Changing Geographic Distributions of Human Pathogens

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Abstract

Since the rise of modern humans, changes in demography and land use and frequent contact with wildlife and domesticated animals have created ongoing opportunities for pathogen loss, gain, and evolution in the human population. Early transportation networks and population expansion created a world where many human-specific pathogens are now ubiquitous, yet zoonoses continue to emerge as humans encroach into the last remaining wild areas, increase livestock production, and plug into vast global trade networks. Pathogens are exploiting almost any change in human ecology that provides new opportunities for transmission, the most recent being rampant use of antibiotics resulting in new multidrug-resistant pathogens. Public health advances have benefitted some nations, but others continue to suffer from pathogens long eradicated by developed nations. Generalities of pathogen occurrence aid in disease prediction, but a systemic approach incorporating ecology, biogeography, public health, and conservation biology is ultimately necessary to fully comprehend the changing geographic distributions of human pathogens.

OVERVIEW

By the twentieth century, improved hygiene, medical advances, and the development of new drug therapies allowed much of the world to greatly reduce the impact of many deadly infectious diseases. Yet, infectious diseases still account for 30% of the major causes of human morbidity and mortality and 25% of deaths globally (Murray & Lopez 1996). Of recent interest is the apparent increase in emerging infectious diseases (EIDs), many of which have been linked to human activities that modify the environment or otherwise spread pathogens to new geographic regions (Jones et al. 2008; Smith et al. 2007, 2009b; Taylor et al. 2001; Woolhouse & Gowtage-Sequeria 2005). At the advent of a century characterized by the breakdown of geographical, ecological, and evolutionary barriers to the spread of infectious disease, there is an ever-growing interest in the natural and anthropogenic factors that influence global disease distributions.

Here, we review the major patterns and processes that have governed the global distribution of pathogens since the appearance of modern humans, focusing on the ecological, evolutionary, and biogeographical literature. We use the term pathogen to include both microparasitic and macroparasitic pathogens, and the phrase infectious disease to represent disease syndromes that are caused by a contagious pathogen. We begin with an overview of major events and patterns that have shaped global pathogen distributions from the rise of modern humans to the present day. We tally the diversity of pathogens known to science in 2010 and review the loss and gain of pathogens through eradication, control, and emergence events since 1900. We present major findings from biogeography to describe the present day distribution of human pathogens on the planet and consider their relationship to natural and anthropogenic drivers. Throughout, we identify key topics in disease biogeography, disease ecology, and global health that are ongoing points of contention or ripe for immediate consideration. We conclude with recommendations for key research that will advance our understanding of where human pathogens occur and why and how these distributions will change in the future.

HISTORICAL DISTRIBUTIONS OF HUMAN PATHOGENS

The Rise and Dispersal of Modern Humans

For millennia, cultural evolution, long distance dispersal, and interpopulation contacts and conflicts have influenced the composition of pathogens infecting human populations (McNeill 1989). Eggs of the nematode roundworm *Ascaris lumbricoides* have been found in fossilized human feces all over the world, and the oldest remains, from France, are thought to be nearly 30,000 years old (Bouchet et al. 1996). *Ascaris* infection is acquired when a human swallows worm eggs that have matured in warm moist soil, and it is believed that ground-dwelling prehistoric people retained this parasite as they migrated out of Africa. Leprosy, which is a chronic human disease due to *Mycobacterium leprae*, might be attributable to a single clone whose dissemination worldwide from its geographical origin somewhere between eastern Africa and the Near East was the result of successive human migrations and settlements since 60,000–50,000 years BP (Monot et al. 2005). Like *Ascaris* and leprosy, many pathogens would have experienced rapid dispersal between geographical regions, reflecting relatively short periods of human migration, whereas others have been associated with modern humans since their appearance *ca.* 150,000 years ago. Viruses in this latter category are mainly those with DNA genomes that have much lower rates of nucleotide substitution, are sexually or vertically transmitted (parent to offspring), and generally cause persistent infections (Holmes 2004). An example is polyomavirus JC virus (JCV, classified within the Papovaviridae), a double-stranded DNA virus that has coevolved with humans since their origin in Africa. JCV has been used as a biological marker to track the diversification of humans over the

past 150,000 years, and its phylogeny suggests that humans expanded out of Africa via two distinct migrations, each carrying a different lineage of the virus (Holmes 2004, Sugimoto et al. 2002).

Many of the pathogens that plague mankind today are believed to have originated in the Old World (Africa, Asia, and Europe). Of the 25 major human diseases recently analyzed by Wolfe and colleagues (Wolf et al. 2007), 18 have a certain or probable Old World origin: hepatitis B, influenza A, measles, pertussis, tetanus, AIDS, cholera, dengue hemorrhagic fever, East and West sleeping sickness, *P. falciparum* and *vivax* malarias, visceral leishmaniasis, diphtheria, mumps, plague, smallpox, and typhoid. Tuberculosis appears to have originated in humans 40,000 years ago, with subsequent radiations resulting in two major lineages—one that spread to animals and the other human-associated lineage that today kills millions yearly (Wirth et al. 2008). Chagas disease is believed to originate from the New World, whereas debate about the origin of syphilis and tuberculosis continues, and the geographic origins for rotavirus, rubella, tetanus, and typhus remain unknown (Wolfe et al. 2007). Human nematode worms of the genera *Trichuris*, *Strongyloides*, and *Ancylostoma* have a tropical and subtropical origin (Araújo et al. 2008). The filoviruses (Marburg and Ebola viruses) and monkeypox virus remain endemic to tropical Africa, and scrub typhus (*Orientia tsutsugamushi*) and Nipah virus (Paramyxoviridae) are uniquely Asian. Yellow fever virus (Flaviviridae) was originally distributed across humid tropical Africa, but early shipping, probably via slave ships, transported it to Central and South America, where it then spread broadly across the tropics (Peterson 2008). West Nile virus, another member of the Flaviviridae, was first described in Uganda in 1935. It is found today in Africa, southern Europe, southwest Asia, North and South America, and the Pacific Ocean islands (Peterson 2008). With the exceptions of yellow fever, dengue fever, and West Nile fever viruses, all other flaviviruses transmitted by *Aedes* mosquitoes are only found in the Old World (Kyasanur Forest hemorrhagic disease, Japanese encephalitic disease, Rocio virus encephalitis, and Ntaya virus). By contrast, viruses in the *Culex* mosquito–transmitted clade show a widely dispersed geographic distribution in the Americas, Africa, Asia, and Australasia (Gaunt et al. 2001).

Crowd epidemic diseases: diseases occurring locally as a brief epidemic and capable of persisting regionally only in large human populations

Between 40,000 and 10,000 B.C., human hunting groups occupied all continents except Antarctica, and by 8,000 B.C. humans existed in fragmented populations from 60°N to 60°S across the globe (McNeill 1989). By migrating out of the tropics, temperate-bound groups left behind a great diversity of pathogens long associated with their ancestors, a release that likely contributed, among other things, to rapid population growth. Escape from the tropics was not, however, without cost. Like any organism invading a new region, migrating humans undoubtedly picked up new pathogens along the way, either zoonoses from contact with novel animal species or from other human groups never before encountered.

Disease in the First Human Settlements

The rise of agriculture and animal domestication in human settlements approximately 11,000 years ago promoted the evolution of strictly animal pathogens into those that today are specific to humans. Before that time, human hunter/gatherer populations in tropical Africa were presumably confronted with pathogens similar to those of other wild primate populations, particularly those able to persist in small host populations (McNeill 1989, Wolfe et al. 2007). When large and dense populations of humans and their livestock began living in close proximity with daily contact, the human crowd epidemic diseases evolved and persisted. Measles virus probably evolved from the rinderpest virus of cattle and diphtheria and pertussis bacteria; and rotavirus probably evolved from pathogens of domestic herbivores (cattle, sheep, goat, pig, horse) (Blixenkrone-Møller et al. 1994, Wolfe et al. 2007). Mumps might have entered the human population from pigs and smallpox from camels. In some cases, the ancestral pathogen has been identified in wild mammals (diphtheria and

pertussis bacteria and rotavirus), but uncertainty remains for the others. The proximate source of the human pathogen in each of these cases is more likely to have been a domestic rather than a wild mammal; because human contact with domestic mammals was (and is) closer and much more frequent (Cleaveland et al. 2001, Diamond 2002, Smith et al. 2009a). Nevertheless, domestic animal herds would have served as conduits for pathogen spillover between humans and local wildlife populations. The first human settlements also provided new ecological niches and specialized habitats for reservoir hosts, including many rodent and vector species such as rats, mice, mosquitoes, and fleas (Wolfe et al. 2007). Reservoirs can enable a pathogen to persist even in the absence of a susceptible human population large enough to sustain the pathogen by itself. Regular contact between humans and these novel hosts facilitated the emergence of new zoonoses (Despommier et al. 2007).

Reservoir host: a nonhuman source of pathogens immediately capable of infecting humans without evolutionary change

The Age of Exploration

The collapse of distance brought about by changes in transport technology over the past 500 years has facilitated ongoing shifts in human pathogen distributions, often with deadly consequences (Cliff et al. 2004a,b). The scattering of King Charles VIII's troops following the 1494 French invasion of Italy launched syphilis into the arena of global diseases. By 1500, the often fatal disease was reported throughout Europe, Russia, the Middle East, and the New World, where it is believed to have originated (Kohn 1995). In 1889, ships from Hong Kong carried bubonic plague to Honolulu, resulting in a raging epidemic that lasted several years (Kohn 1995). Cholera was introduced to the African island of Zanzibar from Indian cargo ships in 1869, killing 70,000 (Kohn 1995). After crossing the Bering Strait, the people of the Americas lived in isolation for thousands of years before the arrival of Europeans introduced crowd diseases common among Old World populations. By the time the explorers arrived, the Aztecs, Maya, and Incas had all built nations large enough to sustain these diseases, which included mumps, measles, whooping cough, smallpox, cholera, gonorrhea, and yellow fever, and against which they were immunologically defenseless (McNeill 1989).

LOSS AND GAIN OF PATHOGENS SINCE 1900

Today, we live in a world where once localized pathogens are now broadly distributed and shared between widely separated regions (Smith et al. 2007). With the rise of preventative medicine, vaccines, antibiotics, antihelminthics, vector control, and public health programs, many of these diseases were brought under control or eradicated, largely in developing nations, by the mid-1900s. Since the 1980s, however, the number of new and reoccurring diseases has grown.

Pathogen Diversity in 2010

With the breakthrough of new molecular techniques in the 1970s, the view that microbes were rare in the environment changed dramatically (Breitbart & Rohwer 2005, Hobbie et al. 1977). Today, scientists believe there are an estimated 10^{31} virus species on Earth, most of which are phages that infect bacteria (Breitbart & Rohwer 2005), and new human pathogens have been discovered at a rate of about three species per year since 1980 (Woolhouse & Gaunt 2007). Despite advances in microbial biology, parasitology, and medicine throughout the 1900s, the first comprehensive accounts of human pathogens were not completed until this century. Taylor et al. (2001) constructed the first list of distinct species known to be infectious to and capable of causing disease in humans under natural conditions. Their review identified 1,415 infectious species known to be pathogenic to humans, including 217 viruses and prions, 538 bacteria and

Table 1 Most recent tallies of the pathogens known to infect humans

Pathogen type	Human pathogens	Zoonotic pathogens[a]	Emerging human pathogens	New since 1980[b]
Total	1,415[a], 1,407[c], 1,399[b]			
Taxonomic group				
Bacteria and rickettsiae	38%[a,d], 39%[b], 41%[c]	31%	30%[a,d], 10%[c]	2%
Viruses and prions	15%[a,c,d], 14%[b]	19%	44%[a,d], 37%[c]	31%
Fungi	22%[a,d], 23%[b,c]	13%	9%[a,d], 7%[c]	4%
Protozoa	5%[a,d], 4%[b,c]	5%	11%[a,d], 25%[c]	5%
Helminths	20%[a,b,c,d]	32%	6%[a,d], 3%[c]	0.30%
Transmission				
Vector	14%[d]	22%	28%[d]	
Direct contact[e]	43%[d]	35%	53%[d]	
Indirect contact[f]	52%[d]	61%	47%[d]	
Unknown	16%[d]	6%	6%[d]	
Zoonotic	61%[d], 58%[c]	–	75%[d], 73%[c]	
Emerging	13%[d,c]	12.50%	–	

[a]Cleaveland et al. 2001.
[b]Taylor et al. 2001.
[c]Woolhouse & Gowtage-Sequeria 2005.
[d]Woolhouse & Gaunt 2007.
[e]Direct contact transmission requires physical contact between an infected person and a susceptible person, and the physical transfer of microorganisms.
[f]Indirect contact transmission refers to situations where a susceptible person is infected from contact with a contaminated surface.

rickettsiae, 307 fungi, 66 protozoa, and 287 helminths (**Table 1**). Since then, subsequent reports have used new criteria to update the list of known human pathogens, and despite often considerable differences in methodologies, including sources, timeframes, and taxonomies, only minor differences exist between the published lists (**Table 1**) (Cleaveland et al. 2001, Woolhouse & Gaunt 2007, Woolhouse & Gowtage-Sequeria 2005). Bacteria and rickettsiae represent the largest fraction of known human pathogens, followed by viruses and prions, fungi, protozoa, and helminths (**Table 1**). The majority of human pathogen species spread through indirect or direct contact (as opposed to vectors) and 58–61% are zoonotic infectious diseases (see **Table 1**). Pathogens such as HIV, which evolved from animal hosts and is no longer transmitted between animals and humans, are not considered zoonotic.

Receding and Emerging Pathogens

The ninteenth and twentieth centuries were major turning points for public health in the developing world. The epidemiological transition theory describes three major shifts; from the "age of pestilence and famine," when population mortality was driven by high rates of childhood infection, to the "age of receding pandemics," when death from tuberculosis, pneumonia, and diarrheal disease declined dramatically, to the current "age of man-made diseases," where mortality from chronic disease predominates (**Figure 1*a***; Armstrong et al. 1999).

Zoonotic infectious disease: disease caused by pathogens naturally transmissible from animals to humans

Significant declines in mortality from infectious disease were made in developing nations throughout the eighteenth and nineteenth centuries, largely due to improved nutrition, living conditions, and sanitation and safer food and water. Yet, in the early 1900s, one-third of the U.S. population still felt vulnerable to deadly infections of tuberculosis, pneumonia, or diarrheal

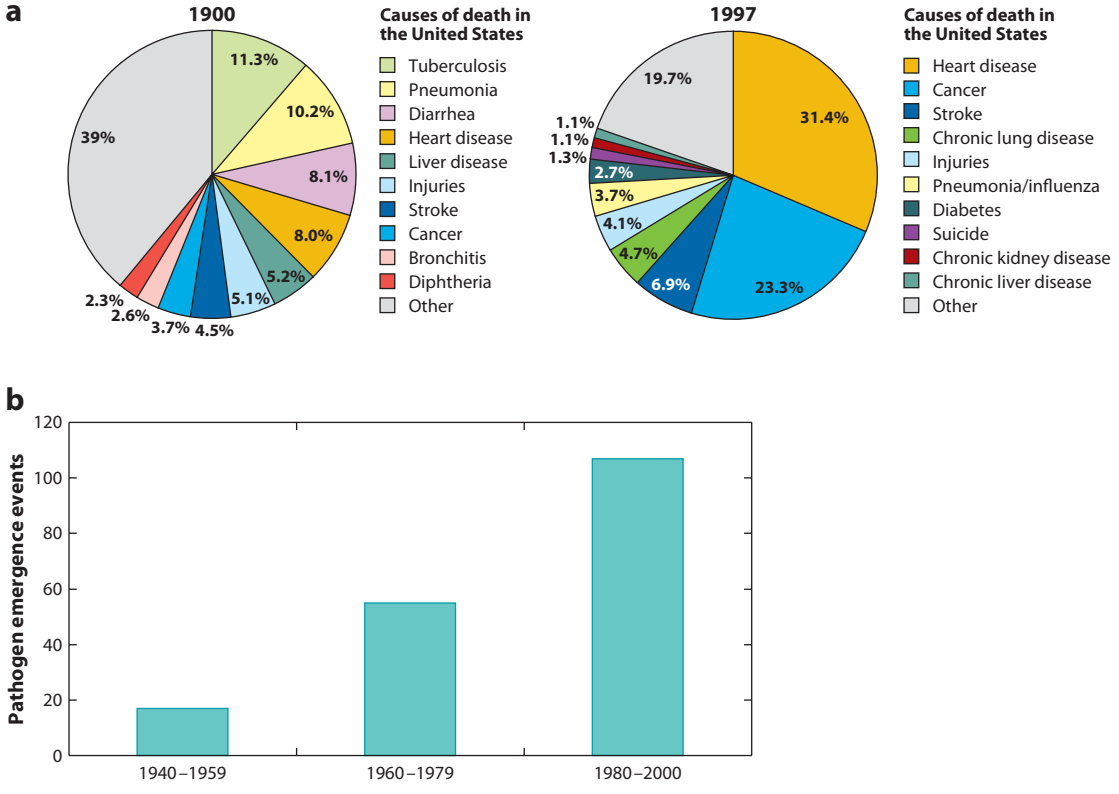

Figure 1

(*a*) Ten leading causes of death in the United States in 1900 and 1997 (adapted with permission from Macmillan Publishers Ltd: *Nature*, Cohen 2000). Infectious diseases that were the most important causes of death at the beginning of the twentieth century were replaced with chronic diseases by the 1990s. (*b*) Number of pathogen emergence events (first temporal origination of an emerging human pathogen) in the United States between 1940 and 2000 (Jones et al. 2008). Mortality from infectious disease in the United States increased 4.8% from 1981 to 1995 and is partly attributed to the surge in emerging infectious diseases (EIDs) (Armstrong et al. 1999). Although variation exists in the composition and number of emerging pathogens between nations of the world, EIDs do not discriminate between developed and developing nations.

disease (**Figure 1*a***). With widespread dissemination of immunizations and antimicrobials by the mid-twentieth century, the presence and impact of infectious disease in developing nations waned significantly (Cohen 2000). In few instances (for example, global smallpox eradication by 1977) did developing nations benefit from these victories. Today, much of the world continues to suffer from the very pathogens that have been long eradicated or controlled in the developing world [for example, malaria and tuberculosis (TB)]. By the end of the twentieth century, new and long forgotten pathogens began to appear in all corners of the world, coinciding with a recent surge in infectious disease morbidity and mortality, suggesting the onset of a new epidemiologic transition (Armstrong et al. 1999, Cohen 2000). These new pathogens are the causal agents behind what we today call EIDs (**Figure 2*b***).

The term EID first appeared in the literature approximately 30 years ago (Lederberg et al. 1992). Today, the commonly applied definition is "those [diseases] that have recently increased in incidence, impact, or geographic or host range; that are caused by pathogens that have recently evolved; that are newly discovered; or that have recently changed their clinical presentation"

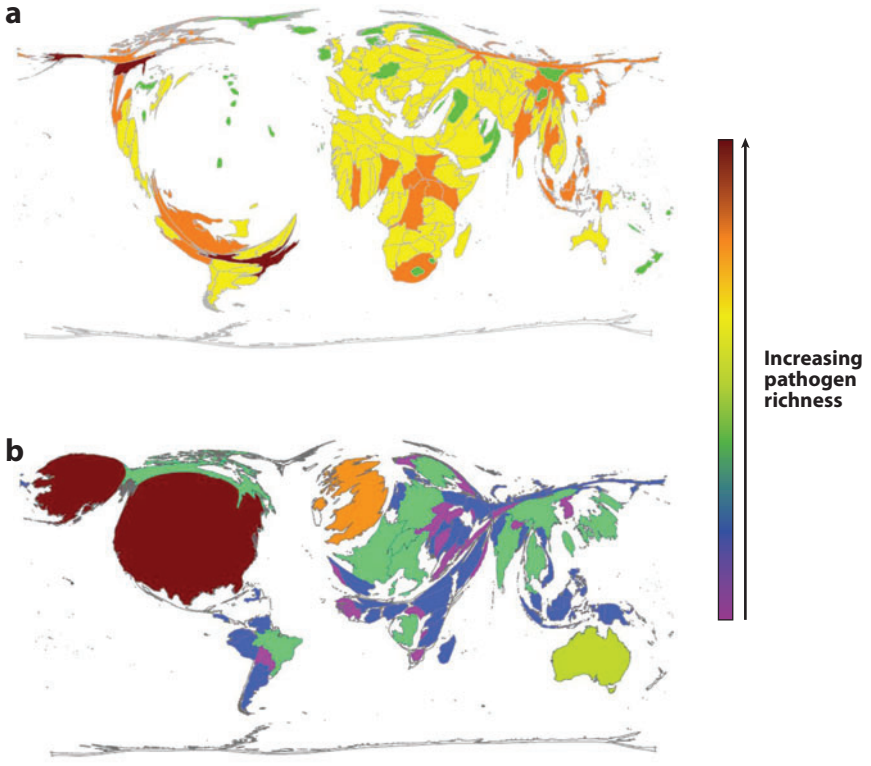

Figure 2

Nations colored and sized in proportion to the number of human pathogens occurring within their borders. Large sizes and warm colors represent higher pathogen richness. When combined, nonemerging and emerging human pathogens (*a*) appear to peak in richness in tropical nations (presumably driven by the larger number of nonemerging pathogens represented in the data). In contrast, pathogen emergence events (*b*) seem to dominate temperate nations. Although climatic factors account for the latitudinal gradient when emerging and nonemerging pathogens are pooled (*a*), the temperate peak in emergence events (*b*) seems to be the result of two factors: (1) the higher reporting efforts in developed nations, the majority of which occur in temperate latitudes, and (2) a preponderance of drug-resistant pathogens, particularly new bacterial strains, in the same nations. Data from Guernier et al. (2004) and Smith et al. (2007) for panel *a* and Jones et al. (2008) for panel *b*.

(Krause 1981, Lederberg et al. 1992, Patz & Confaloneiri 2005) (see the sidebar, Pathways of Emerging Infectious Diseases). Reemerging diseases historically occurred at significant levels, were effectively controlled for a short period, and only recently increased in incidence again (e.g., dengue fever) (Patz & Confaloneiri 2005). Recent examples of human EIDs are the introductions of West Nile virus to the United States, the 2002/2003 SARS epidemic, the discovery of Nipah virus in Malaysia, the avian flu virus (H5N1), and the ongoing influenza A virus (H1N1) human swine flu pandemic (Fauci 2005, LeDuc & Barry 2004, Olsen et al. 2006, Spielman et al. 2004).

Tallies indicate that 13% of identified human pathogens are considered emerging (**Table 1**). Viruses and prions dominate the list (37–44%), whereas few helminths are emerging (3–6%) (**Table 1**). The proportion of EIDs that are bacteria, rickettsiae, and protozoa varies considerably depending on the source (**Table 1**). Taylor et al. (2001) and Cleaveland et al. (2001) classified 30% of EIDs as bacteria or rickettsiae, whereas Woolhouse & Gowtage-Sequeria (2005) identified only

PATHWAYS OF EMERGING INFECTIOUS DISEASES

The definition of an emerging infectious disease (EID) identifies seven potential pathways by which a pathogen can emerge: (*a*) increasing in incidence (e.g., Lyme Disease), (*b*) increasing in impact (e.g., Tuberculosis), (*c*) increasing in geographic range (e.g., West Nile Virus), (*d*) evolving into a new pathogen (e.g., new strains of Influenza virus), (*e*) entering the human population for the first time (e.g., Nipah Virus), (*f*) significantly changing pathology or clinical presentation (e.g., Hantavirus Pulmonary Syndrome), or (*g*) because they are newly discovered (e.g., Hendra Virus). Despite numerous attempts to identify the mechanistic drivers of pathogen emergence (discussed in the text), we know little about the pathways identified in the very definition. Which pathogens emerged via geographic range expansion because they are newly evolved or are recently discovered? Do pathogens emerge via one or many pathways? Do certain pathways dominate the emergence process? Do the pathways to emergence vary with pathogen taxonomy, host requirements, epidemiological characteristics, driving forces, and geography? Quantifying the pathways to emergence will not only improve EID prediction models but allow the infectious disease community to consider whether such a broad definition of an EID is valid, appropriate, and generally useful to public health and science.

10% in this group. This discrepancy likely stems from ongoing adjustments to taxonomies and the discovery of previously unknown pathogen species (Woolhouse & Gowtage-Sequeria 2005). Similar to the complete list of known human pathogens, many EIDs spread through indirect or direct contact, and the majority are zoonotic (73–75%) (**Table 1**).

A recent study presented the first analytical support for the widely held assumption that EIDs have increased significantly in recent time. The survey by Jones et al. (2008) of 335 EID events revealed a significant increase in incidences from 1940 to the present. The global scope, unpredictability, and apparent increase in EIDs have regularly placed human pathogens in the headlines for the past three decades. Equal interest has ensued in the medical and scientific communities, perhaps beginning with a 1992 U.S. Institute of Medicine report entitled *Emerging Infections: Microbial Threats to Health in the United States*. The report identified the major factors that, at the time, seemed to promote disease emergence, including changes in human demographics and behavior, economic development and changes in land use, and microbial adaptation. Researchers from clinical, ecological, and biogeographical fields have since pursued more empirical methods to determine the drivers of emergence and, ultimately, the distribution of human pathogens. We address this question in the sections below, but first consider the past and present-day global distribution of human pathogens.

DISEASE BIOGEOGRAPHY

For centuries biogeographic principles have informed scientists of where life occurs on the planet and why. Here, we review key findings from global disease biogeography that illustrate the contemporary distribution of human pathogens. We focus on large-scale patterns of pathogens across latitude, on islands, between continents, and between nations of the world and briefly consider how these vary in relation to the rest of life on Earth.

The Latitudinal Gradient in Pathogen Richness and Nestedness

One of the most striking biogeographic patterns is the gradient of increasing species richness from the poles to the equator. This pattern holds for most major taxonomic groups and has been

explained by many hypotheses, including temperature variability, differential rates of speciation or extinction, and the consequences of past climate cycles (Rohde 1992, Willig et al. 2003). Guernier et al. (2004) examined the biogeography of more than 300 human pathogens and found a significant relationship with latitude. These researchers did not distinguish between nonemerging pathogens and those emerging at the time of the study (data from the Global Epidemiology and Infectious Disease Online Network). In both hemispheres, pathogen richness is significantly higher in tropical regions and declines predictably toward the poles, although the trend is stronger in the north where human populations are concentrated. Presumably, the pattern is driven by the larger fraction of nonemerging pathogens in the data. The latitudinal variation in two climatic variables, temperature and rainfall, account for the trend, particularly for pathogens that require vector hosts to complete their transmission cycle (Guernier et al. 2004). This is not overly surprising, because the low winter and nighttime temperatures characteristic of temperate and polar latitudes limit the geographic ranges of many vector species such as mosquitoes and flies. Likewise, the decline in precipitation outside the tropics limits the range of vector hosts requiring regular access to moist environments for reproductive purposes (Wasserberg et al. 2003).

More recently, Jones et al. (2008) implied that pathogen emergence events (the first temporal origination of an emerging human pathogen) do not exhibit a relationship with latitude, but this finding was not fully explored by these researchers. Cartogram depictions of the Guernier et al. (2004) and Jones et al. (2008) data reveal varying global distributions in the pathogens represented in each data set and a potential difference between nonemerging and emerging pathogens (**Figure 2**). There are many plausible explanations for potentially conflicting latitudinal patterns exhibited by nonemerging and emerging pathogens, including variation in national reporting efforts or public health systems, and environmental, demographic, or socioeconomic influences. Nevertheless, it seems that the temperate peak in emerging pathogen richness is the result of two factors: (*a*) higher reporting efforts in developed nations, the majority of which occur in temperate latitudes, and (*b*) a preponderance of drug-resistant pathogens, particularly new bacterial strains, in the same nations (**Figure 2*b***). Unfortunately, this is impossible to know without a systematic comparison of the two pathogen groups using comparable data.

Another common macroecological pattern, often detected across latitude and in many animal and plant communities, is a nested distribution of species subsets (Gaston & Blackburn 2000). Nestedness is the hierarchical organization of species composition in which communities with successively lower species richness are nonrandom subsets of those with richer assemblages, and nestedness has been interpreted as a measure of biogeographic order in the distribution of species (Atmar & Patterson 1993). The existence of a high degree of nestedness implies that the patterns of distribution and diversity have been shaped by deterministic processes. Human pathogens are significantly nested across latitude; pathogens occurring in northern latitudes represent subsets of the larger pathogen communities found in the tropics (Guernier et al. 2004). Despite this overall trend, many significant human pathogens are strictly endemic to temperate areas, e.g., Lyme disease. Pathogens that exhibit the broadest geographic distributions, occurring in both tropical and temperate zones, tend to be those with direct human-human transmission, whereas those with external stages (helminth worms and vector-transmitted) are far more localized in their geographic distribution. This variation in pathogen range size is discussed below in relation to biotic homogenization.

Pathogens on Islands

Biogeographers have long noted striking differences between species communities on islands and continents. Continents are typically more species rich than islands, whereas larger islands close to the mainland have more species than those that are small and more isolated. The distribution of

biota across islands has been well described for macro-organisms but surprisingly less well studied for pathogens. Cliff and colleagues (Cliff & Haggett 1995, Cliff et al. 2000) have shown, for a range of islands from the very small (e.g., Tokelau with 1,700 people in 1988) to the very large (e.g., Australia with 16.47 million inhabitants in 1988), that the relationship between island size (surface area) and pathogen species richness is statistically significant. The explanation for this pattern might lie with the theory of island biogeography, which proposes that the number of species found on an island is determined by immigration and extinction (MacArthur & Wilson 1967). Immigration is affected by the distance of an island from a source of colonists, whereas the rate of extinction is affected by island size. As a result, continents are typically more species rich than islands, whereas larger islands close to the mainland have more species than those that are small and more isolated. The role of isolation on insular pathogen richness remains relatively unexplored, but an area effect seems real.

Smith et al. (2007) made the case that host population size might be a more appropriate independent variable when considering species-area relationships for pathogens because it is the host population that serves as the ultimate "area" in which a pathogen occurs. Although data on human population size for various regions are available, comparable data for the population size of nonhuman hosts (important in the case of zoonoses) are not. This presents a problem when attempting to calculate the complete host population size for human pathogens requiring nonhuman hosts. Pathogen-area analyses based solely on human population size are, therefore, difficult to interpret. Nevertheless, there are clear examples illustrating the influence of changing population size on pathogen occurrence (Bartlett 1957), and some of the best examples come from islands. Cliff & Haggett (1995) and Cliff et al. (2000, 2004a,b) offer Iceland and measles as an example.

> The spacing of measles epidemics in Iceland became shorter over time as the island's population grew and contacts with the outside world became more frequent. The average gap between waves in the period 1896 to 1945 was more than five years; from 1946 to 1982 it had fallen to a year and a half. More frequent virus introductions also meant there was less time for the susceptible population to increase and so epidemics became smaller as well as more closely spaced.

An increase in the population of susceptible individuals should also support greater pathogen richness (Price 1990), but supporting evidence remains rare (but see Guégan & Broutin 2008).

Biotic Homogenization of Human Pathogens

Biotic homogenization is the process by which species invasions and extinctions increase the taxonomic, genetic, or functional similarity of multiple locations over a specified time interval (Olden 2008). Given the frequency and extent of human movement around the planet, it is no surprise that biotic homogenization also applies to human pathogens. Human pathogens are broadly and uniformly distributed around the globe, but the magnitude of distribution varies greatly with host requirement, mode of transmission, and pathogen taxonomy (Smith et al. 2007). Pathogens specific to humans are extremely homogenous across the nations and continents of the world; most pathogens in this host group occur in all 220 nations examined. By contrast, pathogens that require nonhuman hosts to complete their life cycle are far more localized in their distribution (**Figure 3**). Likewise, non-vector-borne pathogens exhibit a greater degree of global homogenization than those requiring vectors for host-to-host transmission. For human-specific pathogens, viruses are the most ubiquitous across nations, followed by helminths and finally bacteria. Among zoonotic pathogens, however, bacteria are the most ubiquitous, followed by parasites and finally viruses (Smith et al. 2007).

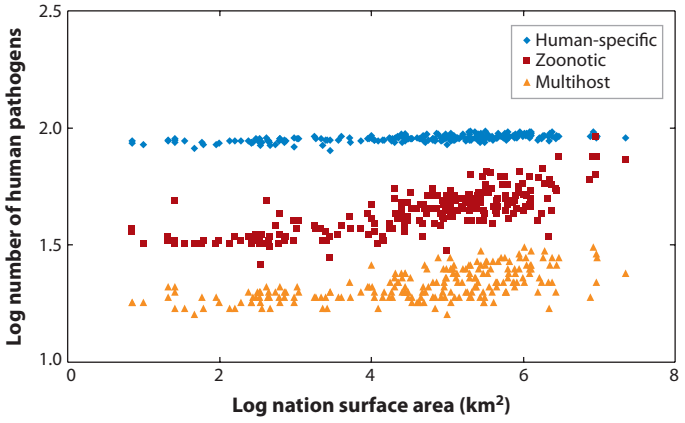

Figure 3

Pathogen richness plotted against nation surface area to depict the degree of homogenization for three host groups (from Smith et al. 2007). Linear slopes are significantly different: Human-specific pathogens are highly homogenized across nations, followed by multihost and finally zoonotic pathogens. Zoonotic slope > human-specific slope: $F_{1,440} = 245.308$, $P < 0.0001$; zoonotic slope > multihost slope: $F_{1,440} = 38.201$, $P < 0.0001$; multihost slope > human-specific slope: $F_{1,440} = 73.756$, $P < 0.0001$. Human-specific pathogens: Many pathogens that afflict humankind are currently entirely restricted to human reservoir hosts (that is, contagious only between persons), even though they historically might have arisen in other species, such as measles that originated in cattle. Zoonotic pathogens: These are pathogens that develop, mature, and reproduce entirely in nonhuman hosts but which have the potential to spill over and infect human populations. Humans are a dead-end host for pathogens in this group, and examples include rabies, plague, and Hantavirus. Multihost pathogens: Some pathogens can use both human and nonhuman hosts to complete their life cycle. Oftentimes these pathogens are lumped with zoonotics, but they were distinguished by Smith et al. (2007).

Although the extent of pathogen homogenization is striking, it is perhaps not surprising. For many pathogens, a basic characteristic is their transmission cycle. Generally, these cycles involve several host species, one or more reservoir hosts, vector(s) and incidental hosts, and the pathogen itself. In this way, the pathogen transmission cycle represents a suite of species, each distributed according to its own ecological needs and thereby constraining the pathogen to the region where the host ranges intersect. Humans have occurred in all corners of the globe for millennia, and so it is only natural for the pathogens that rely solely on this ever-present host to also occupy the same broad geographic distribution. Almost no other species occurs as broadly and uniformly as humans, and therefore the many pathogens that require nonhuman hosts are restricted to the more localized distributions of their animal hosts. In this way, endemic pathogens occur at the intersection of specific environmental and biological conditions, and their expansion strongly depends on the capacities of their hosts to disperse and sustain viable populations outside their typical boundaries or on their exposure to new but suitable hosts. The distribution of pathogen occurrences and geographical patterns can be seen as the joint spatial distribution of suitable ecological and demographic conditions for all the species involved in a pathogen's life cycle (Combes 2005, Peterson 2008).

CONTEMPORARY AND FUTURE DRIVERS OF HUMAN PATHOGENS

We can use the growing number of studies on EIDs as a starting point for considering the contemporary drivers of human pathogen distributions. Despite the growing acceptance that disease emergence is related, at least in part, to human-induced changes to the socioeconomic

and ecological environment (Jones et al. 2008, Woolhouse & Gowtage-Sequeria 2005), only a small number of studies has demonstrated an empirical link (Plowright et al. 2008). This is not entirely surprising given that environmental change and pathogen emergence are often the result of complex processes occurring over broad scales that are difficult to study using the traditional tools of ecology. Nevertheless, a handful of systematic literature surveys and correlational studies of the relationship between the spatial pattern of EID events and socioeconomic and ecological variables suggests that disease emergence is not random but increasingly the result of human activity.

A seminal assessment in 2005 provided one of the first data-driven rankings of the drivers associated with emerging human pathogens. Drivers (ranked by the number of pathogen species associated with them—most to least) include the following: (1) changes in land use or agricultural practices, (2) changes in human demographics and society, (3) poor population health, (4) hospital and medical procedures, (5) pathogen evolution, (6) contamination of food supplies or water sources, (7) international travel, (8) failure of public health programs, (9) international trade, and (10) climate change (Woolhouse & Gowtage-Sequeria 2005). In a sample of 335 EID events since 1940, human population density was the most common independent predictor of emergence, regardless of host or transmission requirements (Jones et al. 2008). The increasing number of EID events caused by zoonotic pathogens from wildlife was significantly correlated with wildlife biodiversity, implying a recent change in the factors that mediate contact between wildlife and humans (Jones et al. 2008). Emerging infectious diseases caused by drug-resistant pathogens are significantly correlated with socioeconomic conditions, suggesting a potential link to antimicrobial drug use, particularly in the developed nations of temperate latitudes (**Figure 2**). These recent findings support previous hypotheses that disease emergence is largely a product of anthropogenic and demographic change and is a hidden cost of human economic development (Jones et al. 2008). Below, we review several of the more commonly proposed drivers of disease emergence, paying particular attention to those that have not received recent and extensive review elsewhere.

Climate Change

Climate change is often cited as an increasingly relevant, albeit controversial, driver of pathogen emergence. Given space constraints in this review and a very recent high-profile forum on the topic in the journal *Ecology*, we do not review climate change here (but see the sidebar, Pathogen Losses and Gains from the Global Population). Instead, we refer readers directly to the forum, *Climate Change and Infectious Disease*, which demonstrates the complex link between climate change and infectious disease, and calls for rigorous empirical evaluation to differentiate the pathogens that will experience a net increase versus decrease in their geographic distribution as a result of changing climate conditions. (Dobson 2009; Harvell et al. 2009; Lafferty 2009a,b; Ostfeld 2009; Pascual & Bouma 2009; Randolph 2009; Wilson 2009).

Trade, Travel, and Transport

Rapid changes in transportation technology since the Age of Exploration have brought about the end of natural isolation as a defensive barrier to pathogen introduction (Cliff & Haggett 1995). Trade and travel continue to increase at astonishing rates. Since the mid-1800s, growth in the international movement of passengers across national boundaries has been ~7.5–10% annually. Pathogen pollution, the introduction of a pathogen to a new host species, population, or region, is a direct result of the magnitude and frequency of global transportation. There are several ways that pathogen pollution can occur, but in each case human activity results in a pathogen crossing a geographical, ecological, or evolutionary boundary (Cunningham et al. 2003). After thousands

PATHOGEN LOSSES AND GAINS FROM THE GLOBAL POPULATION

Conservation biology tells us that species are being lost at unprecedented rates, largely as a result of human impacts to the environment. Climate change, for example, is widely predicted to cause substantial regional and global species extinctions (Araújo et al. 2006, Lawler et al. 2009). Interestingly, the argument is reversed for infectious diseases, which appear to be accumulating in the human population in response to environmental change. It has been long assumed that a warmer planet will facilitate the expansion of pathogens out of the tropics to occupy larger geographic ranges; however, a new argument suggests that pathogens will be lost from low latitudes, shifting northward into more favorable climates and smaller ranges (Dobson 2009; Harvell et al. 2009; Lafferty 2009a,b; Ostfeld 2009; Pascual & Bouma 2009; Randolph 2009; Wilson 2009). Is the discrepancy between global species loss and human pathogen gain real, or are we simply focused on the negative? Because pathogen distributions are ultimately determined by host and vector distributions, we should expect the loss of species to lead to regional (perhaps global) losses of zoonotic pathogens. Considering the socioeconomic and environmental changes that might lead to this outcome will provide a more realistic picture of human pathogen distributions and true gains and losses from the global pathogen pool over time.

of years of human colonization, migration, and travel, pathogen introductions have resulted in the homogenization of human-specific pathogens (Smith et al. 2007). Zoonoses, however, have room to expand (Smith et al. 2007), and their dominance among EIDs suggests they are doing just that (Jones et al. 2008). Three factors are likely to account for the majority of emergent zoonoses over the past century: (*a*) the increased movement of human populations into uninhabited regions, where they come into contact with a large and novel diversity of wildlife (that is, following deforestation in the tropics and increased bushmeat hunting notably in central African nations), (*b*) increased livestock and poultry production, and (*c*) the increased trade and transport of wildlife and domesticated animals over vast distances on a sizeable scale that continues to escalate (that is, for food, pet trade, zoos, and research). The comingling of humans and animals, at both regional and global scales, creates numerous opportunities for pathogens to spread between host groups that had only minimal contact in the ancestral environment. There are many pathways by which humans facilitate the movement of species around the globe, including via ship ballast water, agricultural commerce, and accidentally in our travels. But the global trade in livestock, poultry, and wildlife is, perhaps, most significant (Smith et al. 2009b). These trades have facilitated the introduction of novel pathogens to new regions, including, for example, the 2003 introduction of the monkeypox virus to the United States via a shipment of infected rodents imported from Africa for sale in the pet trade (Di Guilio & Eckburg 2004). Early outbreaks of H5N1 high-pathogenicity avian influenza virus across Southeast Asia, the Middle East, and several African countries seemed to be the result of legal and illegal poultry trade and the trade in poultry products (e.g., feces used in agricultural fertilizer) (Kilpatrick et al. 2006). Each year, 7–70 West Nile virus infectious mosquitoes are predicted to reach Hawaii by airplane (Kilpatrick et al. 2004). As the global transportation network reaches deeper into remaining frontiers, we should continue to see an increase in zoonotic pathogen emergence at all scales.

Land-Use Change

Even 11,000 years after the rise of agrarian societies and the emergence of the first crowd diseases, land-use change remains among the most cited drivers of pathogen emergence (Woolhouse & Gowtage-Sequeria 2005). Land-use change and agriculture seem to be statistically more prominent

in bacterial disease emergence than for viruses and, in general, more strongly influence zoonoses than nonzoonoses (Despommier et al. 2007). Nipah virus (a paramyxovirus belonging to the genus *Henipavirus* within the family Paramyxoviridae) is among the more recent examples of disease emergence following land-use change. Nipah emerged as a new human disease in Malaysia in 1999 and resulted in the death of 105 humans and the slaughter of approximately 1.1 million pigs. This highly pathogenic virus emerged from its natural reservoir host, pteropid fruit bats (suborder Megachiroptera), and has been circumstantially amplified via domestic pigs (Yob et al. 2001). A complex series of environmental, ecological, and anthropological circumstances have been involved in the spillover of this virus to humans. Deforestation in Indonesia coupled with severe drought in the mid-1990s and forest fires in Sumatra have dramatically altered native fruit bat habitats. Yob et al. (2001) proposed that fruit bats, forced to migrate to peninsular Malaysia for food, were particularly drawn to fruit tree crops (e.g., mango, rambutan) around pig farms, resulting in close contact between Nipah-infected bats and susceptible pigs and farmers (Daszak et al. 2000). The emergence of pathogens like Nipah demonstrates the existence of an indirect link between land-use change and pathogen spread to new host species (Daszak et al. 2004). A related driver of emerging human pathogens is biological diversity.

Biological Diversity

Debate ensues about the relationship between biological diversity and infectious disease. A potential causal link between biodiversity loss and disease emergence is frequently discussed, but much of the science remains theoretical, and little data are available for testing hypotheses (Dobson 2004). It is intuitive to accept the idea that higher overall animal biodiversity might facilitate a greater diversity of pathogens, and thereby a greater incidence of zoonotic disease in humans (Sattenspiel 2000, Wolfe et al. 2005). This line of thinking might explain the finding that EID events in the past century caused by zoonotic pathogens from wildlife were significantly correlated with both wildlife biodiversity and human population density (Jones et al. 2008). The simple act of bringing a large number of humans in contact with a diverse pool of wildlife species sets the stage for the spillover of zoonotics. On the flip side, a growing body of research in disease ecology supports the opposite outcome, where high biological diversity reduces the risk of pathogen spillover to humans. This concept, known as the dilution effect, was first demonstrated in New England forest communities, where high vertebrate host diversity reduced contact rates between white-footed mice and deer ticks (the primary reservoir and vector host for Lyme disease) and subsequently reduced the risk of Lyme disease spread to humans (Ostfeld & Keesing 2000a,b). The dilution effect has largely been observed in the context of Lyme disease, but might also explain West Nile virus incidence in the United States and rodent-borne hemorrhagic fevers (Allan et al. 2009, Swaddle & Calos 2008). Findings such as these suggest an important ecosystem service provided by biodiversity, further supporting the growing view that protecting biodiversity is a boon to public health. Ironically, it does not matter whether biodiversity facilitates or dilutes pathogen spillover to humans, because experts on both sides argue for the same outcome—that is, to conserve biological diversity. By limiting human access to regions rich in biodiversity, we simply reduce opportunities for pathogens to spill over from wildlife to humans. Likewise, by preserving biological diversity in close proximity to humans, we can dilute the number of infected hosts and thereby reduce the likelihood of spillover to humans.

Pathogen Evolution

The emergence of crowd epidemic diseases during the rise of agriculture demonstrates the powerful role that evolution plays in the diversity and distribution of human pathogens. Newly evolved

pathogens and those recently introduced to humans continue to account for a significant number of emerging pathogens. Wolfe et al. (2007) suggested that the latter are of particular concern, having not been previously subject to evolutionary constraints on their virulence (for example, Ebola virus and the SARS coronavirus). The successful spread of an animal-derived pathogen in the human population strongly depends on its genetic background. It is not surprising, then, that the majority of animal-derived diseases in humans arose from the pathogens harbored by other mammals. Primates represent a small fraction of mammalian diversity but, because of their close phylogenetic relationship to humans, have contributed ~20% of major human pathogens. In contrast to pathogen establishment by relatedness is pathogen establishment by opportunity. Despite their distant relationship to humans, many zoonoses have been acquired from rodents because of their high abundance and frequent contact with humans (Wolfe et al. 2007). How then does genetic change allow an animal pathogen to successfully invade a human population occur?

R_0: mean number of secondary cases a typical single infected case will cause in a population with no immunity in the absence of interventions

On one hand, pathogen invasion depends on adaptation in the human population. The probability that an animal pathogen will adapt to successfully establish in humans depends on several factors such as (*a*) the number of primary infections, (*b*) the initial R_0 of the infection in the population, (*c*) the number of mutations or other genetic changes required, and (*d*) the likelihood of these changes occurring and how R_0 changes at each step (Woolhouse et al. 2005). The final step in a successful species jump is for the pathogen to be sufficiently transmissible between individuals in the human population. This relates to the value of R_0, with $R_0 > 1$ indicating a successful invasion and $R_0 < 1$ resulting in pathogen extinction in humans. On the other hand, genetic change within the original reservoir (whether animal or environmental) is crucial for producing variants capable of infecting humans in the first place. Examples include the RNA viruses that comprise 37% of all emerging pathogens, many of which only recently entered the human population (for example, HIV) (Woolhouse & Gowtage-Sequeria 2005). Higher nucleotide substitution rates in these viruses facilitate rapid adaptation, greatly increasing the chances of successfully invading a new host population such as humans (Woolhouse et al. 2005). Despite growing interest in the role of evolution in pathogen emergence, little information exists on the genetic diversity of human pathogens or their ancestral nonhuman reservoirs (exceptions being the simian immunodeficiency viruses). Advances in genomics and a growing interest in antibiotic resistance should change this in coming decades.

Antibiotic resistance can occur either as a consequence of genetic change (that is, mutations) or the acquisition of resistant genes through horizontal gene transfer (Martinez et al. 2009). Today, various genera of *Streptococcus*, *Staphylococcus*, and members of the *Enterobacteriaceae* and *Pseudomonas* families are resistant to most antibiotics, and multidrug-resistant tuberculosis is causing pandemics among human subpopulations with weakened resistance, such as HIV patients. The significance of emerging drug-resistant bacteria was recently illustrated in the Jones et al. (2008) study of EID events since 1940. Unlike previous studies on emerging human pathogens, their analyses classified each individual drug-resistant microbial strain as a separate pathogen, revealing that 21% of EID events were caused by drug-resistant microbes, which have increased significantly with time, particularly in developing nations. These findings, along with the fact that different bacterial strains have often caused unique outbreaks (Cohen 2000), demonstrate the global significance of antimicrobial drug resistance.

Human Population Size and Density

More than 50 years ago, Bartlett's (1957) study of measles identified the concept of critical community size (CCS); the population threshold above which pathogen fade-out is unlikely and below which infections do not persist. The CCS for measles, and many other pathogens is ~250,000

(Grenfell et al. 2001). Minimum CCS for long-term persistence ranges from 200,000 to 500,000 inhabitants in populations with good hygienic standards, but can be as low as 50,000–150,000 in populations with poor standards of hygiene. Larger host populations can harbor greater numbers of susceptible individuals, an important parameter for long-term persistence, whereas higher density facilitates transmission for contagious and vector-borne diseases such as dengue fever (Broutin et al. 2004, Rohani et al. 1999, Scott & Morrison 2003). Rapid urbanization during the nineteenth century in Europe facilitated the spread of infectious diseases such as childhood pneumonia, diarrhea, and tuberculosis and more recently contributed to the emergence of pathogens such as SARS in Hong Kong in early 2003 (Cohen 2003). Poverty and malnutrition that come with urbanization in impoverished neighborhoods and the weakening of public health infrastructure perpetuates vulnerability to disease. The finding that human population density is the single best predictor of pathogen emergence, regardless of host or transmission requirements (Jones et al. 2008), suggests that short of halting population growth and urbanization, we can expect continued encounters with emerging pathogens well into the future. This is a timeless tale where host population size and density continue to be key parameters in disease population dynamics. As predicted, rapid population growth in the developing nations of tropical Southeast Asia will be the hardest hit by emerging pathogens (Jones et al. 2008).

CONCLUSIONS AND FUTURE DIRECTIONS

Our review identifies three timeless actions by humans that create key opportunities for pathogens to change their geographic or host range: (*a*) the magnitude and diversity of landscape changes, including deforestation and agricultural development, that alter vector and reservoir host communities, (*b*) changes in contact rates with wildlife and domestic animals at local scales, and at global scales where wildlife, livestock, and poultry are introduced to new regions with susceptible human populations, and (*c*) national variation in public health practices, including the development and distribution of antibiotics and vector control. Because human population growth, disparities in development that trickle down to public health, and expansion of global transportation networks will continue, we can anticipate two future outcomes. First, zoonotic diseases will continue to emerge locally, and a fraction will evolve to spread human to human and achieve global distributions and potential pandemic status. Second, developing nations will continue to experience a rise in multidrug-resistant strains of various pathogens. In contrast to the past, we are fortunate to have advanced molecular tools at our disposal that allow us to quickly indentify newly emerging pathogens such as SARS, which was described in less than six weeks. Our general understanding of why these pathogens occur where they do, however, remains relatively incomplete. Below, we list some of the key questions and future areas of research we believe are critical to advance our understanding of where human pathogens occur, why, and how these distributions shift over time:

1. Equal consideration of pathogen loss, through control and eradication, in addition to gains from emergence will provide a more accurate picture of changing global pathogen distributions. A balanced approach will determine if we are winning or losing the war against infectious disease and where the most critical battles are being fought. The outcome of these tallies will depend on how we choose to define an EID.
2. Individual drivers of pathogen emergence have been identified, but how do they act synergistically? Do certain combinations of drivers create worst case scenarios for pathogen emergence? If there are predictable relationships between the drivers and pathways to emergence, these need to be built into future prediction models for disease occurrence.
3. People of developing nations, many of whom live in poverty, are at greater risk of infectious disease, yet illness contributes to poverty. Disease-mediated poverty traps exist worldwide

and should be included among the overwhelmingly environmental and evolutionary drivers of global pathogen distributions.

4. How do the geographic distributions of nonemerging and emerging human pathogens vary in real time? Comparing the similarities and differences between these two pathogen groups can help identify general patterns and processes in disease biogeography.
5. What lessons can we borrow from conservation biology and research on the drivers of species extinction to identify the socioeconomic and environmental changes most likely to cause pathogen loss in human populations at regional and global scales?

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