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Linking environmental nutrient enrichment and disease emergence in humans and wildlife

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Abstract. Worldwide increases in human and wildlife diseases have challenged ecologists to understand how large-scale environmental changes affect host–parasite interactions. One of the most profound changes to Earth's ecosystems is the alteration of global nutrient cycles, including those of phosphorus (P) and especially nitrogen (N). Along with the obvious direct benefits of nutrient application for food production, anthropogenic inputs of N and P can indirectly affect the abundance of infectious and noninfectious pathogens. The mechanisms underpinning observed correlations, however, and how such patterns vary with disease type, have long remained conjectural. Here, we highlight recent experimental advances to critically evaluate the relationship between environmental nutrient enrichment and disease. Given the interrelated nature of human and wildlife disease emergence, we include a broad range of human and wildlife examples from terrestrial, marine, and freshwater ecosystems. We examine the consequences of nutrient pollution on directly transmitted, vector-borne, complex life cycle, and noninfectious pathogens, including West Nile virus, malaria, harmful algal blooms, coral reef diseases, and amphibian malformations.

Our synthetic examination suggests that the effects of environmental nutrient enrichment on disease are complex and multifaceted, varying with the type of pathogen, host species and condition, attributes of the ecosystem, and the degree of enrichment; some pathogens increase in abundance whereas others decline or disappear. Nevertheless, available evidence indicates that ecological changes associated with nutrient enrichment often exacerbate infection and disease caused by generalist parasites with direct or simple life cycles. Observed mechanisms include changes in host/vector density, host distribution, infection resistance, pathogen virulence or toxicity, and the direct supplementation of pathogens. Collectively, these pathogens may be particularly dangerous because they can continue to cause mortality even as their hosts decline, potentially leading to sustained epidemics or chronic pathology. We suggest that interactions between nutrient enrichment and disease will become increasingly important in tropical and subtropical regions, where forecasted increases in nutrient application will occur in an environment rich with infectious pathogens. We emphasize the importance of careful disease management in conjunction with continued intensification of global nutrient cycles.

Key words: dead zones; eutrophication; global change; harmful algal blooms (HABs); host–parasite interaction; human health; nitrogen; zoonotic disease.

Disease Emergence in Humans and Wildlife

Despite major advances in human medicine, infectious disease remains the largest cause of human mortality worldwide (World Health Organization 2004). While some pathogens have been eliminated or controlled, the combination of newly emerging diseases and the resurgence of extant diseases engenders an annual human death toll of ~12 million people. New diseases such as acquired immunodeficiency syndrome (AIDS), Lyme borreliosis, ebola, sudden acute respiratory syndrome (SARS), bovine spongiform encephalopathy (BSE), and hantavirus pulmonary syndrome (HPS) have

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emerged, while significant increases in established infections such as malaria, tuberculosis, cholera, and measles have also occurred. Importantly, however, this trend is not unique to human pathogens. Emergence of wildlife diseases has exhibited a similar pattern in recent decades, largely overturning the once-dominant paradigm that disease is not an important cause of wildlife mortality (May 1988, Daszak et al. 2000, Dobson and Foufopoulos 2001). Examples are numerous and include viral hemorrhagic septicemia virus (VHSV) in fishes, colony collapse disorder in honeybees, mycoplasmosis in birds, toxoplasmosis in sea otters, and chytridiomycosis in amphibians (Daszak et al. 2000, Miller et al. 2002, Lips et al. 2006). Emerging infections can sometimes lead to population extirpations or even species extinctions, particularly when reservoir hosts, small host population sizes, or frequency-dependent transmission are involved (de Castro and Bolker 2005, K. F. Smith et al. 2006).

The parallel emergence of human and wildlife diseases reflects the facts that (1) each have similar etiologies involving ecological changes in the environment and (2) the division between medical and veterinary diseases is largely an artificial one. Most emerging diseases of humans are zoonotic, meaning they involve animal hosts at some stage of transmission (Taylor et al. 2001, Woolhouse and Gowtage-Sequeria 2005). Consequently, patterns of infection in humans are often linked to the levels of infection in wildlife, and a thorough understanding of disease emergence thus requires knowledge of the ecological factors that influence humans, wildlife hosts, and their interactions (National Research Council 2001, Smith et al. 2007). A growing number of examples illustrate the value of an ecological approach for understanding disease and collectively suggest that broad patterns of emergence are best understood by examining human and wildlife populations concurrently (Guernier et al. 2004, Jones et al. 2008). Here we adopt such an approach to explore the relationships between environmental nutrient enrichment and disease. Recognizing the parallel and often inter-related patterns between pathogens of humans and those of wildlife, we do not differentiate between medical and veterinary diseases, and interweave examples of each to broadly examine the effects of nutrients on diseases.

Changing N and P Cycles

Human activities have driven massive changes in the major biogeochemical cycles, particularly those of nitrogen (N) and phosphorus (P). For example, N fixed via fossil fuel combustion, fertilizer production, and cultivation of N-fixing crops now outpaces N inputs from all natural processes on the land surfaces of the planet combined (Galloway et al. 2004). Similarly, the extraction, refining and application of P fertilizer has amplified the natural P cycle by about two- to threefold (Howarth et al. 1995, Bennett et al. 2001). The regional variation in the acceleration of these nutrient cycles is remarkable. While some regions of the world such as northern Canada and Siberia have seen little if any change, other regions such as western Europe, the northeastern United States, and east Asia have seen 10- to 15-fold increases in nutrient flows in rivers and in the atmospheric deposition of nitrogen (Howarth et al. 2005, Howarth 2008). Nutrient use for human enterprises has a range of effects on the Earth system, both positive and negative. For example, mineral fertilizer production and legume crop cultivation fueled the Green Revolution, significantly increasing crop yields that support growing human populations, decreasing malnutrition, and enhancing economic prosperity (Smil 2001, 2002, Sanchez 2002). On the other hand, environmental N loading can cause a cascade of negative effects (sensu Galloway et al. 2003), including declines in forest health (Schulze 1989, Aber 1998), changes in species composition and losses of biodiversity (Vitousek et al. 1997, Stevens et al. 2004), eutrophication and loss of habitat quality in aquatic ecosystems (Howarth et al. 2000, National Research Council 2000, Schindler 2006, V. H. Smith et al. 2006), acidification of soils (Högberg et al. 2006), and changes to the chemistry and radiative balance of the atmosphere (Intergovernmental Panel on Climate Change 2007). P enrichment has a less diverse set of consequences, but is a major driver of aquatic eutrophication, particularly in freshwaters (Carpenter et al. 1998, Schindler 2006, V. H. Smith et al. 2006). Thus, in spite of the clear benefits to humans of the increased uses of fertilizer N and P, the widespread and increasing use of anthropogenic nutrients is also transforming the state of natural ecosystems and the myriad services and functions they provide (Vitousek et al. 1997). Here we explore the consequences of such nutrient enrichment for patterns of disease in both human and wildlife populations.

Nutrient Enrichment and Disease

Our understanding of the effects of nutrient enrichment on patterns of disease remains limited. Direct exposure to nutrients (especially nitrate ingestion via drinking water) can cause or contribute to pathology in humans and wildlife, with examples ranging from blue-baby syndrome (methyglobinemia) to reproductive problems to various cancers (Ward et al. 2005). Increases in food production associated with fertilizer usage can also reduce malnutrition and enhance human health (Sanchez and Swaminathan 2005, Smith et al. 2005). Our goal here, however, is to explore the indirect effects of environmental nutrient enrichment on diseases, which are often ecologically complex and potentially far reaching. Both theoretical and empirical studies suggest that, unlike many stressors, nutrient enrichment often enhances pathogen abundance (Lafferty 1997, Lafferty and Holt 2003, Townsend et al. 2003, McKenzie and Townsend 2007, Johnson and Carpenter 2008). Anthropogenic inputs of nutrients to the environment frequently correlate with increases in the prevalence, severity, or

distribution of infectious diseases in nature (Coyner et al. 2003, Rejmankova et al. 2006, Johnson et al. 2007, Voss and Richardson 2007). Postulated mechanisms for these linkages include changes in host abundance and distribution, shifts in pathogen virulence, or changes in host susceptibility (see reviews by McKenzie and Townsend 2007, Johnson and Carpenter 2008).

However, interpretation of these correlations is often confounded by the fact that nutrient enrichment is frequently accompanied by additional forms of environmental change (e.g., land use changes, chemical pollution, changes in species composition), precluding precise identification of causal mechanisms. Moreover, levels of nutrient enrichment are infrequently measured directly, making it difficult to understand the range of enrichment values over which pathogens will be most responsive. The problem is further confounded by the tendency of nutrient enrichment to have non-linear effects on ecological response variables, including primary production, decomposition, habitat quality, food web structure, and species diversity (Dodson et al. 2000, Howarth et al. 2000, National Research Council 2000). Thus, extremely high nutrient inputs may induce different effects for host–pathogen interactions relative to low or moderate levels of enrichment (Johnson and Carpenter 2008).

Recent experimental research focused on the nutrient–disease linkage offers new and direct insights about the mechanisms underpinning observed field patterns. Collectively, these experiments encompass a broad range of human and wildlife disease examples, including field and laboratory studies in marine, freshwater, and terrestrial ecosystems. Our goal is to highlight these recent experimental advances and use them to discuss general mechanisms linking nutrients and disease. Recognizing that the effects of nutrients will vary with the type of pathogen and its mode of transmission, we evaluate the effects of nutrient enrichment on directly transmitted diseases, vector-borne infections, complex life cycle parasites, and noninfectious diseases. By synthesizing existing information from a range of systems and transmission modes, we aim to elucidate how nutrient-mediated changes in disease levels may affect human health, economic sustainability, and wildlife conservation.

Direct horizontal transmission

Directly transmitted diseases are caused by parasites that require only one type of host to maintain the life cycle. They are usually transmitted via direct contact between hosts or by the spread of infective propagules (e.g., fungal spores, viral particles, eggs, cysts) in the environment. Examples include many viruses, bacteria, fungi, protists, and some metazoan parasites. Nutrient enrichment is hypothesized to influence directly transmitted parasites by (1) changing the density of hosts (and therefore the parasite transmission rate), (2) altering the duration of infectivity by hosts (e.g., by increasing host survival), (3) exacerbating the pathology associated with infection, or (4) by directly or indirectly providing additional resources to the pathogen (Johnson and Carpenter 2008). For example, Mitchell et al. (2003) examined the response of fungal foliar pathogens to experimental N deposition (as well as elevated carbon dioxide and decreased plant diversity) on 16 species of host plants, and found a significant increase in fungal disease severity in species that also displayed increased foliar N content. The correlation between foliar N and disease severity suggests that increased N availability may benefit foliar pathogens by promoting higher infection establishment rates, lesion growth (Sander and Heitefuss 1998), and spore production (Jensen and Munk 1997).

Some coral pathogens also respond positively to nutrient enrichment, perhaps through a similar mechanism. Outbreaks of disease in some coral reefs have been correlated with increases in nutrient runoff (Kim and Harvell 2002, Sutherland et al. 2004), and Bruno et al. (2003) used time-release fertilizer pellets to experimentally evaluate the effects of nutrient enrichment on naturally infected sea fans and reef-building corals in situ. Added nutrients nearly doubled the severity of both aspergillosis and yellow band disease (YBD) and the rate of host tissue loss (Bruno et al. 2003). Voss and Richardson (2006) used a combination of field and laboratory experiments to test the effect of nutrient additions on black band disease (BBD; Fig. 1A) in Caribbean corals. Their results also revealed the positive effects of nutrient additions on disease, with BBD progressing approximately 2.5 times faster in experimentally exposed corals than in unmanipulated controls (Fig. 2A). Corresponding laboratory trials confirmed that host tissue loss increased in a dose-dependent manner with increasing nitrate (Voss and Richardson 2006).

The mechanism(s) linking accelerated pathogen spread and nutrient additions remain unclear. BBD, like YBD, is a microbial consortium of more than 50 different heterotrophic bacteria, as well as some sulfide-oxidizing bacteria and filamentous cyanobacteria (Carlton and Richardson 1995, Cooney et al. 2002), making its responses to environmental change difficult to ascertain. The causal pathway could be similar to that observed for foliar plant pathogens discussed above, whereby nutrients benefit the pathogen by directly stimulating growth and development. Given that *Aspergillus* infections are caused by a single pathogen and that Voss et al. (2007) did not find BBD community shifts in response to nutrients, the mechanism of direct resource benefits to the pathogen is plausible. Experiments by Kline et al. (2006), however, suggested that the mechanism may be indirect; elevated nutrients increase the production of organic carbon (through primary production), which in turn leads to an increased abundance of coral-associated microbiota and in opportunistic parasitism. In either case, these examples from completely different systems (grasslands and coral reefs) suggest the broad potential

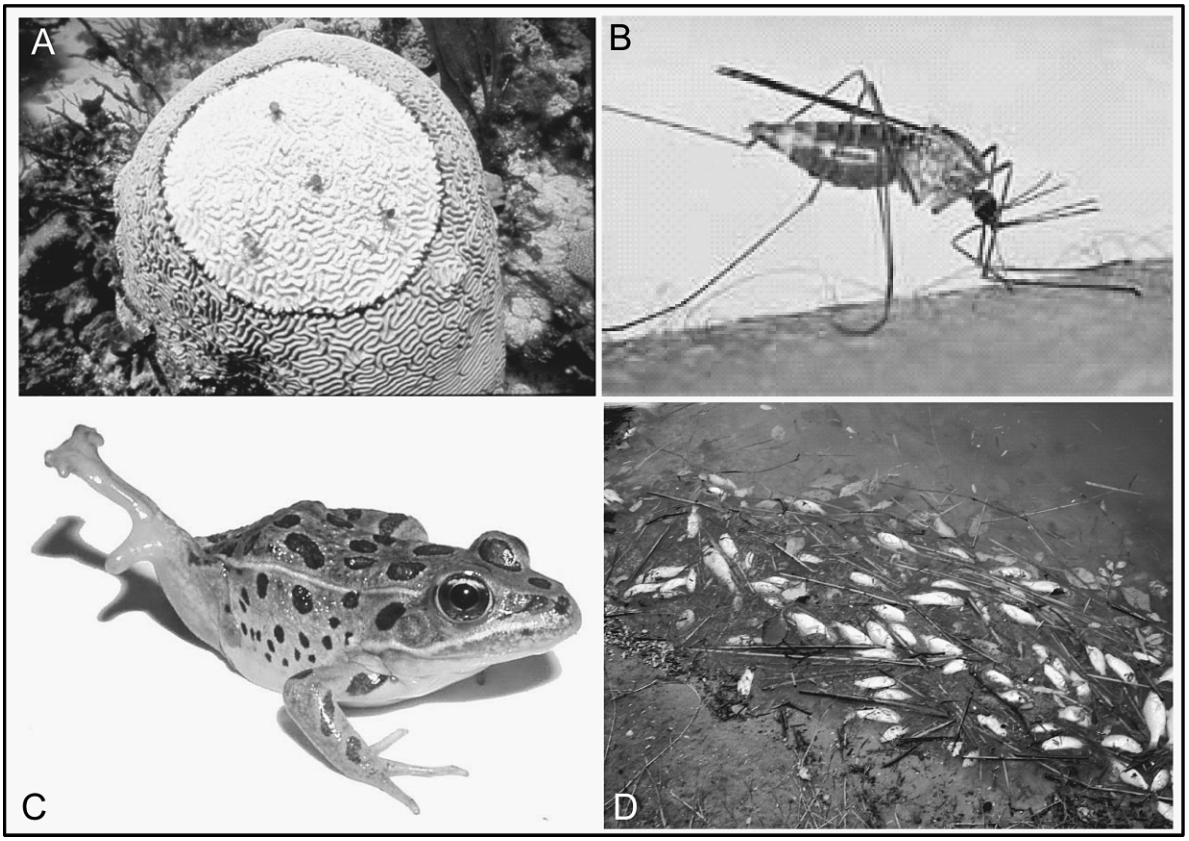

FIG. 1. Representative diseases or hosts that respond to nutrient enrichment. (A) Black band disease (BBD), a directly transmitted disease, in reef-building corals (photo courtesy of USGS). (B) Vector-borne pathogens, such as malaria and West Nile virus, may be enhanced with nutrient enrichment owing to changes in mosquito production or larval habitat. (C) Complex life cycle parasites, including the trematode (*Ribeiroia ondatrae*) that causes limb deformities in amphibians, can increase in abundance or pathology due to changes in intermediate host abundance or parasite production (photo credit: P. Johnson). (D) Noninfectious diseases such as harmful algal blooms (HABs) may directly or indirectly cause a broad range of pathologies in human and wildlife populations (photo credit: P. Glibert).

for nutrient enrichment to enhance the availability of resources for some pathogens, thereby facilitating their rate of spread and the resulting host pathologies.

Indirect effects associated with environmental nutrient enrichment can also enhance the pathology of directly transmitted parasites. For example, hypoxia caused by eutrophication can accelerate parasite spread and enhance pathology. Ectoparasitic copepods and monogenean parasites, which colonize the gills and skin of fishes, can accelerate asphyxiation in oxygen-starved fish, sometimes leading to large die-offs (Möller 1987, Kuperman et al. 2001). Similarly, Robohm et al. (2005) found that experimental exposure to moderate hypoxia greatly accelerated death in lobsters exposed previously to pathogenic bacteria.

Indirect transmission: vector-borne

Indirect transmission of vector-borne pathogens requires three components: a disease agent (parasite), a vector (often an arthropod such as a mosquito), and a host (Fig. 1B). While an increase in nutrient availability could conceivably affect any of these components, published research has often focused on how nutrients affect the vector, as vector abundance strongly affects overall transmission. For example, changes in land use can alter both the type of habitat and the amount of food available for larval mosquitoes, with higher food resources enhancing the production of adults and increasing disease risk (Lawler and Dritz 2005, Munga et al. 2006, Yanoviak et al. 2006). Recent work on malaria offers a particularly compelling example of the relationship between nutrient enrichment and the vector community.

Malaria has once again become a global killer, with an estimated 2 million human deaths per year, most of which involve children under the age of five (World Health Organization 2004). Understanding the ecology of this disease is therefore an important public health priority. Transmission of malaria requires a protist parasite (*Plasmodium* spp.), a mosquito vector, and a primate host. The presence and abundance of mosquito larvae in aquatic habitats and the resulting number of adults capable of malaria transmission are regulated by a variety of ecosystem processes operating at several

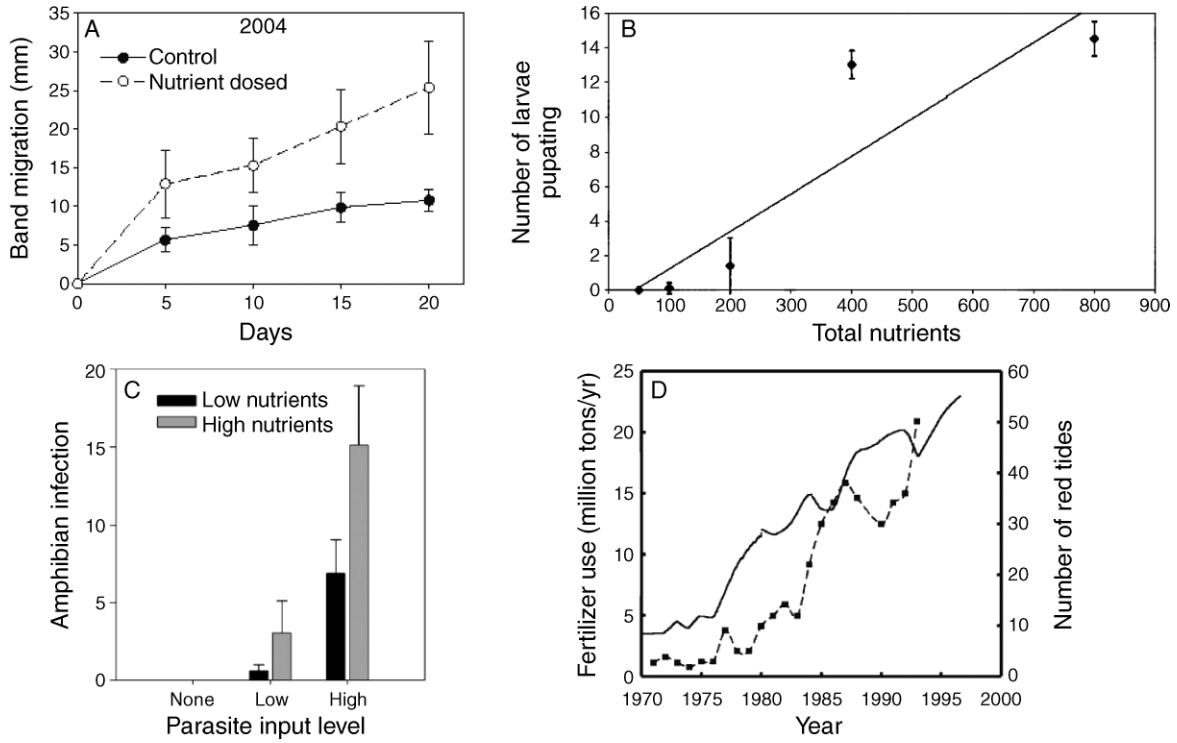

FIG. 2. Select examples of how nutrient enrichment affects different types of disease conditions. (A) Effects of experimental nutrient addition on black band disease in reef-building corals in the Bahamas; (reprinted from Fig. 2 in Voss and Richardson [2006], with permission of Springer Science+Business Media and the authors). (B) Influence of total nutrients (nutrient concentration multiplied by water volume) on survival of larval mosquitoes (*Culex restuans*) (from Reiskind et al. [2004], reprinted with permission of the Entomological Society of America). (C) Experimental nutrient additions (N and P) indirectly increased *Ribeiroia* infection in larval amphibians through changes in infected snail abundance and per capita parasite release (from Johnson et al. [2007], reprinted with permission of the National Academy of Sciences, USA). (D) Trends in nitrogen fertilizer use (solid line) and the number of red tides (dashed line) reported for Chinese coastal waters through the mid-1990s (sources: Smil [2001] for fertilizer use and Zhang [1994] for red tide abundance; from Glibert and Burkholder [2006], reprinted with permission of Springer Science+Business Media and the authors).

organizational levels and spatial/temporal scales. Aquatic plants (both micro- and macrophytes) provide protection from predators and contribute detritus that supports the bacterial community, which, in turn, serves as food for larval mosquitoes. A change in any component within this complex structure may have a substantial impact on the mosquito population and can even lead to a replacement of one species with another. Since not all mosquito species are equally efficient in transmission of malaria, replacement of a less efficient vector with a more efficient one would increase the risk of malaria transmission.

A series of experimental and correlative studies in the malaria-endemic country of Belize have revealed the mechanistic linkages among nutrient enrichment, wetland vegetation, and vector production. Oligotrophic, limestone-based wetlands of the Caribbean are strongly phosphorus (P) limited. In wetland habitats, phosphorus-enriched runoff from agricultural lands and human settlements causes a replacement of sparse macrophyte (rush) vegetation with tall dense macrophytes (cattail), with important consequences for the larval mosquito community (Pope et al. 2005, Rejmankova et al. 2008). Rushes provide typical habitat for *Anopheles albimanus* larvae, whereas cattails represent a typical habitat for *A. vestitipennis*, which is a superior vector of *Plasmodium* to humans (Grieco et al. 2006, 2007). Nutrient-mediated changes in wetland plant communities can thereby lead to the replacement of *A. albimanus* by *A. vestitipennis*, increasing the risk of malaria transmission risk in the region (Achee et al. 2000). Indeed, recent spatial data on malaria incidence showed a weak but positive correlation between the distribution of cattail marshes and number of malaria cases in humans (K. Pope, *unpublished data*).

Other mosquito-vectored diseases may also respond positively to nutrient enrichment. For instance, following its introduction to the United States in 1999, West Nile virus has spread rapidly across North America, adapting to endemic mosquito vectors in the genus *Culex*. Experimental work has demonstrated a link between nutrient enrichment and breeding success of *Culex* mosquitoes. Reiskind and Wilson (2004) found that female *Culex restuans* oviposited more than ten times the number of egg clutches in containers with added nutrients compared to control containers. Larval

survival and the mean size of emerging adults were greater in higher nutrient treatments compared with controls (Fig. 2B; Reiskind et al. 2004). Similarly, in California rice fields, Lawler and Dritz (2005) reported that nutrient enrichment through incorporation of rice straw led to increased production of *Culex tarsalis*, another important vector of West Nile virus (Lawler and Dritz 2005). Given the importance of both *C. restuans* and *C. tarsalis* as vectors for West Nile virus in the United States, these data suggest that nutrient-rich water bodies nearby to human and bird populations could increase disease risk.

For both West Nile virus and malaria, nutrient enrichment enhanced production of the necessary mosquito vector, thereby increasing potential disease risk. However, mosquito species have diverse habitat requirements for breeding and larval development, and it is probable that, in other cases, competent disease vectors will respond negatively to nutrient enrichment, underscoring the need for more experimental studies that address species-specific ecological responses. Moreover, the importance of understanding nutrient–mosquito interactions extends beyond malaria and West Nile virus; other widespread tropical diseases vectored by mosquitoes include dengue fever, yellow fever, vector-borne encephalitis, and Bancroftian filariasis, and almost no studies have addressed the relative risk of these diseases with respect to land use change and nutrient enrichment.

Indirect transmission: complex life cycle

Parasites with complex life cycles require multiple hosts to complete their life cycles and reproduce, frequently alternating between free-living infectious stages (e.g., cercariae, zoospores, miracidia) and endoparasitic forms. These life cycles are common to many helminths, such as trematodes (flatworms), cestodes (tapeworms), nematodes (roundworms), acanthocephalans (spiny-headed worms), as well as some myxozoans and chytridiomycetes. Importantly, because infection must progress sequentially among hosts, the parasites cannot generally reinfect the same hosts, as might occur with a virus living inside its host. As a result, the number of parasites in a host—which determines the risk of pathology—is a function of how many times the host has been independently infected (intensity-dependent pathology). Because complex life cycle parasites are sensitive to changes in the distribution and/or abundance of all required hosts, predicting the effects of environmental change on infections is often challenging (Lafferty and Holt 2003). Depending upon the parasite's specificity, the loss of even one host species can effectively eliminate the parasite from the system, even when the remaining hosts persist. Field data suggest that many complex life cycle parasites (especially trematodes) increase in abundance with low to moderate levels of eutrophication (Lafferty 1997, Johnson and Carpenter 2008). This often occurs because of (1) increases in intermediate host density following nutrient-mediated changes in primary and secondary production and (2) an increased ability of intermediate hosts to withstand infection under nutrient-rich conditions (i.e., decrease in parasite-induced mortality). Many of these parasites depend on invertebrate intermediate hosts, such as snails, worms and crustaceans, which can respond quickly and strongly to nutrient inputs (Zander and Reimer 2002, Johnson and Carpenter 2008). The resulting increase in infection can enhance disease and pathology in some host species.

Because of the difficulties inherent in manipulating complex life cycle parasites, experimental research involving more than one host species or parasite stage in the life cycle are rare. However, a recent combination of field surveys and experiments suggest a link between aquatic eutrophication and infection by the digenetic trematode *Ribeiroia ondatrae*. *Ribeiroia* uses freshwater snails as first intermediate hosts, larval amphibians as second intermediate hosts, and birds as definitive hosts (Johnson et al. 2004). In amphibians, *Ribeiroia* infection can cause high frequencies (>50%) of severe limb malformations, including missing, misshapen, and extra limbs (Fig. 1C; Sessions and Ruth 1990, Johnson et al. 1999, 2002). Such deformities, which are considered a major detriment to amphibian survival, are widely suspected to have increased in recent decades (Johnson et al. 2003), but the reasons for the apparent increase remain speculative. Previous field surveys suggested a link between wetlands with deformed amphibians and nutrient runoff from agricultural fertilizers, cattle grazing, and urbanization (Johnson et al. 2002, Johnson and Chase 2004). Johnson and Chase (2004) hypothesized that, by stimulating algae growth in wetland habitats, nutrient runoff enhanced the population of herbivorous snails, providing greater intermediate host availability for *Ribeiroia*.

Johnson et al. (2007) tested this hypothesis by manipulating nutrient inputs into a series of outdoor mesocosms stocked with snails, larval amphibians, and parasites. Eutrophication indirectly increased infection through changes in the aquatic food web. Experimentally elevated nutrient levels led to an increase in periphytic algal growth, which enhanced growth and reproduction of snail hosts (*Planorbella trivolvis*). Higher snail densities increased the likelihood that hatching parasites (miracidia) successfully found a snail host, thereby leading to a larger number of infected snails. Infected snails from the high-nutrient condition also produced, on average, twice as many parasites per 24 hours relative to snails in the low-nutrient treatment, likely as a result of higher food (algae) availability and lower mortality (Johnson et al. 2007). The combination of more infected snails and a greater per snail release of parasites led to a three- to fivefold increase in amphibian infection (Fig. 2C), which is a direct predictor of disease risk (Johnson et al. 2007). Other experiments have demonstrated similar increases in parasite production in

TABLE 1. Overview of human illnesses and associated symptoms caused by harmful algae.

Illness	Major vector	Symptoms
Amnesic shellfish poisoning	domoic acid from *Pseudo-nitzschia* sp. in shellfish	short-term memory loss; vomiting, cramps
Diarrhetic shellfish poisoning	okadaic acid from *Dinophysis* sp. in shellfish	diarrhea, vomiting, cramping
Neurotoxic shellfish poisoning	brevetoxin from *Karenia* sp. in shellfish, aerosolized toxins	nausea, diarrhea, respiratory distress, eye irritation
Paralytic shellfish poisoning	saxitoxin from *Alexandrium* sp. and other species in shellfish	numbness around lips and mouth, respiratory paralysis, death
Cyanotoxin poisoning	microcystins and other toxins from *Microcystis* and other cyanobacteria in water	skin irritation, respiratory irritation, tumor promotion, liver cancer, failure
Ciguatera fish poisoning	gambiertoxins/ciguatoxins from *Gambierdiscus* sp. that accumulate in reef fish	gastrointestinal distress, numbness around mouth, reversal of hot and cold sensations, hypotension

response to food quantity and quality (Keas and Esch 1997, Sandland and Minchella 2003).

Results from various unplanned "natural" experiments further support links between nutrient enrichment and elevated infection by complex life cycle parasites. For example, Coyner et al. (2003) found a strong association between sewage treatment runoff and infection by the nematode *Eustrongylides ignotus*, which can increase nestling mortality in wading birds. Inputs of N and P were positively correlated with the density of first intermediate hosts (a tubificid worm) and with infection in second intermediate hosts (mosquitofish). Following diversion of the sewage and a corresponding reduction in nutrient concentrations, infections in mosquitofish declined from 54% in 1990 to 0% in 1998 (Coyner et al. 2003; see also Weisberg et al. 1986 and Muzzall 1999 for additional examples). Similarly, sewage inputs into Gull Lake, Michigan, were linked to a fourfold increase in infection of mayflies by the trematode *Crepidostomum cooperi* (Marcogliese et al. 1990). Deep-water hypoxia caused by nutrient-mediated eutrophication of the lake altered the distribution of oxygen-sensitive mayflies, forcing them into shallower water and into closer proximity with sphaeriid clams, which are the first intermediate hosts of *Crepidostomum*. After the lake's sewage system was improved in 1984, infection prevalence in mayflies declined by 70% within five years (Marcogliese et al. 1990), presumably owing to the movement of mayflies into deeper water.

Noninfectious diseases

Finally, environmental nutrient enrichment can influence levels of noninfectious diseases. Noninfectious disease represents a broad category of health conditions ranging from cancer to hypoxia; etiological factors can include chemical exposure, temperature, oxygen availability, and biotoxins produced by algae, plants, fungi, and bacteria. In aquatic systems, the most common noninfectious condition associated with environmental nutrient enrichment is hypoxia, which can result from nutrient-induced eutrophication. Excess fertilizer runoff into rivers and coastal systems has been linked to expanding "dead zones" in the Earth's oceans, with serious consequences for fisheries production and ecosystem process (see Diaz and Rosenberg 2008). Unlike with infectious diseases, the dynamics of "pathogens" responsible for noninfectious diseases may have limited or no dependency on the dynamics of the species experiencing pathology. Some allergic diseases, for example, have exhibited substantial increases in recent decades, and currently affect millions of peoples in developed countries (e.g., Sly 1999). High pollen counts cause hayfever, allergenic rhinitis, and allergenic asthma, and for those already suffering from other pulmonary ailments, these pollen-induced responses can be especially serious (National Institutes of Health 1993). Pollen counts have increased in multiple highly populated regions (e.g., Clot 2003, Spieksma et al. 2003), for reasons that may be related climate change, shifts in species composition, and increased atmospheric CO_2 and environmental nutrient enrichment (Wayne et al. 2002). Pollen production in many weedy species frequently increases following nutrient enrichment (Lau et al. 1995). For example, N fertilization caused substantial increases in pollen production of ragweed, one of the most problematic sources of allergenic pollen (Townsend et al. 2003), and recent evidence suggests that pollen grains in polluted atmospheres—to which reactive N is an important contributor—display an altered surface structure and chemistry that led to enhanced allergenicity (Majd et al. 2004).

Increased inputs of nutrients into aquatic ecosystems can also cause pronounced changes in harmful algal blooms (HABs), which are proliferations of algae and cyanobacteria that can cause massive fish kills, marine mammal kills, contaminate seafood or drinking water with toxins, or alter ecosystems in ways that are detrimental (Glibert and Pitcher 2001, Backer and McGillicuddy 2006). Algae produce a wide range of toxins (Table 1) which may accumulate in predators and organisms higher in the food web, ultimately affecting humans when seafood is consumed, when toxin-laden aerosols are inhaled, or when contaminated water is consumed. Toxic syndromes include paralytic, amnesic, diarrheic, neurotoxic, and cyanotoxic shellfish poison-

ing, among others. Evidence is also mounting that HABs can elicit subtle effects on fish and wildlife (Fig. 1D). For example, domoic acid, a neurotoxin produced by the diatom *Pseudo-nitzschia* spp., induces seizure and memory loss in laboratory animals (Tiedeken and Ramsdell 2007). Toxins from dinoflagellates can cause reproductive dysfunction in whales (e.g., Doucette et al. 2006), and embryonic deformities in oysters (Glibert et al. 2007*a*). In addition, aerosolized red tide toxins can exacerbate respiratory symptoms among asthmatics (Milian et al. 2007). Exposure to peptide toxins produced by cyanobacteria have also been suggested as contributing to increased rates of liver cancer in populations consuming water from nutrient rich lakes (Grosse et al. 2006).

Throughout many parts of the world, marine and freshwater HABs are increasing in geographic extent, in duration of occurrences, in numbers of toxins and toxic species identified, in numbers of fisheries affected, and in economic costs (Anderson 1989, Hallegraeff 1993, Anderson et al. 2002, Glibert et al. 2005). While many factors likely influence these increases, nutrient runoff in freshwater and marine ecosystems is likely an important contributor (National Research Council 2000, V. H. Smith et al. 2006). For example, in the Gulf of Mexico, the sedimentary record of potentially toxic diatoms (*Pseudo-nitzschia* spp.) has increased in parallel with increased nitrate loading over the past several decades (Turner and Rabalais 1991, Parson et al. 2002). Similarly, blooms of toxic HABs off the coast of China have expanded in recent years in geographic extent (square kilometers to tens of square kilometers), duration (days to months), and in harmful impacts. These changes are strongly correlated to increases in fertilizer use over the past two decades (Fig. 2D; Anderson et al. 2002, Zhou et al. 2003, Li et al. 2009). Moreover, the Baltic Sea, Aegan Sea, Northern Adriatic, and Black Seas have all experienced increased HAB occurrences in relation to nutrient loading (e.g., Larsson et al. 1985, Bodeanu 1993, Moncheva et al. 2001, Heisler et al. 2008).

Changes in the type of nutrients or their relative proportions can also influence the frequency and severity of HABs. Off the coast of Germany, time series analysis of nutrient concentrations over several decades has revealed that a fourfold increase in the ratio of nitrogen: silicate (N:Si) coincided with an increase in the HAB *Phaeocystis* (Radach et al. 1990). The specific forms of available N and P, particularly with respect to organic nutrients, also play an important role in the nutrition of many HABs (Glibert and Legrand 2006). For example, blooms of the HAB species *Aureococcus anophagefferens*, which have been linked to reductions in shellfish reproduction (Tracey 1988, Gallagher et al. 1989), correlate with increases in organic compared to inorganic loading (LaRoche et al. 1997, Glibert et al. 2007*b*). Other work has shown that nutrient availability or composition may even alter the toxin content of individual species without altering their total abundance. For the diatom *Pseudo-nitzschia australis*, the form of N influences both the growth rate as well as the toxin content. Cells grown on urea, for example, had higher levels of the toxin, domoic acid, relative to those grown on nitrate or ammonium (Armstrong-Howard et al. 2007). Similarly, the toxin content of urea-grown cells of the dinoflagellate *Alexandrium tamarense*, which causes paralytic shellfish poisoning, was significantly higher than cells grown on nitrate (Leong et al. 2004).

Summary of nutrients and disease

While the effects of nutrients vary with enrichment levels, the types of host and pathogen, and the characteristics of ecosystems, the above examples illustrate that eutrophication can have important indirect effects on human and wildlife diseases. Recent experiments have shed new light on the mechanisms underpinning the observed links between nutrient enrichment and disease. Depending on the mode of transmission, these mechanisms may affect the pathogen, the host, or their interaction, and include changes in the density or distribution of suitable hosts/vectors, alterations in physical habitat, increases in parasite production, selection for more virulent or toxic pathogens, and the provisioning of pathogens with supplemental resources.

It is important to note that the effects of nutrient enrichment vary among pathogens and do not always elicit higher disease risk; exacerbation of a broad suite of diseases does appear possible, but the decline or elimination of others is also possible. Moreover, increases in parasite species richness or abundance do not always reflect an increase in disease risk, as disease is also a function of the host's response to infection. Current evidence suggests that nutrient inputs will favor generalist or opportunistic pathogens with direct or simple life cycles. Importantly, however, because these pathogens are generalists with little dependency on the dynamics of any one host species, they may cause sustained epidemics or host extirpations without suffering a reduction in transmission. Noninfectious diseases such as HABs, pollen allergies, and avian botulism represent the extreme position in this gradient in that the dynamics of the "pathogen" (e.g., a harmful alga) are completely divorced from the species experiencing pathology. Thus, declines in "hosts" do not necessarily lead to declines in the pathogen. Parasites with complex life cycles that depend on multiple, interacting species within a community to complete transmission are often more sensitive to environmental disturbance, as losses in any one host can reduce or eliminate the infection cycle (see Hudson et al. 2006). However, if intermediate hosts are tolerant of (or thrive under) elevated nutrient conditions, such as some hypoxia-tolerant snails and tubificid worms, infection and pathology can respond positively to inputs of N and P. Such situations can lead to increased disease within other hosts in the life cycle (e.g., amphibian malformations).

Although many examples discussed here focus on wildlife diseases, we argue that the same patterns, interactions and controls are relevant for understanding the effects of nutrient enrichment on many zoonotic human diseases. For example, as discussed for malaria and WNV, nutrient runoff into freshwater habitats can increase mosquito oviposition, larval growth rate, and alter the vector community to favor disease transmission in humans. While vector abundance is an important predictor of disease transmission, more work is needed to definitively link nutrient inputs with infection incidence in humans from endemic areas. Similarly, in addition to affecting wildlife, HABs can cause significant disease in humans and costly economic losses. Collectively, there are >60 000 incidents of human exposure to algal toxins annually in the USA, resulting in ~6500 deaths (Hoagland et al. 2002). Costs associated with public health, shellfish recalls, and decreased tourism approach US$50 million annually. (Hubbard et al. 2004). Finally, complex life cycle parasites of medical and veterinary importance may be influenced by changing nutrient levels. In livestock, the ruminant liver fluke (*Fasciola hepatica*) has caused more than US$2 billion in livestock industry losses (Boray and Munro 1998). Infected snail hosts respond strongly to food quality and quantity, altering the output of infectious parasites by nearly sevenfold over starved snails (Kendall 1949). Infections by some schistosomes (human blood flukes), which continue to afflict 200 million people in Africa, South America, and Asia, have also been associated with increased algal growth and organic nitrogen in wetland habitats (Garcia 1972). Considering the strong response of *Ribeiroia* infection to elevated nutrient conditions and the ecological parallels between the life cycles of *Ribeiroia* and *Schistosoma*, these results may have important epidemiological implications.

A look to the future

Many diseases that affect both humans and wildlife have increased in incidence or severity in recent decades, frequently resulting from changes in the ecological interactions among a pathogen, its hosts, and the environment in which they co-occur (Daszak et al. 2000). The importance of incorporating ecology into the study of parasites and emerging diseases has been emphasized with increasing urgency in recent years (National Research Council 2001, Millennium Ecosystem Assessment 2005). In their synthesis of the Grand Challenges in Environmental Sciences, the National Research Council (2001) listed infectious disease as one of the eight most pressing environmental issues, advocating a "systems-level" approach to understanding disease emergence. Nevertheless, the ecology of zoonotic diseases is often remarkably complex, rendering predictions of their responses to anthropogenic change notably difficult (Daszak et al. 2000, Patz et al. 2004). Such challenges are exacerbated by the fact that human-induced changes to the environment rarely occur in isolation; for example, nutrient loading to surface waters is nearly always combined with substantial land use changes in the surrounding watersheds, with concomitant shifts in species abundances. Thus, parsing out the potential effects of a single factor such as nutrient loading is often a tall order, one which typically requires controlled, mechanistic studies to begin the construction of more prognostic models. For example, limited evidence has linked cholera to coastal eutrophication and seasonal plankton blooms. The bacterium responsible, *Vibrio cholerae*, can become concentrated in fishes, shellfishes, and especially in biofilms on the surface of crustacean zooplankton (Epstein 1993, Colwell 1996). However, patterns of human behavior, climate, and ocean circulation also influence infection dynamics, making it difficult to identify the relative importance of nutrient inputs (Colwell and Huq 2001, Rodo et al. 2002, Cottingham et al. 2003).

We have summarized a few experimental studies that focused on nutrient effects, but such experiments remain rare and are thus a priority in advancing our ability to forecast the future of both human and wildlife infectious disease (McKenzie and Townsend 2007, Johnson and Carpenter 2008). Based on the evidence to date, we expect that environmental nutrient enrichment will remain an important factor in the etiology of human and wildlife diseases for decades to come. Although awareness and technological innovations have slowed the problem in some regions, ongoing patterns of atmospheric deposition of reactive nitrogen, losses of wetland and riparian areas, increasing use of fertilizers in developing nations, growing livestock populations, and an increasing human population all suggest that eutrophication will continue to expand (Millennium Ecosystem Assessment 2005). Moreover, even if the contributing drivers are reversed, eutrophication tends to be a persistent condition because of feedback loops and the internal recycling of nutrients (e.g., Carpenter 2005, V. H. Smith et al. 2006).

The disease-related outcomes of nutrient enrichment are likely to exhibit pronounced regional variation. Our growing understanding of spatial and temporal patterns in both emerging infectious diseases (e.g., Jones et al. 2008) and in rapidly changing nutrient cycles (Galloway et al. 2004) allows a focus on regionally targeted efforts that may pose the greatest risks. For example, in heavily industrialized regions such as the United States, Europe, and parts of Asia, anthropogenic inputs of N and P to the environment have been exceptionally high for decades, resulting in ecosystems already demonstrating significant change in response to such disturbance. From the perspective of human infectious diseases, the overall risk of nutrient–disease interactions may be lower in these temperate regions simply because the diversity of infectious diseases responsive to nutrients is lower than that in tropical regions (e.g., Guernier et al. 2004). However, a warming climate and global transport systems continue to increase the potential for a suite of

vector transmitted diseases to expand into higher latitude zones (Patz and Olson 2006, Smith et al. 2007). Noninfectious diseases, including HABs and pollen-based allergies, are already intensifying in temperate regions with ongoing nutrient deposition. In the short term, some of the most pressing threats from elevated nutrients may be to wildlife: in heavily industrialized temperate regions, many critical habitats are already greatly reduced in size and subject to a suite of other disturbances from invasive species to acidic precipitation; here, increased disease prevalence from nutrient loading may further complicate conservation efforts.

Conservation challenges are also rising in tropical regions, which in recent decades have exhibited the most dramatic increases in land clearing and industrialization. Following the precedents observed in higher latitudes, such changes are causing rapid increases in the loading of excess N and P to the environment; over the next 50 years, the tropical latitudes will see the most significant increases in fertilizer use and atmospheric deposition of N (Galloway et al. 2004, Dentener 2006). At the same time, these regions support the highest diversity of human pathogens with the potential to respond to nutrient enrichment (see Guernier et al. 2004, McKenzie and Townsend 2007). Given this high degree of overlap in tropical regions, the potential for nutrients to affect patterns of human disease in the future is predicted to be very high (McKenzie and Townsend 2007). Some of the major plagues of low latitudes, such as malaria and schistosomiasis, show worrisome signs of elevated risk in more eutrophic conditions, suggesting that forecasted increases in environmental nutrient enrichment could incur increases in human disease risk. Taken as a whole, the intersection of a high diversity of human parasitic and infectious diseases with rapid changes in the environment, including those to nutrient cycles, suggests that some of the greatest nutrient-driven risks to humans from infectious diseases are likely to be in low latitude countries. In a recent analysis of global trends in emerging infectious diseases, Jones et al. (2008) emphasized both the risks and challenges of the tropics by pointing out that not only are such zones a likely hotspot for emerging diseases of humans and wildlife, but are also typified by poor heath infrastructures and limited reporting of disease outbreaks.

Thus, while a better understanding of links between nutrients and disease is needed on a global basis, we emphasize its particular importance in tropical and subtropical Africa, Asia, and Latin America. All three continents contain regions experiencing explosive growth and development, while still contending with rampant poverty, widespread environmental damage, and a huge disease burden. Without question, increases in fertilizer application and food production in these regions will likely have substantially positive effects on human health by reducing malnutrition and improving quality of life. However, a significant concern lies with the unintended side effects of such efforts: will increases in the alteration of environmental nutrient concentrations incur and increased risk of disease? Ecologists, epidemiologists, and agronomists are collectively challenged to determine (1) under what conditions nutrient enrichment will enhance disease risk and (2) through what strategies agricultural intensification can be accompanied by careful management of disease-related outcomes.

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