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GLOBALIZATION OF HUMAN INFECTIOUS DISEASE

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Abstract. Globalization has facilitated the spread of numerous infectious agents to all corners of the planet. Analysis of the Global Infectious Disease and Epidemiology Network (GIDEON) database quantitatively illustrates that the globalization of human infectious agents depends significantly on the range of hosts used. Infectious agents specific to humans are broadly and uniformly distributed, whereas zoonotic infectious agents are far more localized in their geographical distribution. Moreover, these patterns vary depending on transmission mode and infectious agent taxonomy. This dichotomy is unlikely to persist if certain aspects of globalization (for example, exotic species introductions) continue unabated. This raises a serious concern for public health and leaves nations with the task of determining the infectious agents that have the greatest potential to establish within their borders. At the advent of a century characterized by an apparent increase in emerging infectious diseases, these results have critical implications for public-health policy and future research pathways of infectious disease ecology.

Key words: *globalization; humans; infectious agents; public health; transmission; zoonoses.*

INTRODUCTION

For thousands of years, globalization has facilitated a steady increase in the cross-border trading of goods, ideas, cultures, and people. Today, while the social and economic impacts of globalization are contentious, the effects on public health are more clear. The breakdown of barriers to human movement and international trade exchanges have enhanced the spread of novel infectious agents to susceptible populations across the planet (McNeill 1989, Settipane 1995). Recent examples include the introduction of West Nile virus to the United States, the 2002–2003 SARS epidemic, and avian influenza H5N1 (CDC 2003, Spielman et al. 2004, Fauci 2005, Olsen et al. 2006), though these are not new phenomena. Indeed, the magnitude of globalization has created a world where many historically localized infectious agents are now broadly distributed and shared between widely separated regions (McNeill 1989, Settipane 1995). What, then, constrains the globalization of the remaining localized infectious agents?

Among the factors that contribute to the geographic distribution of human infectious agents, the presence of appropriate hosts is a primary driver (Hayden et al. 2002, Guernier et al. 2004). More than 1400 infectious agents are known to afflict mankind, three-quarters of which also infect wildlife and domesticated species (Taylor et al. 2001). Given the range of hosts used by these infectious agents, the propensity for human infectious agents to establish in a new region should differ depending on their hosts' geographical distribution.

Using the Global Infectious Disease and Epidemiology Network (GIDEON) database, we examined the extent to which human infectious agents with varying arrays of reservoir hosts are globalized in their distribution. We use the term globalized to mean broadly and uniformly distributed across geographic (continental) and political (national) boundaries. Our analyses tested the Baas-Becking hypothesis for microbial taxa, "everything is everywhere–the environment selects," at two large scales (Beijerinck 1913, Baas-Becking 1934, Hughes et al. 2006). Dutch microbiologist Lourens G. M. Baas-Becking coined the phrase to describe the ability of microbes to disperse broadly and flourish in suitable environments, provided they can adapt to survive these new habitats.

We further examined how these patterns vary depending on two additional drivers: (1) general mode of transmission and (2) infectious agent taxonomy. We

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quantitatively show that infectious agents specific to humans are highly globalized, while those that use non-human hosts remain far more localized; further, these patterns vary depending on transmission mode and infectious agent taxonomy.

Materials and Methods

Data compilation

GIDEON is a subscription-based diagnostic and reference web application that provides extensive geographic and epidemiological information for 332 human infectious agents.[6] The data are accessed and collated through a system of computer macros and dedicated source lists developed over the past 15 years. A monthly search of Medline is conducted against a listing of all GIDEON key words, and titles and abstracts of interest are reviewed. All available national Health Ministry publications are scanned, as are standard publications of the World Health Organization (WHO) and the Centers for Disease Control (CDC). Relevant peer-reviewed publications are continually examined for relevant articles.

GIDEON organizes infectious agents into five basic taxonomic groups: bacteria, fungi, parasites (cestodes, nematodes, trematodes, and acanthocephalans), protistans, and viruses. Infectious agents are reported as present in or absent from over 223 nations or territories of the world. GIDEON designates presence based on the reported occurrence of autochthonous, or locally acquired, cases at a particular point in time. In some instances, a given infectious agent has been reported in only recent years, as opposed to continued, ongoing occurrences. For example, monkeypox virus was present in the United States during its 2003 outbreak; however, since that time the infectious agent is no longer found in the USA or listed with the country in GIDEON.

We compiled presence–absence data for the 332 human infectious agents established in 223 nations or territories from GIDEON (Appendix). Infectious agents with unknown presence/absence information for >10% of nations were excluded from analyses. We also excluded the following: syndromes, infectious agents with no information on reservoir–host or vector–host requirements, and those that exclusively depend on non-animal hosts (soil, water, vegetation). Some infectious agents met more than one of these removal criteria. For the remaining 298 infectious agents, when presence/absence was unknown for a given nation, we assumed the infectious agent was absent (only 0.006% of all nation–infectious agent pairs were unknown). Human infectious agents were sorted into five "continental groups": Asia, Africa, Europe, North America, and South America (Australia was excluded due to a lack of intracontinental nation states required for analyses).

[6] ⟨http://www.gideononline.com/⟩

GIDEON characterizes infectious agents by the associated "reservoir" and "vector" hosts. GIDEON defines reservoir hosts as any animal, plant, or substrate on which the infectious agent normally lives and/or multiplies, on which it depends primarily for survival, and/or where it reproduces in such a manner that promotes its transmission to other susceptible hosts. Vector hosts are defined as organisms that facilitate transmission of infectious agents between hosts. In cases where the infectious agent undergoes development in the vector host, GIDEON also assigns the vector host to the reservoir host list. We divided infectious agents into three reservoir host categories based on GIDEON's host designations (Appendix) and definitions:

1) Human specific ($n = 109$): Many infectious agents known to afflict mankind are currently entirely restricted to human reservoir hosts (i.e., contagious only between persons), even though they historically may have arisen in other species, such as measles which originated in cattle. Examples of human-specific infectious agents represented in the GIDEON database include measles, smallpox, and syphilis.

2) Zoonotic ($n = 152$): Infectious agents that develop, mature, and reproduce entirely in non-human hosts, but nonetheless have the potential to spill over and infect human populations, are referred to herein as zoonotic infectious agents. Humans are a dead-end host for infectious agents in this group. Examples of zoonotic infectious agents in the GIDEON database include rabies, plague, and hantavirus.

3) Multi-host ($n = 37$). Some infectious agents can use both human and non-human hosts to complete their lifecycle. Oftentimes these infectious agents are lumped with zoonotics, but for the purposes of this study we distinguish them with the term multi-host infectious agent ("multi" referring to both human and non-human hosts). Examples of multi-host infectious agents in the GIDEON database include the three forms of leishmaniasis (cutaneous, mucocutaneous, and visceral) that can use humans, wild, and/or domestic animals as reservoir hosts.

Twenty-three infectious agents had vector hosts that were also listed as reservoir hosts. Only one of these, malaria, would have been classified in a different host category (zoonotic instead of multi-host infectious agent), had GIDEON excluded vector hosts from the reservoir host list. Infectious agent taxonomy (bacteria, fungus, parasite, protista, virus) and mode of transmission (vector or nonvector borne) were noted for each infectious agent. Given a substantial lack of data, we did not consider protistans or fungi in taxonomic analyses.

Analyses

Efforts to quantify similarity in the composition of biota between disparate regions have primarily used (1) Jaccard's and other community indices (Krebs 1999) and (2) the linear slope of log-transformed species–area curves (McKinney 1998, Rahel 2000, Rosenzweig 2001,

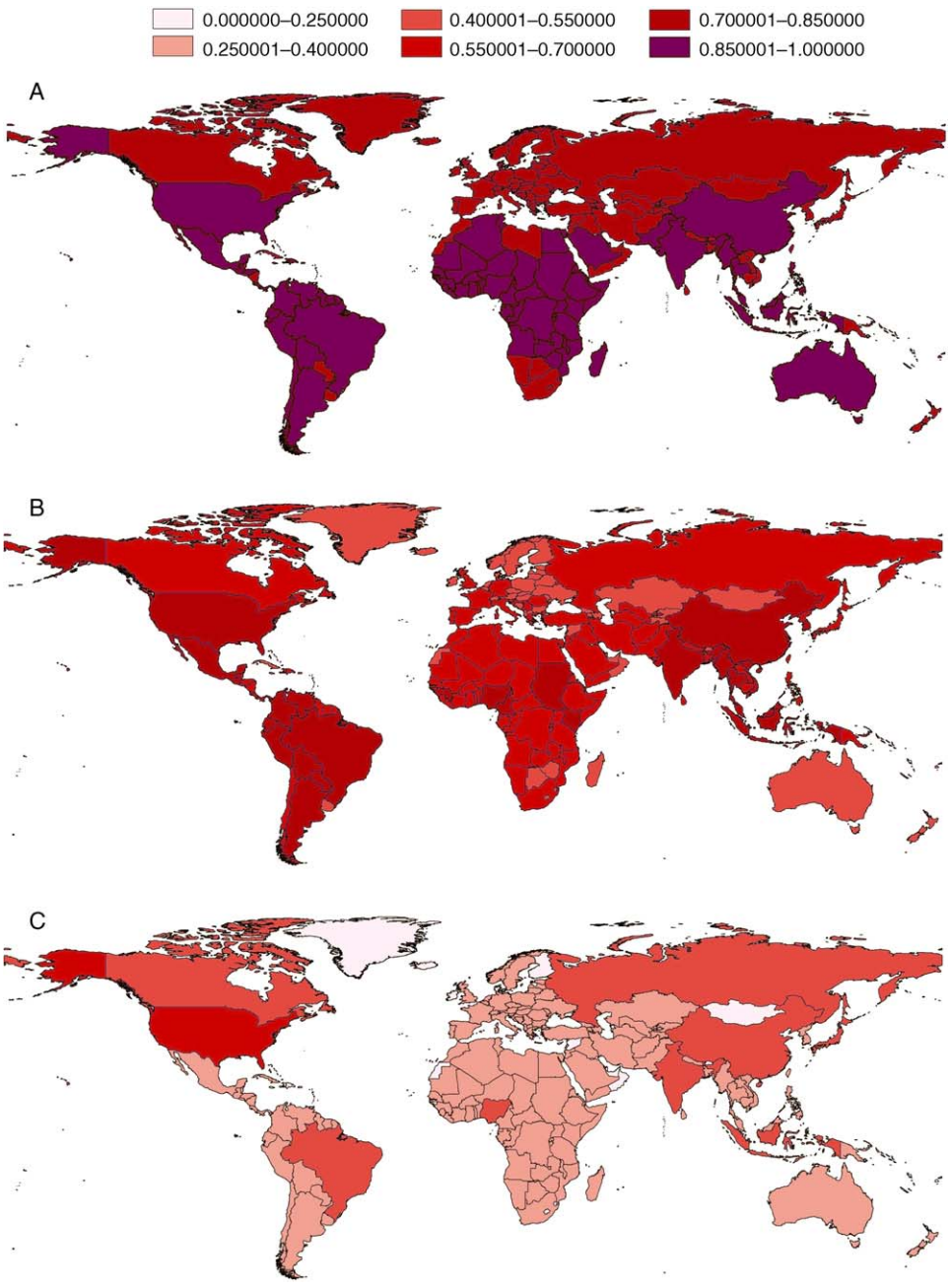

FIG. 1. Nations of the world color coded by the proportion of autochthonous, or locally acquired, human infectious agents. Large proportions are denoted by dark colors, and low proportions are denoted by light colors. (A) Infectious agents specific to humans, (B) multi-host infectious agents, (C) zoonotic infectious agents.

Azovsky 2002, Collins et al. 2002, Finlay 2002, Horner-Devine et al. 2004, Smith et al. 2005). We used both methods to quantify the globalization of human infectious agents at the scale of continents and nations. Analyses at the level of infectious agent genera were conducted to account for potential overrepresentation of certain taxa. Results at both taxonomic levels were qualitatively and quantitatively similar. As such, we only present results from species-level analyses.

Continental scale.—Jaccard's index of similarity is one of the most commonly used methods in ecology for quantifying overlap in community similarity (Krebs 1999, Rahel 2000). Jaccard's indices range from 0 (e.g., no infectious agents in common between two populations) to 1 (e.g., identical infectious agent composition between two populations) and is calculated as $J(x_1 \cdot x_2) = a/(a+b+c)$, where x_1 and x_2 represent two regions, a is the number of human infectious agents present in both

TABLE 1. Jaccard's similarity indices depict the degree of overlap in (A) human infectious agent, (B) multi-host infectious agent, and (C) zoonotic infectious agent composition among continents.

Continent	Africa	Europe	North America	South America
A) Human specific				
Asia	0.92	0.96	0.92	0.92
Africa		0.92	0.95	0.93
Europe			0.92	0.92
North America				0.96
B) Multi-host				
Asia	0.76	0.87	0.87	0.79
Africa		0.84	0.92	0.92
Europe			0.89	0.87
North America				0.92
C) Zoonotic				
Asia	0.72	0.72	0.63	0.61
Africa		0.69	0.70	0.67
Europe			0.72	0.61
North America				0.79

Notes: High indices represent a large degree of compositional overlap, while low indices represent a lesser degree of compositional overlap. A pairwise median test was used to rank continental similarity indices based on host category (highest to lowest degree of overlap in infectious agent composition among continents): human specific > multi-host, $\chi^2_2 = 9.2800$, $P = 0.0023$; human specific > zoonotic, $\chi^2_2 = 29.0$, $P < 0.0001$; multi-host > zoonotic, $\chi^2_2 = 21.782$, $P < 0.0001$.

x_1 and x_2, b is the number of human infectious agents present exclusively in x_1, and c is the number of human infectious agents present exclusively in x_2. Jaccard's indices were calculated to quantify overlap in the composition of human infectious agents for all continental pairs (i.e., Asia–Africa, Asia–Europe, Asia–North America, Asia–South America) and for each host category (human specific, multi-host, and zoonotic infectious agents). Island nations were excluded from this analysis. A median test was used to test whether Jaccard's indices were significantly different among the three host categories. Bonferroni-corrected pair-wise median tests were then used to rank the mean values of Jaccard's indices (highest indices, i.e., greatest overlap; lowest indices, i.e., least overlap) for the three host categories.

National scale.—Recently, species–area relationships have been employed as a tool to assess uniformity in biotic composition across regions (e.g., Rahel 2000, Collins et al. 2002). This is done using the slope of the line (z) when log number of species is plotted against log area. The slope of this relationship depends strongly on the overlap in the biotic composition of the localities analyzed. When regions, regardless of their size, share the majority of infectious agents, z approaches 0 (shallow slope). In contrast, when larger areas harbor more infectious agents, z is relatively large (steep slope). Here we use the species–area relationship to quantify uniformity in the composition of human infectious agents among nations. In doing so, we are concerned with discerning the globalization of human infectious agents, and not the drivers of national infectious agent richness (again, this latter topic is fully addressed by Guernier et al. 2004 using the same data set). We selected nation land surface area as our independent variable and number of human infectious agents as our dependent variable. This analysis included both continental and island nations. National land surface area (km^2) was compiled from the 2003 Central Intelligence Agency (CIA) World Factbook.[7] The total numbers of human specific, multi-host, and zoonotic infectious agents present in each nation were plotted against nation surface area on log–log plots to determine the linear slope (i.e., z value). Slopes were compared (using two-way ANOVA) among host categories, infectious agents with different transmission requirements (vector borne vs. nonvector borne), and taxonomic categories (bacteria vs. parasites vs. viruses).

Because the occurrence of infectious agents is largely dependent on host availability, we recognize that host population size, in addition to land surface area, may also be used as the independent variable in the relationships described (where the host population serves as the ultimate "area" in which an infectious agent occurs). Unfortunately, while data on human population size by nation are available, comparable data for the population size of non-human hosts (in the case of multi-host and zoonotic infectious agents) is largely unavailable. This presents a problem when attempting to calculate the complete host population size for human infectious agents requiring non-human hosts. Analyses based solely on human population size are therefore difficult to interpret. Nevertheless, we examined uniformity in the composition of human infectious agents among nations using human population size (compiled for nations from the 2003 CIA World Factbook) as the independent variable. As these analyses produced the same qualitative results as those described for land surface area, we do not present these findings (see Guernier et al. 2004 for analyses that explore population size and land surface area as mechanistic drivers of infectious agent richness).

RESULTS

The majority of human infectious agents are present on each continent. However, human-specific and multi-host infectious agents are more broadly distributed than zoonotic infectious agents (Fig. 1). Uniformity in the composition of human infectious agents present on each continent is significantly different for the three host categories (median test: $\chi^2_2 = 29.39$, $P < 0.0001$; Table 1). Human-specific infectious agents exhibit the greatest degree of globalization among continents, followed by multi-host infectious agents, and finally zoonotic infectious agents (Table 1). A similar pattern emerges at the

[7] ⟨https://www.cia.gov/cia/publications/factbook/index.html⟩

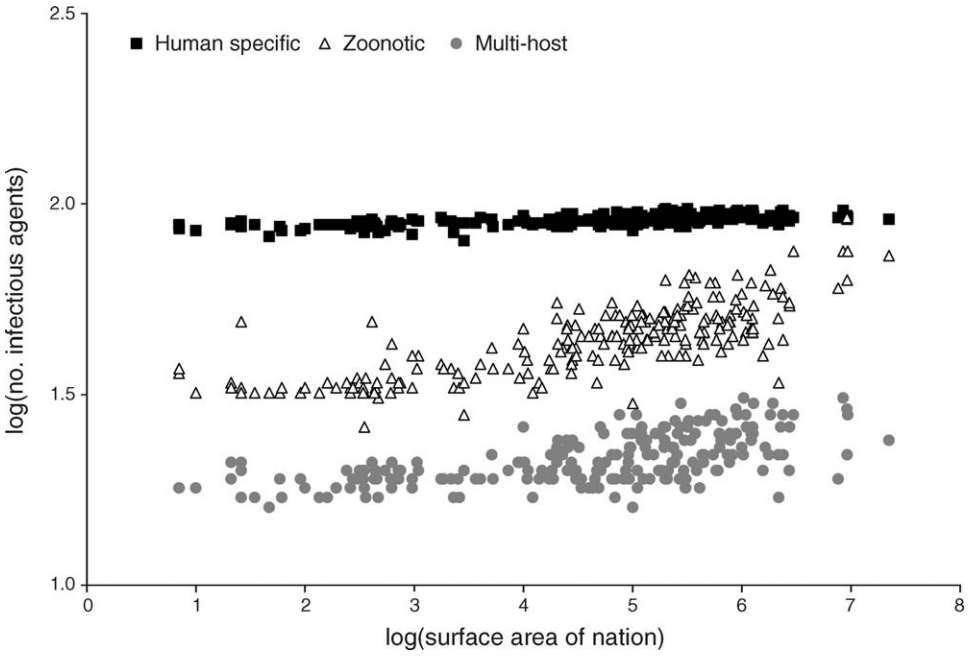

FIG. 2. Log number of infectious agents plotted against log nation surface area (km^2) for the three host categories: human specific ($y = 1.94 + 0.0060x$, $r^2 = 0.40$, $P < 0.0001$); zoonotic ($y = 1.44 + 0.0508x$, $r^2 = 0.62$, $P < 0.0001$); multi-host ($y = 1.22 + 0.0260x$, $r^2 = 0.37$, $P < 0.0001$). Linear slopes are significantly different for the three host categories. Two-way ANOVA was used to compare linear slopes and thus assess variation in the globalization of infectious agents among host categories (small slope = high globalization/uniformity on infectious agent composition): zoonotic slope > human specific slope $F_{1,440} = 245.308$, $P < 0.0001$; zoonotic slope > multi-host slope: $F_{1,440} = 38.201$, $P < 0.0001$; multi-host slope > human specific slope: $F_{1,440} = 73.756$, $P < 0.0001$.

scale of nations (Fig. 1). On average, nations harbor more than 75% of all human specific infectious agents represented in GIDEON, but only 30% of all zoonotic infectious agents. Uniformity in the composition of infectious agents present among the nations of the world also varies with the range of hosts used ($F_{2,660} = 105.462$, $P < 0.0001$; Fig. 2). Infectious agents specific to humans are highly globalized, followed by multi-host infectious agents which are less so, and finally zoonotic infectious agents which are least globalized (Fig. 2). The extent of globalization within host categories further varies with transmission mode and infectious agent taxonomy.

For human specific, multi-host, and zoonotic infectious agents, nonvector-borne infectious agents are significantly more ubiquitous than those that require vectors (human specific, $F_{1,440} = 35.077$, $P < 0.0001$; multi-host, $F_{1,440} = 121.083$, $P < 0.0001$; zoonotic, $F_{1,440} = 86.35$, $P < 0.0001$). Nonvector-borne human-specific infectious agents exhibit the highest degree of globalization, followed by nonvector-borne multi-host, vector-borne human-specific, nonvector-borne zoonotic, vector-borne zoonotic, and finally vector-borne multi-host infectious agents (Table 2A). The extent of globalization also varies significantly depending on infectious agent taxonomy for each of the three host categories (human specific, $F_{2,660} = 20.934$, $P < 0.0001$; multi-host, $F_{2,660} = 19.953$, $P < 0.0001$; zoonotic, $F_{2,660} = 131.275$, $P < 0.0001$). For both human-specific and multi-host infectious agents, viruses are most ubiquitous at the national scale, followed by parasites, and finally bacteria. Among zoonotic infectious agents, however, bacteria are the most ubiquitous, followed by parasites, and finally viruses (Table 2B).

DISCUSSION

We have shown that human infectious agents are broadly and uniformly distributed around the globe, but the magnitude of distribution varies greatly with host requirement, mode of transmission, and infectious agent taxonomy. Infectious agents specific to humans are highly globalized, supporting the Baas-Becking hypothesis, while multi-host and, most significantly, zoonotic infectious agents, are much more localized. This suggests that the latitudinal gradient of infectious agent richness reported by Guernier et al. (2004) is driven, in part, by the disproportionate number of zoonotic and multi-host infectious agents endemic to tropical nations. Within host categories, nonvector-borne infectious agents are more globalized than those that require vectors for transmission. Bacteria, parasites, and viruses also vary in geographic scope depending on whether humans act as reservoir hosts.

The global scale of this study increases the likelihood of missing or imprecise data. It may be argued, for example, that infectious agents present in underdeveloped nations are less well studied than those in highly

TABLE 2. Linear regression variables for the three infectious agent host categories broken down by (A) transmission mode and (B) infectious agent taxonomy.

Transmission and taxonomy	Slope (95% CI)	Intercept (95% CI)	R^2	P	N
A) Transmission mode, by host type					
Human specific					
Vector	0.0300 (0.0216–0.0384)	0.6121 (0.5719–0.6523)	0.1818	<0.0001	13
Non-vector	0.0045 (0.0037–0.0052)	1.9071 (1.9040–1.9110)	0.4109	<0.0001	96
Multi-host					
Vector	0.1195 (0.1001–0.1388)	−0.0179 (−0.1103–0.0745)	0.4001	<0.0001	12
Non-vector	0.0097 (0.0067–0.0126)	1.2009 (1.1870–1.2150)	0.1598	<0.0001	25
Zoonotic					
Vector	0.1056 (0.0923–0.1188)	0.4107 (0.3474–0.4740)	0.5261	<0.0001	57
Non-vector	0.0390 (0.0343–0.0436)	1.3714 (1.3490–1.3940)	0.5499	<0.0001	95
B) Taxonomic group, by host type					
Human specific					
Bacteria	0.0059 (0.0048–0.0069)	1.6435 (1.6390–1.6480)	0.3670	<0.0001	58
Helminth	0.0138 (0.0100–0.0175)	1.0409 (1.0230–1.0590)	0.1903	<0.0001	18
Virus	0.0036 (0.0027–0.0043)	1.4282 (1.4240–1.4320)	0.2547	<0.0001	30
Multi-host					
Bacteria	0.0199 (0.0164–0.0233)	0.9428 (0.9262–0.9595)	0.3637	<0.0001	14
Helminth	0.0504 (0.0407–0.0600)	0.5099 (0.4639–0.5559)	0.3240	<0.0001	17
Virus	0.0183 (0.0091–0.0275)	0.5061 (0.4622–0.5499)	0.0653	0.0001	4
Zoonotic					
Bacteria	0.0218 (0.0178–0.0257)	1.2211 (1.2020–1.2400)	0.3460	<0.0001	39
Helminth	0.0598 (0.0525–0.0669)	0.8617 (0.8273–0.8961)	0.5462	<0.0001	54
Virus	0.1843 (0.1609–0.2076)	−0.3234 (−0.4350 to −0.2119)	0.5215	<0.0001	51

Note: Here, "slope" is analogous to z value.

developed nations. However, this should not represent a major bias in our study as the majority of underdeveloped nations are also the nations with the highest recorded number of infectious agents (Guernier et al. 2004). Nevertheless, we recognize that future research in these regions will undoubtedly yield the discovery of additional infectious agents. As with any analyses based on the best available data, our results may be modified by future contributions to GIDEON, though we do not expect this to qualitatively change the results presented here. Indeed, GIDEON does not yet include all infectious agents known to afflict humans (though the number of infectious agents in each host category that is represented in the database is in proportion to that of known human infectious agents; Taylor et al. 2001, Woolhouse and Gowtage-Sequeira 2005). GIDEON does, however, offer the most comprehensive public database on the geographic occurrence of human infectious agents. We are confident that the patterns presented here are representative of the greater pool of human infectious agents.

The globalization of human infectious agents is perhaps not surprising, although the degree to which this has occurred is somewhat unexpected. Even though biological diversity is becoming increasingly uniform across the globe (McKinney and Lockwood 1999, Lockwood et al. 2000, Rahel 2000), typical levels of overlap among taxa across nations are much lower. Consider that slopes of species–area relationships published for well-studied groups (like plants and birds) typically range from 0.15 to 0.35 (Rosenzweig 1995), whereas the z values described here for human specific infectious agents range from 0.003 to 0.03, which is approximately an order of magnitude smaller in value. Thus, human specific infectious agents present an extreme outlier in biotic patterns of globalization. This is likely the result of two factors: (1) the extreme size and movement of human populations among regions of the world and (2) the habitat homogeneity that human hosts provide for infectious agents, as opposed to the greater habitat heterogeneity experienced by noninfectious taxa in their invaded environments. The less extreme z value observed in zoonotic viruses ($z = 0.18$), which is closer to values seen for non-infectious taxa, is likely due to the limiting role that appropriate non-human hosts play in the establishment of zoonoses in new regions. This implies that future increases in the globalization of zoonoses are likely to be tied to the introduction and establishment of exotic animal taxa that can serve as host species. The z values observed among nations of the world for zoonotic, multi-host, and human specific infectious agents present an extreme example of what may be possible for other taxonomic groups as globalization continues.

Our findings offer a unique opportunity to prepare for the future. The lack of chronological records of establishment makes it is difficult to discern how recently human infectious agents became globally ubiquitous. However, the present pattern suggests that infectious agents specific to humans, particularly viruses,

bacteria, and those that do not require vector transmission, have had the greatest opportunity for rapid spread across the globe. Although many multi-host and zoonotic infectious agents are also broadly distributed, a much larger proportion remains localized to specific continents and nations. Among these, parasites, viruses, and those that are vector-borne have the most limited distribution. Consequently, it is these infectious agents that should be the most likely candidates to emerge in the future, as they still have the opportunity to establish in nations where they have been historically absent. There is mounting evidence that this is already happening. Indeed, infectious agents that rely on non-human hosts represent more than three-quarters of recent emerging infectious agents, the majority of which are viruses (Taylor et al. 2001, Woolhouse and Gowtage-Sequeira 2005).

Ten factors have recently been identified as the main drivers of contemporary emerging infectious agents, many of which also contribute to globalization and environmental change: changes in land use/agricultural practices, changes in human demographics/society, poor population health, hospitals and medical procedures, pathogen evolution, contamination of food sources/water supplies, international travel, failure of public health programs, international trade, and climate change (Woolhouse and Gowtage-Sequeira 2005). The importance of these drivers varies with infectious agent taxonomy. For example, pathogen evolution and contamination of food/water are more important drivers of bacterial emergence than international travel and land use change, while the opposite is true for viruses. Equally discrepant, changing land use and agriculture appear to be greater drivers of emerging zoonotic infectious agents than for nonzoonoses (Woolhouse and Gowtage-Sequeira 2005). Beyond general host requirements, however, emerging infectious agents are not strongly linked to specific host groups (i.e., carnivores vs. rodents; Morse 1995, Woolhouse and Gowtage-Sequeira 2005), suggesting that opportunities that present new transmission routes should also increase the likelihood for infectious agent transfer between humans and wildlife.

If certain drivers of globalization and environmental change, such as exotic species introductions, are not slowed or regulated they may play an increasing role in the establishment of novel infectious agents. This raises a serious concern for public health and leaves nations with the tasks of determining the infectious agents that have the greatest potential to establish within their borders. The foremost candidates include infectious agents that use non-human hosts. Of these, viruses, parasites, and those that do not require vectors for transmission have the greatest room for geographic expansion. However, shifts in contemporary climatic regimes have the potential to increase the distribution potential of certain vector-borne infectious agents. Indeed, Dengue fever and malaria are predicted to spread dramatically in the face of global warming as high temperatures lead to higher rates of pathogen reproduction and time to maturity, as well as increased geographic ranges, proliferation, and bite frequency of the mosquito hosts (Epstein 2000). The next step will be to study potential future invading infectious agents on a case-by-case basis, examine the risk of emergence in more detail, and determine which infectious agents have the potential to cause major epidemics in the human population. Achieving this will require immediate and sustained collaboration among public health officials, epidemiologists, and scientists studying wildlife disease ecology and biogeography—a collection of individuals that currently rarely interact. Individual nations will have to work particularly hard at fostering such transdisciplinary collaboration, as each faces a different set of potential infectious agent introductions. As always, prevention is key.

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APPENDIX

A table listing 332 human infectious agents, their taxonomic grouping, and reservoir and vector hosts as determined by the Global Infectious Disease and Epidemiology Network (GIDEON) Database (*Ecological Archives* E088-114-A1).