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Abstract: Background: Every day, billions of people - especially those living in poverty - are exposed to infectious pathogens in the environment and are at risk of contracting 'environmentally mediated' infections: those with environmental reservoirs that affect disease persistence and control. The complex ecology of environmental pathogens creates a global health problem not easily solved with medical treatment alone.

Methods: Here, we quantified the global disease burden caused by environmentally mediated infections and used a structural equation modeling approach to explore correlated factors at the global scale.

Findings: We found that 80% of pathogen species known to infect humans are environmentally mediated, causing about 40% of today's burden of infectious disease (global loss of 130 million years of healthy life annually). More than 91% of environmentally mediated burden occurs in tropical countries, and the poorest countries carry the highest burdens across all latitudes. We found weak or absent effects of biodiversity or agricultural land use at the global scale. In contrast, the strongest proximate indicator of environmentally mediated infectious disease burden is rural poor livelihoods. Political stability and wealth are associated with improved sanitation, better health care, and lower proportions of rural poor people, indirectly resulting in lower burdens of environmentally mediated infections.

Interpretation: The high and uneven burden of environmentally mediated infections highlights the need for innovative social and ecological interventions to complement biomedical advances in the pursuit of global health and sustainability goals.

Funding: B&M Gates Foundation, National Institutes of Health, National Science Foundation, Alfred P. Sloan Foundation, Stanford University, and the DARPA PREEMPT program.

More than one third of global human infectious disease burden is environmentally mediated, with disproportionate effects in rural poor areas

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Summary

Background: Every day, billions of people – especially those living in poverty – are exposed to infectious pathogens in the environment and are at risk of contracting 'environmentally mediated' infections: those with environmental reservoirs that affect disease persistence and control. The complex ecology of environmental pathogens creates a global health problem not easily solved with medical treatment alone.

Methods: Here, we quantified the current global disease burden caused by environmentally mediated infections and used a structural equation modeling approach to explore correlated factors across all countries of the world.

Findings: We found that 80% of pathogen species known to infect humans are environmentally mediated, causing about 40% of today's burden of infectious disease (global loss of 130 million years of healthy life annually). More than 91% of environmentally mediated burden occurs in tropical countries, and the poorest countries carry the highest burdens across

all latitudes. We found weak or absent effects of biodiversity or agricultural land use at the global scale. In contrast, the strongest proximate indicator of environmentally mediated infectious disease burden is rural poor livelihoods. Political stability and wealth are associated with improved sanitation, better health care, and lower proportions of rural poor people, indirectly resulting in lower burdens of environmentally mediated infections.

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Research in context

Evidence before this study

The World Health Organization (WHO) has published some estimates of the global burden of disease caused by environmental and occupational risks (termed the Environmental Burden of Disease) but these previous efforts have focused largely on environmental burden of non-communicable disease (with a minor sub-focus on a subset of communicable diseases such as diarrhea).

Added value of this study

This work not only updates estimates by referencing 2015 WHO global health estimates data, but we also uniquely explore, in depth, the infectious disease burden caused by all human pathogens that involve a substantial biotic or abiotic environmental reservoir. We categorize (as

environmentally mediated or direct person-to-person transmitted) all of the classifiable pathogens tracked by the WHO and a random subset of all known pathogens of humans. This work offers an updated summary of the global burden of environmentally mediated human infectious disease as well as a global analysis of the complex factors associated with higher burdens, which we find to be mostly associated directly or indirectly with rural poor livelihoods that put people in contact with pathogenic landscapes.

Implications of all the available evidence

Here we compliment the current understanding of environmentally mediated human disease by exploring infectious causes to a greater depth than previously reported. We provide empirical evidence to support a stronger focus on interrupting environmental transmission and investing in sustainable development in parallel with patient care to address the large and uneven global burden of environmentally mediated human infectious diseases.

Introduction

For most people living in modern, high-income countries, it is easy to forget about human pathogens that are transmitted, not via direct human contact, but through contact with contaminated environments. Yet, some of these 'environmentally mediated' infections create a significant global burden of disease, such as malaria and diarrheal diseases. Others are rare, but capture attention because of their dramatic and deadly effects, including valley fever (*Coccidiodes immitis*), caused by a fungus carried on dust in the wind [1], the brain-eating amoebae (*Naeglaria fowleri*) contracted through swimming in lakes [2], and Nipah virus, contracted by drinking tree sap contaminated by the urine of fruit bats [3]. As these examples illustrate, environmental transmission pathways are diverse and can involve a number of environmental reservoirs (e.g., fomites, soil, water or surfaces contaminated with infective stages), vectors (e.g., mosquitoes), food (e.g., by contamination or trophic transmission), or

non-human hosts (e.g., rabies or Nipah virus from bats; Figure 1, Table 1). Physicians can successfully treat infected patients, but when the source of infection is environmental, such treatments have limited ability to prevent new infections. In order to design effective control, we must understand the pathways by which infectious agents come to infect people.

We examine the diversity and abundance of all human pathogens, describe their transmission pathways, and quantify the global burden of disease they cause. For those infectious diseases spread via environmentally mediated transmission pathways, we examine how and why this burden is unevenly distributed geographically, when compared with direct-contact transmitted diseases (DTDs) of humans, better known in developed countries. We define DTDs as those infectious diseases caused by human pathogens that are transmitted primarily by direct-contact transmission from person-to-person (although vertical transmission and autoinfection are additional pathways for some DTDs; Figure 1). We assembled a dataset characterizing the main and alternative transmission pathways of the c.a. 560 World Health Organization (WHO) tracked pathogens [4], as well as a random subset of a broader list of all >1400 documented human pathogens to examine whether the WHO-tracked pathogens accurately represent patterns among all human pathogens [5]. In the following sections we: (*i*) elaborate on traits of environmentally mediated pathogens, (*ii*) quantify the diversity, distribution, and global burden they cause, (*iii*) use a structural equation modeling approach to examine the direct and indirect drivers of disease burden, and (*iv*) outline recent challenges and advances in developing creative solutions to interrupt environmentally mediated infectious diseases through understanding their ecological and social contexts. Though many environmentally mediated pathogen species collectively pose a major challenge to global health, they are rarely studied as a single category; here, we begin to remedy this by reporting some important synthetic insights. In contrast to the biomedical focus for controlling direct-contact transmitted diseases, socio-environmental factors may be key for controlling environmentally mediated diseases.

Environmentally mediated diseases are diverse and distinct from direct-contact transmitted diseases of humans

While direct-contact transmitted infectious disease is spread primarily by human contact (e.g., HIV, measles, human influenza, human tuberculosis – 'DTDs'), 'environmentally mediated' infectious agents are transmitted primarily via contact with biotic or abiotic reservoirs in the environment (Figure 1). Sometimes these environmental reservoirs are short-lived, but in many cases pathogens persist in their environmental reservoirs for long periods of time (e.g., Lyme disease, tetanus, coccidiomycosis, anthrax). Where environmental reservoirs exist, medical treatment of sick patients can alleviate disease burden, but in most cases does not prevent reinfection from environmental sources. For instance, the parasitic worm that causes river blindness (onchocerciasis) is transmitted to humans by black fly vectors, a biotic environmental reservoir. Treating infected people with ivermectin can eliminate the parasitic larvae inside them, but treatment must be repeated every 6–12 months due to frequent re-infection from new black fly bites [6, 7]. Complementing medical treatment with aerial spraying for black fly vectors for nearly twenty years, before switching to biannual ivermectin treatment, was key in achieving dramatic success in controlling onchocerciasis across Africa [8]. Classical biomedical disease control like drugs and vaccines might not work, alone, to reduce transmission of environmentally mediated diseases. This is especially true when infected people are sinks for the pathogen (e.g. Lyme disease), and therefore are not involved in onward transmission. In such cases, environmental and ecological complexities pose a challenge to public health.

Many pathogens have multiple pathways by which they infect their hosts. For example, cholera can pass directly by human-to-human contact, fecal–orally, or through consumption of contaminated water or food (Figure 1). Ebola can spill over from environmental reservoirs, but then turn into full-blown, direct-contact transmitted, human-to-human epidemics [9]. Due to this

complexity, we define a pathogenic species' transmission by characterizing the most common pathway that moves an infectious agent from people to people or the environment to people. In this way, we attempt to identify the dominant pathways that would need to be interrupted to lower prevalence or persistence of disease in human populations. Narrower uses of the term 'environmental transmission' (which sometimes signify only those pathogens that pass through abiotic reservoirs like water or soil) can obscure the ubiquity and diversity of environmentally mediated pathogens, which can lead to overlooked details required to inform control strategies.

Environmentally mediated pathogens fall along a continuum from brief to indefinite environmental persistence (Figure 1). Because this continuum is broad, we further divide environmentally mediated pathogens by characterizing the sources and sinks of the transmission pathways: e.g. lifecycles from infected people through environmental pathways to other people (e.g., many human diarrheal pathogens and schistosomes, Figure 1c), versus those that infect people via unidirectional 'spillover' from the environment, with people acting as sinks, or dead end hosts for the pathogen (e.g., rabies virus, *Toxoplasma*, Figure 1d). Sapronoses are a subset of unidirectional spillover agents that can persist and reproduce in the environment without any host, typically obtaining their nutrition by consuming detritus or other organic matter [10]. Sapronoses are especially challenging to control in the environment, as these infectious agents can be free-living and ubiquitous (e.g. tetanus). Because sapronoses are only opportunistically parasitic, they only rarely cause severe disease, but a sapronotic life history strategy nevertheless remains a common strategy among many human pathogens (Table 1), including almost all infectious fungi of humans (e.g., coccidiomycosis, histoplasmosis), about one-third of bacterial pathogens (e.g., mellioidosis), and some parasitic agents (e.g., strongyloidosis) [10].

Environmentally mediated infections are sometimes, but not always, zoonoses. Zoonoses are defined as infectious diseases that are naturally transmissible between humans and non-human *vertebrate* hosts, but many environmentally mediated pathogens do not require non-human vertebrates to pass to humans (e.g. human schistosomiasis, faciparum malaria, polio, and many diarrheal pathogens). Conversely, zoonotic diseases are not all environmentally mediated; zoonoses are not environmentally mediated when non-human vertebrates are incidental, rather than instrumental, to the cycle of infection in humans (sometimes called 'reverse zoonoses' or 'anthroponoses', e.g., measles in great apes), or when non-human vertebrate infections were historically, but are not currently, relevant to the spread of human disease (e.g., HIV). However, a common strategy among many zoonotic diseases involves infecting both humans and other vertebrate animals through the same environmentally mediated pathways (e.g. food-borne, water-borne, vector-borne, fomites, Table 1, Figure 1), meaning that understanding environmental pathways is a critical link to designing effective control for many zoonotic and non-zoonotic diseases, alike.

How common are environmentally mediated human infectious diseases?

We found that at least 80% (455 out of 560) of human pathogens that cause substantial human disease (and are therefore tracked by the WHO) use some form of environmentally-mediated transmission as their primary pathway to infecting humans (Table 1, Figure 1, Table S1). To address for potential biases that result from the selection of common vector-borne or food-borne pathogens that the WHO tracks, we also examined the transmission strategies of a random subsample of 250 diseases from a broader set of 1415 described human pathogen species compiled by Taylor et al. in 2001 [5], that is dominated by rare opportunistic pathogens (Table 1). Both datasets corroborate the estimate that ~80% of human infectious agents exhibit environmentally mediated transmission (Table 1).

What is their burden and geographical distribution?

To quantify the global burden caused by environmentally mediated infections, we examined the WHO Global Health Estimates data for 2015 [4]. This dataset measures disease burden in all countries around the world in Disability Adjusted Life Years (DALYs), a standardized measure of the impact of disease on human wellbeing. DALYs are calculated as "years of life lost due to mortality" summed with "years of healthy life lost due to disability" [11, 12].

We summed estimated DALYs for all human pathogens in the WHO database that were classifiable as environmentally mediated or not, and we found that an estimated 40% of the global infectious disease burden is due to environmentally mediated infections (Table 1). Among these, malaria and environmentally transmitted diarrheal diseases (e.g., shigellosis, cholera) collectively carried the highest burdens of DALYs in 2015, followed by environmentally mediated 'neglected tropical diseases' (e.g., schistosomiasis, Chagas disease, leishmaniasis) and fungal and parasitic meningeal infections, Table S1. While this is a lower total burden than DTDs, environmentally mediated transmission pathways cause a substantial global infectious disease burden, at nearly 130 million years of life lost annually to death and disability (Table 1).

Environmentally mediated human infectious diseases follow a strong latitudinal gradient: burdens decline away from the equator, such that the tropics account for 91.5% of the total global burden of environmentally mediated human infectious diseases, and the poorest countries carry the highest proportions of disease across all latitudes, especially in Africa (Figures 2,3).

What drives the high and uneven global burden of environmentally mediated human infectious diseases?

Hypothesized drivers of disease burden are usually either human-centric (population density, wealth, health care access), and/or ecological (climate, biodiversity, or proxies thereof) [13-15]. We hypothesized that perhaps their environmental affiliations predisposed environmentally mediated human infectious diseases to be more sensitive to ecological and climatic shifts along latitudinal gradients, such as shifts in biodiversity, land conversion to agriculture, or temperature, compared to direct-contact transmitted human diseases.

We used a partial least-squares structural equation modeling (henceforth referred to as PLS-SEM path modeling) framework to explore this hypothesis. In particular, we assessed which social, economic, environmental, and ecological indicators most strongly predicted environmentally mediated and direct-contact transmitted human disease burdens across the globe. PLS-SEM path modeling is a statistical method for partitioning complex covariance relationships that is particularly suited to disentangling complex webs of predictors and outcomes that are all highly correlated (see Supplemental methods). Here, we compared many plausible drivers and consequences of the country-level burden estimates for environmentally and directly transmitted pathogens of humans from the World Health Organization in 2015 (summarized in Table S2) in the software package 'SmartPLS' (SmartPLS GmbH, Ahornstr. 54, 25474 Boenningstedt, Germany). We compiled environmental and social variables at the country scale from various public data repositories (Table S3), including: political stability, land area in agriculture, wealth, access to improved sanitation, fertility, 'rurality' (% population living rurally, which is by World Bank definition = 1 – % of the population living in urban areas), biodiversity (area-adjusted mammal, bird, and amphibian species richness, plus % forested area and % protected area in each country) [16], access to health care, average lifespan, malnutrition, food production, altitude, age-distribution, and climate (Table S3). We first assembled a full model (Table S4) and then, to reduce over-fitting, used bootstrapped p-values to retain only the significant correlations, including marginally significant direct correlations (p

<0.1), in the final model. (The p<0.1 links can be ignored if a cutoff of p<0.05 is preferred, but were included for reference in Figure 4.)

We found that, counter to our hypothesis, environmental variables were only weakly correlated with environmentally mediated disease burdens. Biodiversity and land area in agriculture (% of total land area) were correlated with weak increases in burden of environmentally mediated diseases in the PLS-SEM path models (Table 3, Figure 4, Table S5). In contrast, human-centric variables, in particular, rural poor livelihood, were the variables most strongly directly associated with burden of environmentally mediated human infectious diseases (i.e. with largest relative effect size, Figure 4). This finding was robust to various iterations such as including or removing amphibian biodiversity and including or removing area of terrestrial or marine protected areas as components of the latent variable 'biodiversity'; and to inclusion or exclusion of additional variables like agricultural yield in terms of KCals/person and/or malnutrition as % of the population malnourished (Table S2). Strong latitudinal effects were mediated indirectly through the tropical distribution of rural poor livelihoods (as measured by: the proportion of that country's population living in rural areas, lack of access to improved sanitation, and the average fertility rate – the latter of which is highly correlated with the other two, Table S2). This may be due to increased exposure to environmental pathogens in the course of a rural, subsistence lifestyle and supports the 'poverty trap'[15, 17] hypothesis, which posits that poor people become stuck in a self-reinforcing cycle of poverty and disease. The toll of environmentally mediated pathogens is highest where humans rely on and interact frequently with parasite-infested ecosystems. In addition, political stability, wealth, and health care effects were not directly correlated with either environmentally mediated or direct-contact transmitted disease burdens. However, because political stability was correlated with wealth and wealth leads to improved access to sanitation, clean water, health care, health prevention, and other factors influencing rural, poor livelihoods (Table 3, Figure 4, Table S3), these social and

economic predictors remain important indirect variables to consider. Still, direct investment in health care or development will need specific allocation to the rural poor populations that are most vulnerable (Figure 4) in order to impact environmentally mediated infections.

Although total environmentally mediated infectious disease *burdens* were not strongly associated with biodiversity or land use, environmentally mediated disease *diversity* was affected by latitudinal and climatic factors, and range limits were more evident for the environmentally mediated human infectious diseases compared to the direct-contact transmitted diseases (Figure S1). This suggests that, not surprisingly, diseases for which humans serve as the main reservoirs (DTDs) are less restricted by climatic factors, and less subject to latitudinal gradients in biodiversity, than those reliant on non-human hosts (especially invertebrates and ectotherms) or abiotic reservoirs [18]. Finer (sub-country scale) data might reveal tighter associations of environmentally mediated disease burdens with climatic, biodiversity, or land use predictors.

A call for creative solutions focusing on socio-environmental interventions

Controlling environmentally mediated pathogens, in contrast to directly transmitted human pathogens, is harder in some ways and easier in others. For example, on the one hand, for environmentally mediated infectious diseases, treatment of people is often plagued by reinfection from environmental reservoirs. On the other hand, simple socio-environmental interventions that are not practical for directly transmitted person-to-person infections, such as provision of water filters, may be available for environmentally mediated diseases. In other words, environmental transmission pathways are complex but allow for environmental 'levers' – interventions that interrupt environmental transmission – that may complement conventional medical approaches. For example, the most dramatic declines in malaria in recent decades have occurred with the rapid scale-up of environmental interventions (insecticide-treated bed

nets to thwart malaria-hosting mosquitos [19], although areas of high transmission and low access to care and prevention still remain [20]). Similarly, for schistosomiasis elimination, control programs have been most successful when countries implement strategies to reduce the abundance of schistosomiasis-carrying snails in the environment [21, 22]. Guinea worm is another environmentally mediated parasite that has been reduced from 3.5 million cases in the 1980's to less than three dozen detected cases worldwide in 2019, without a drug or a vaccine [23]. This dramatic success was achieved through behavior change, simple filters, and safe water [24].

For human infectious disease control and elimination, opportunities for environmental interventions exist wherever there are strong human–environment feedbacks [25-27], as is common among environmentally mediated infectious diseases [17]. For example, conservation biologists and ecologists point out links between human malaria incidence and deforestation in some areas [28, 29], though not everywhere [30, 31]; between schistosomiasis incidence and dam construction and irrigation schemes across Africa [32-34]; and between some vector-borne and parasitic diseases and biodiversity loss [14, 35]. Despite the growing awareness about links between environmental degradation and human infectious disease, there are few concrete examples of environmental solutions that have capitalized on these environmental connections for improving human health sustainably and at a broad scale. Thus, although we are gaining a better understanding of the complex environmental drivers of human disease, future research will need to answer many basic questions about the socio-ecological systems that underpin environmentally mediated transmission in order to implement effective solutions.

Challenges for controlling environmentally mediated pathogens are multi-faceted and substantial, including an expanding funding gap [20, 36], rising insecticide and drug resistance [37, 38], and poor surveillance [36]. These challenges further argue for a renewed focus on

creative environmental interventions that can reduce disease transmission at affordable cost and with low damage to non-target hosts or local human livelihoods. Environmental interventions may be most important for poor communities in low income, tropical countries, where individuals lack access to health care, but where they can still benefit from community-wide environmental risk reductions and transmission-prevention measures. However, high-income countries still have some fatal environmentally mediated infections (e.g. coccidiomycosis) that merit attention. In addition, better interventions are needed to curb Hendra virus spillover from bats in Australia, and Lyme disease from ticks and wildlife in North America and Europe. Climate change may also extend the range of many environmentally mediated diseases to higher latitudes or altitudes, forcing some additional countries to develop control mechanisms for these 'moving targets' in the future [39].

Focusing on environmental interventions to improve public health offers some opportunities to achieve win–win synergistic outcomes for global health and sustainability goals. For example, in West Africa, scientists are partnering with communities to restore natural snail predators (prawns) in ecosystems where they have been excluded by dams and irrigation expansion, and this intervention promises to reduce schistosomiasis, fight poverty, and improve nutrition [40]. Strong local partnerships between scientists, policymakers, and communities, with a dedication to economic and ecological sustainability, could aid in devising new solutions to other environmentally mediated human infectious diseases.

Conclusions

The United Nations' Sustainable Development Goals [41] and the recent academic emphasis on the new field "planetary health" [26] are drawing renewed attention to the connections between human health and environmental change. But even as evidence amasses about how environmental integrity affects health, actionable solutions are few, and this hinders

control efforts. Here we provide empirical evidence to support a stronger focus on interrupting environmental transmission in parallel with patient care to address the large and uneven global burden of environmentally mediated human infectious diseases [42].

We show that environmentally mediated pathogens pose a substantial and unsolved problem in global health and development: they account for 80% of all human pathogens assessed and cause more than one third of the global burden of human infectious disease. Infectious disease burdens are well known to be unevenly distributed across the globe, with a higher toll in poor tropical countries, but our results show that this disparity is even more stark for environmentally mediated pathogens than for direct-contact transmitted human pathogens (Table 3, Figure 2, 3, 4). Most environmentally mediated pathogens lack effective vaccines and treated patients are rapidly re-infected due to their continued contact with unhealthy environments. Therefore, recent global increases in access to vaccines and medicines will have limited effect on the transmission of this important class of human infectious diseases. New interventions to address and interrupt environmental transmission are urgently needed.

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403 Tables and Figures

404 Table 1. Frequency of environmentally-transmitted human parasites and pathogens (with
405 transmission details)

406 Species identified as environmentally-transmitted among a random subset (250) of the
407 1415 described human parasites and pathogens described in Taylor et al (2001) and among the
408 560 human parasites and pathogens tracked by the World Health Organization for the Global
409 Burden of Disease Estimates, in the category I.A: "Communicable, maternal, perinatal and
410 nutritional conditions: Infectious and parasitic diseases" in 2015
411 (http://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html).

Transmission category	Transmission pathway	Random subset of all human pathogens		WHO-tracked human pathogens		Example pathogen	Total global DALYs, thousands (%)
		#	(%)	#	(%)		
Environmentally-mediated human infectious diseases	Sapronotic	75	(30%)	158	(28%)	histoplasma	
	Foodborne	24	(10%)	112	(20%)	salmonella	
	Vectorborne	35	(14%)	85	(28%)	human malaria	
	Environmental contact (water, soil, etc.)	27	(11%)	60	(11%)	schistosomes	
	Zoonotic (direct contact: wildlife)	4	(1.6%)	19	(3%)	rabies	
	Transmission unclear	20	(8%)	11	(2%)	rhodococcus	
	Zoonotic (direct contact: domestic spp.)	4	(1.6%)	9	(1.6%)	pasteurella	
	Prion	1	(0.4%)	1	(0.2%)	mad cow disease	
	Subtotal: env. mediated	**195**	**(76%)**	**455**	**(81%)**		**129,488 DALYs (38.7%)**
Non-environmentally mediated human infectious diseases	Direct-contact transmitted (direct, sexual, etc.)	13	(5%)	79	(14%)	HIV	
	Opportunistic (auto-infection with normal flora)	28	(11%)	13	(2.3%)	staphylococcus	
	Transmission unclear	4	(1.6%)	1	(0.2%)	selenomonus (gingivitis causing bacterium)	
	Subtotal: non-environmentally transmitted	**45**	**(18%)**	**93**	**(17%)**		**205,353 DALYs (61.3%)**
Unknown	Insufficient data	15	(2%)	12	(2%)		-----
Total assessed		**250**		**560**			**389,316 classifiable DALYs (100%)**

Table 2. Results of the PLS-SEM path modeling analysis: total effect of latent variables (rows) on direct-contact versus environmentally-mediated infectious disease burdens (columns); total effects are calculated from the sum of all direct and indirect paths between a variable and disease burdens (see Figure 4 for details of significant paths). NE = no effect.

Total effect:	*Direct-contact infectious burden*	*P Values*	*Environmentally mediated infectious burden*	*P Values*
Ag yield in kCal per person	**-0.12**	0.001	0.05	0.52
Land area in agriculture	-0.04	0.37	**0.04**	0.02
Biodiversity	**0.27**	<0.001	**0.13**	0.006
Elevation	-0.02	0.13	-0.02	0.13
Health care access	**-0.20**	<0.001	**-0.47**	<0.001
Latitude	**-0.36**	0.001	**-0.25**	<0.001
Malnutrition	NE	---	NE	---
More tropical climate	**0.23**	<0.001	**0.20**	<0.001
Political stability	**-0.16**	<0.001	**-0.30**	<0.001
Rural poor livelihood	**0.52**	<0.001	**0.86**	<0.001
Total land area	0.03	0.07	0.02	0.15
Wealth	**-0.24**	<0.001	**-0.28**	<0.001

Figure 1. Common transmission pathways that fall along a gradient of direct and environmental transmission: 'direct-contact transmission' strategies include A) auto-infection, as occurs with many hospital or iatrogenic infections, B) and human-to-human horizontal transmission by direct contact, whereas 'environmental transmission' encompasses C) transmission cycles whereby humans indirectly infect other humans via environmental pathways, like food, vectors, alternative hosts, fomites, and abiotic reservoirs (soil, water) and D) one-way spillover from environmental sources to people (with humans as dead end hosts in the cycle). Artwork credit: N. Nova

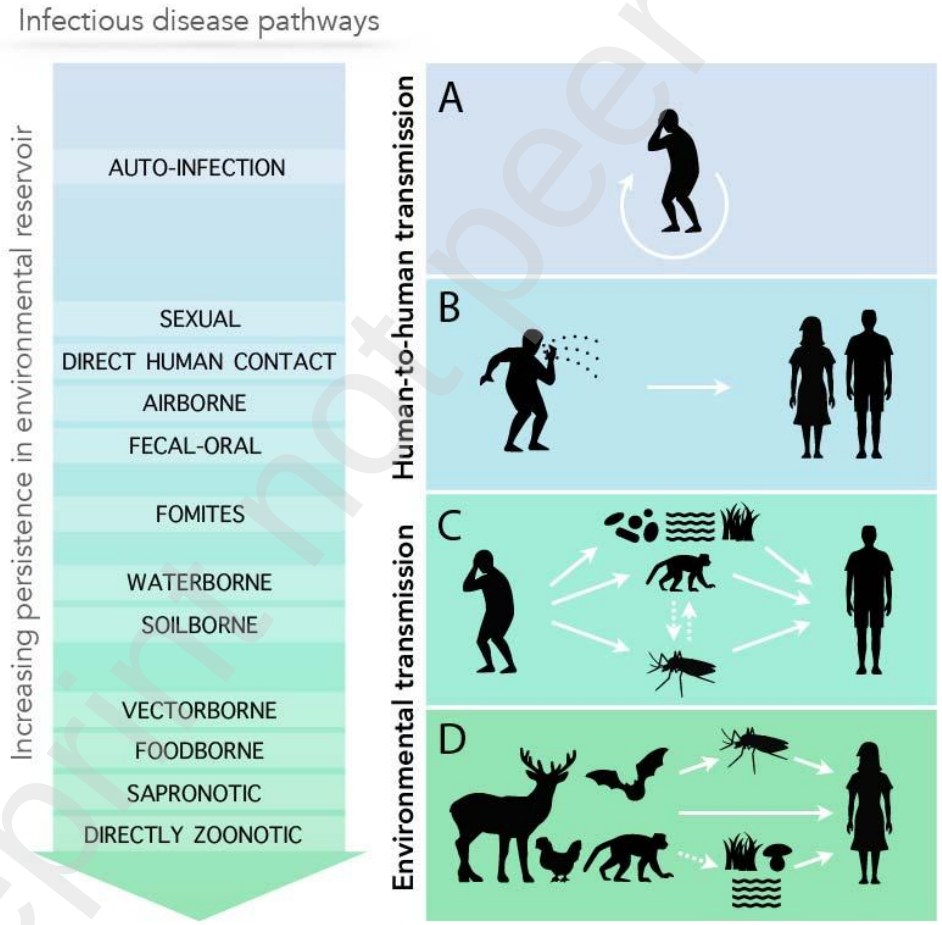
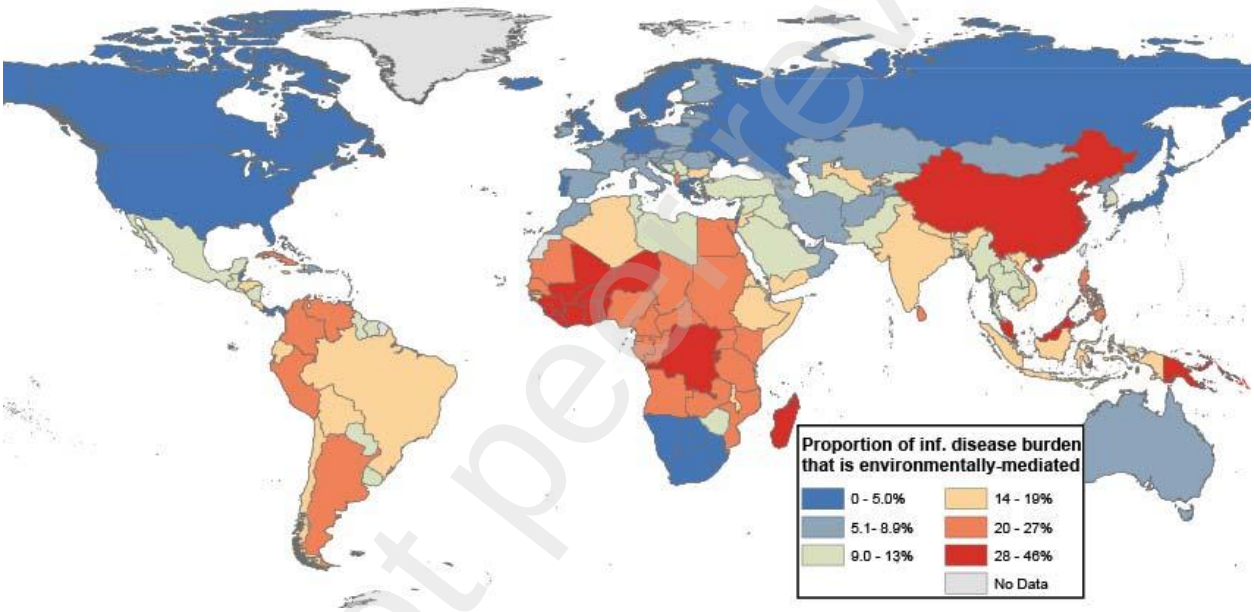
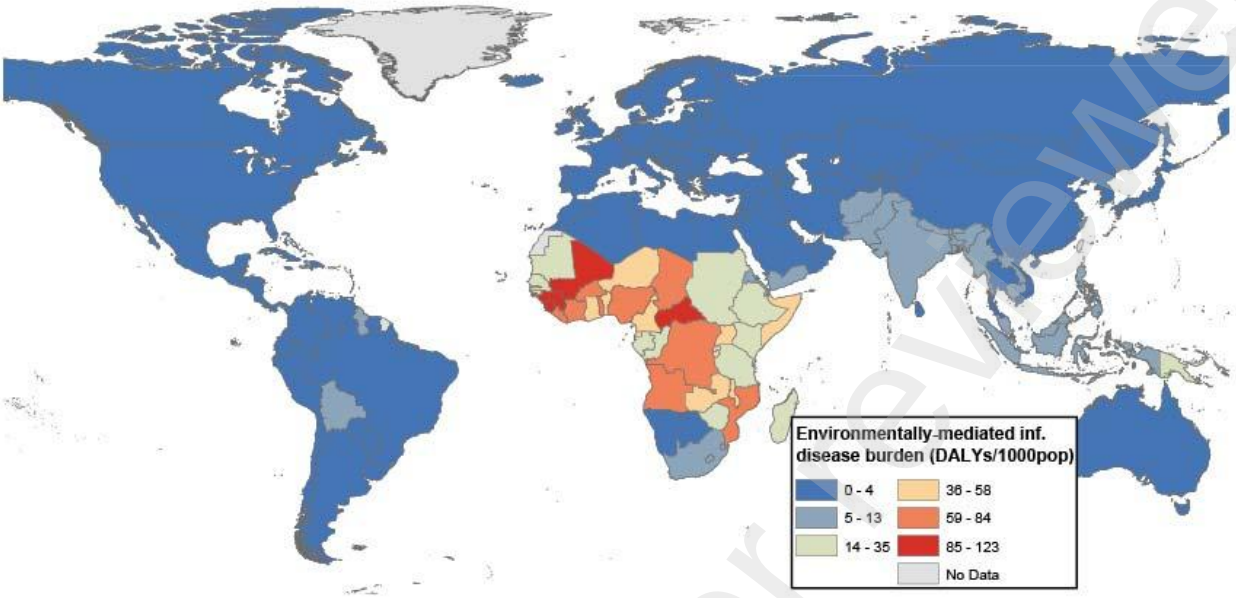


Figure 2. Uneven global distribution of environmentally mediated human infectious disease burdens; A) as a proportion of all “infectious and parasitic diseases” (proportion of DALYs attributable to environmentally mediated infections per country of total DALYs attributable to infectious diseases); B) as total global per capita environmentally mediated infectious disease DALYs in each country.

A)



437 B)



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443 Figure 3. A) Latitudinal gradients in environmentally mediated infectious disease DALYs as a
444 proportion of all “infectious and parasitic disease” DALYs tracked by the WHO’s Global Burden
445 of Disease study in 2015; Countries at lower latitudes have a higher proportion of their disease
446 burdens caused by environmental pathogens. B) Latitudinal gradients in total environmentally
447 mediated infectious disease DALYs per 1000 people in 2015. Each circle represents one
448 country and the size of the circle is proportional to each country’s per capita Gross Domestic
449 Product (GDP, sourced from World Bank 2015 World Bank Open Data. See
450 http://data.worldbank.org/). Poorer countries in all latitudinal bands (smaller dots) carry higher
451 (A) proportions as well as (B) total burdens of environmentally mediated infectious disease.

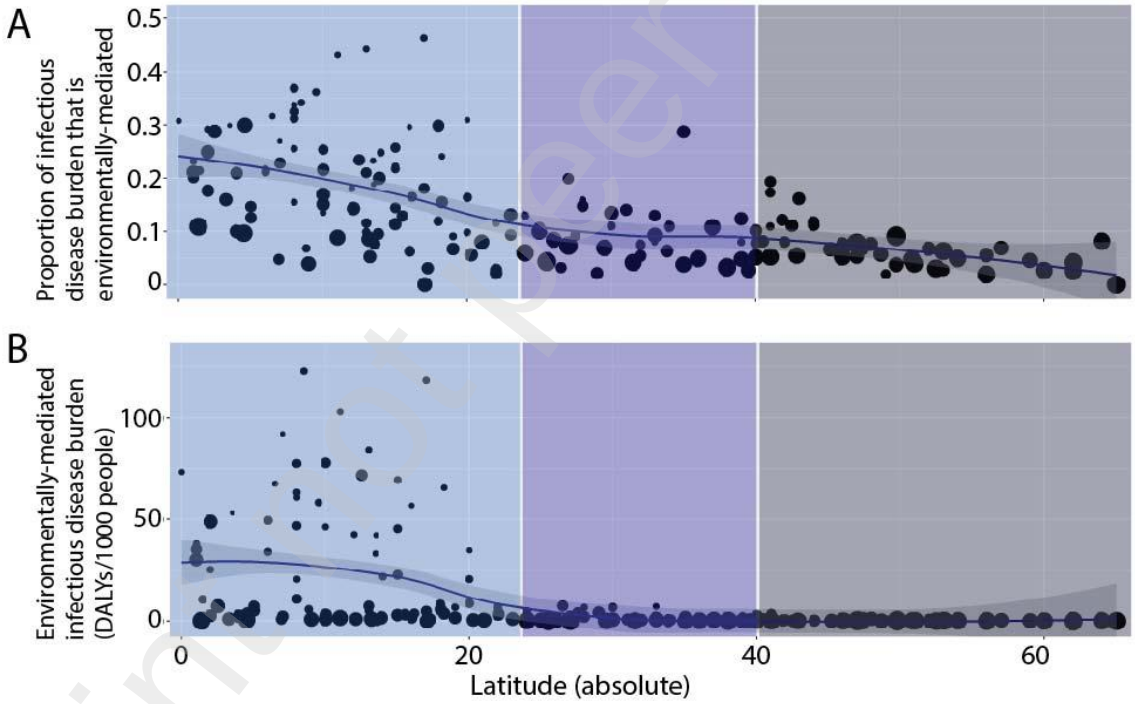

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Figure 4. Results of partial least squares structural equation model. Statistically significant direct paths and indirect paths (with indirect paths defined as those paths that involve multiple intermediary connections) are shown, with symbols representing the relevant latent variables (definitions, sample sizes, and measurement indicators for each latent variable are given in Table S2) and all of their links to total per capita burden of all classifiable direct-contact transmitted versus environmentally mediated infectious diseases globally (listed in Table S1). Dashed lines represent negative associations, and solid lines positive associations, among the variables linked by those lines. Numbers along paths (and also path thickness) correspond to the weighted correlation coefficients which signify the strength of the association between two linked variables; total effects can be estimated by multiplying path coefficients along one or more segments, and summing across all possible paths, from one to another variable, and total significant effects on disease burdens are summarized in Table 2; stars represent bootstrapped p values for the coefficients: no stars = $p < 0.1$, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$. Paths with $p > 0.1$ were removed from the full model to produce the final model shown here (see Table S3). Green symbols represent environmental variables/drivers and blue symbols human-centric variables/drivers. Symbol sizes are for emphasis. Artwork credit: N. Nova.

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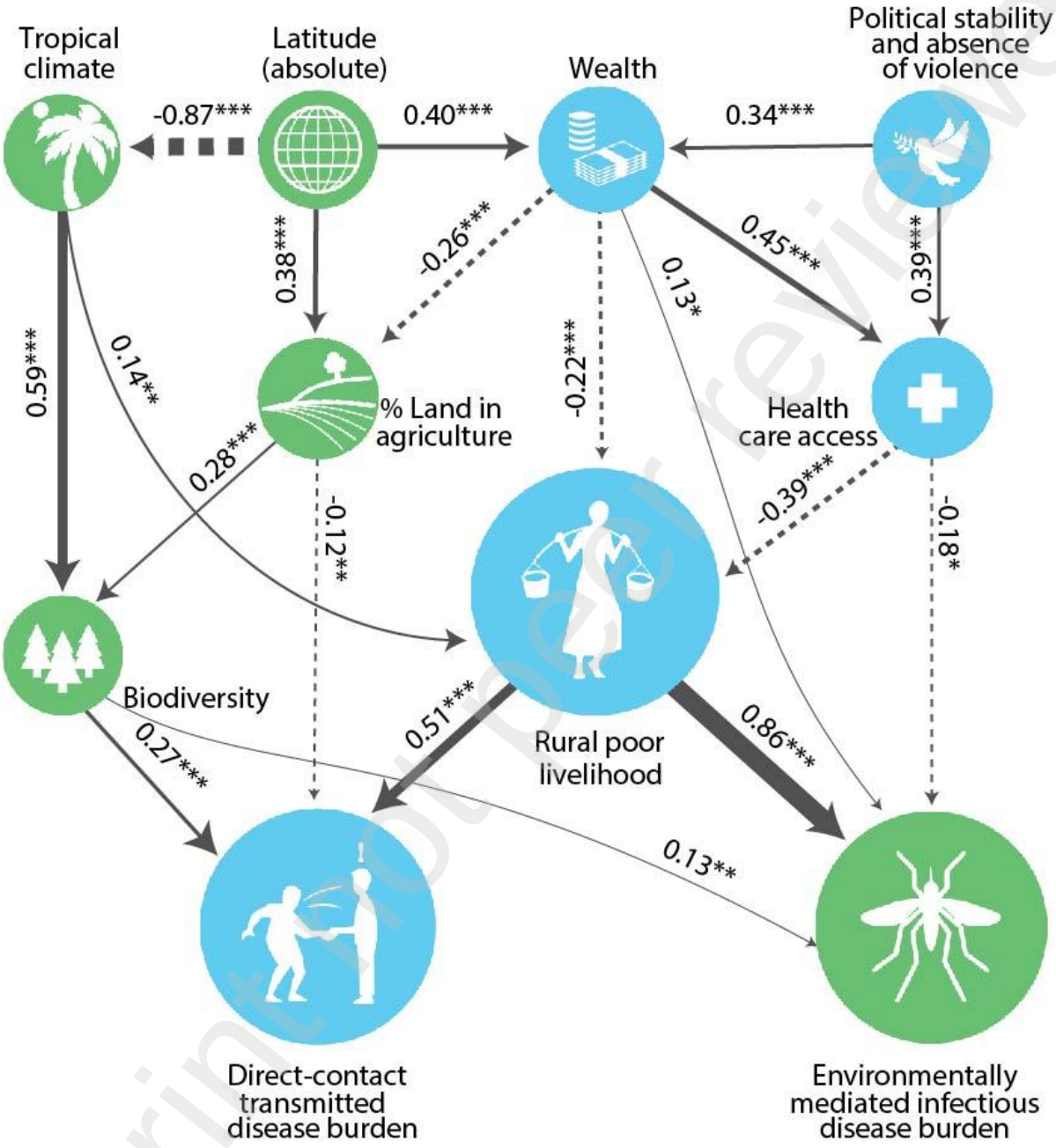

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Supplemental Methods, Tables and Figures:

Supplemental Methods: the structural equation modeling approach

Supplemental Table S1. Global burden of environmentally mediated and direct-contact transmitted infectious diseases across cause categories

Supplemental Table 2. SEM path model measurement and latent variable definitions

Supplemental Table 3. PLS-SEM path model: Full and reduced model (reduced after removing non-significant variables based on bootstrapped p values <0.1)

Supplemental Table 4. PLS-SEM path model fit statistics for full and reduced models.

Supplemental Table 5. Comparing the reduced (final) PLS-SEM path model effects on direct-contact transmitted and environmentally mediated infectious disease burdens

Supplemental Figure 1. Latitudinal range limits of direct-contact transmitted and environmentally mediated infectious diseases

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Supplement

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