agriculture or development, though it is also worth noting that sometimes the value arising from agriculture or development disproportionately accrues to outside commercial interests, while the health tolls are disproportionately borne by local communities[89]. Just as importantly, there are many reasons to conserve, restore and manage biodiversity that are unrelated to infectious disease, including other ecosystem services as well as ethical, aesthetic and cultural motivations. Additional health benefits from conservation can help make such actions more palatable when weighed against other land-use options.

Research frontiers

There are several outstanding questions in the biodiversity–disease literature that we have organized into five research frontiers: (1) pattern and process in biodiversity–disease relationships; (2) the shape of biodiversity–disease relationships; (3) metrics of disease and diversity; (4) context dependencies; and (5) public health and conservation.

Pattern and process in biodiversity–disease relationships. The foundational principles of disease ecology rest on a few well-studied disease agents, with many studies describing associations between biodiversity and disease rather than revealing the mechanisms that drive those patterns. We submit that the field needs to diversify, by both developing a broader understanding of biodiversity–disease patterns (that is, testing associations between biodiversity and disease beyond the disease agents that are already well studied) and narrowing in on the processes (that is, the mechanisms) that generate these patterns. A few macro-ecological investigations of biodiversity–disease pattern have already been conducted at the global scale (for example, refs. [26,28,86]), but there is substantial promise in adopting this approach at regional or local spatial scales, which could reveal the conditions under which biodiversity–disease relationships are ecologically influential[48]. To discover what drives these ecologically influential relationships, experimental studies are needed to isolate mechanisms. For instance, most of the mechanisms posited to explain the dilution effect involve substitutive community (dis)assembly, but it remains unclear how often community (dis)assembly is additive versus substitutive, how strongly this affects biodiversity–disease relationships, and whether the most competent hosts for infections are also the most robust to biodiversity loss under historical and current conditions[20,31,34,75,90]. The degree of correlation between species composition and biodiversity and the relative importance of stochastic and deterministic community assembly mechanisms are also not well established. The less deterministic community assembly is, the less effective biodiversity management might be as a tool for disease control. Finally, ecological communities can also change stochastically through time (that is, ecological drift), which could cause temporal shifts in the roles of different dilution mechanisms at a given location.

The shape of biodiversity–disease relationships. Although there is consensus that biodiversity–disease relationships must be unimodal for dilution to occur, their propensity to be skewed to the left or right, and where they sit relative to the peak is unclear. For right-skewed biodiversity–disease relationships, a larger proportion of the diversity axis would produce dilution, whereas for left-skewed biodiversity–disease relationships, a larger proportion of the diversity axis would produce amplification. An even more challenging but equally important issue is determining how species richness values in nature are distributed along the diversity axis, and whether these tend to cluster on the portion of that axis where increasing biodiversity increases disease, or vice versa (Fig. 3).

Metrics of disease and diversity. Metrics of disease and diversity can vary widely across biodiversity–disease studies, but whether the choice of metric influences the study outcome is poorly understood. For instance, because infections do not necessarily manifest in disease burden (that is, loss of host fitness), it is possible that parasite prevalence or intensity might be more sensitive to biodiversity than is disease burden. Like disease, biodiversity can also be measured or represented in many ways and this too has the potential to affect outcomes[91]. For instance, whether alpha, beta or gamma diversity affect disease differently is uncertain. Moreover, different subsets of biodiversity might have different effects on disease. For example, it remains unclear how parasite diversity affects the number of infections per host or disease[78,85]. Additionally, natural enemies of parasites (for example, predators[58]), symbionts of hosts (for example, host microbiomes[47]), and other non-host species can influence biodiversity–disease relationships, but the common mechanisms by which non-hosts affect infectious disease remain equivocal[27,34,58].

Context dependencies. Some attribute disagreements over the biodiversity–disease relationship to an overemphasis on generality[30]; while there might be context dependencies for the biodiversity–disease relationship, we think it is worthwhile to seek the rules that govern when and where each form of biodiversity–disease relationship might emerge. For example, there might be common traits of parasite species that are affected by biodiversity and common traits of host species that amplify or dilute disease[13,14,58,59]. If all host species are unequal, then it raises the question: how strongly are biodiversity–disease relationships a product of the identity of particular host species ('sampling effects')[1,34,51,58,92], an emergent property of biodiversity in general ('complementarity effects'), or spurious correlations driven by other factors?

Other ecological disciplines have identified relationships similar to the dilution effect. For instance, in the plant–herbivore literature, host plant diversity decreases herbivory, a phenomenon coined associational resistance[93]. The biodiversity–ecosystem functioning literature has documented consistent positive relationships between biodiversity and ecosystem functions[1], and the Red Queen hypothesis is based on the notion that genetic diversity within

a host species decreases infections per host[65]. What are the commonalities and differences among the dilution effect, associational resistance, biodiversity–ecosystem functioning and Red Queen hypotheses[1,17,54,58,65,71,93], and are any differences a product of context dependencies?

An important potential context dependency for biodiversity–disease relationships is spatial scale. How much of the variation in outcomes of biodiversity–disease studies arises from differences in the scale at which studies are conducted (spatial and temporal scales and the scope of the biodiversity gradient)[12,34,48]? There is a rich literature on the scale-dependent effects of ecological drivers on biodiversity patterns[91]. Can it inform the biodiversity–disease discipline? More specifically, recent work shows that species composition often changes when it is measured at different spatial scales, and that measures of biodiversity are therefore often uncorrelated across scales[94]. Can this phenomenon, coupled with neutral sampling effects, cause different biodiversity–disease patterns to emerge at different scales? How important is the temporal scale of community assembly in revealing novel mechanisms linking host diversity to disease[95]?

Public health and conservation. Much of the controversy surrounding the biodiversity–disease discipline has arisen from the suggestion that human health would benefit from biodiversity conservation. Not surprisingly, many questions and considerable work remain on the application of biodiversity management to public health. For instance, some studies suggest mutual interference among co-infecting pathogens, such that an increase in parasite diversity generally decreases overall infections[75]. What is the general shape of the response surface for the relationships among disease and per-capita parasite diversity and abundance, and what are the public health trade-offs between more cases of one disease versus more different types of parasitic infections? How large is the unique effect of biodiversity compared to the unique effect of factors that commonly co-vary with biodiversity loss due to habitat conversion to more urban settings, such as increases in sanitation, access to health care and area of impervious surfaces? What are the trade-offs of investing in conservation as a disease management approach versus other public health interventions?

Conclusions

We believe that most disease ecologists can agree on several elements of the biodiversity–disease debate. First, biodiversity should have a greater effect on multi-host, wildlife, vector-borne and zoonotic diseases, especially those parasites with complex life cycles and free-living stages, than on directly transmitted, host-specialist diseases. Second, the relationship between biodiversity and disease can be nonlinear, and identifying the shape of these relationships and where the diversity of a community falls on this continuum is critical for understanding when decreasing biodiversity will increase, decrease or have no effect on disease risk. Third, not all diseases are equal. Ebola is not the same as head lice, and from a conservation perspective, a disease causing widespread extirpations or extinctions is different from one that is not consistently causing wildlife declines. Fourth, biodiversity–disease relationships may be scale-dependent. Understanding the mechanisms that underlie this possible scale dependency could lead to insights into which management targets (biodiversity, particular species and human behaviour) and which scales of action are most effective for disease control. Outcomes with co-benefits for biodiversity and human health should be actively sought. Establishing consensus on these guiding principles will help to set a research and policy agenda for simultaneously improving ecosystem and human health.

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Author contributions

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Competing interests

The authors declare no competing interests.

Additional information

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