Review

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Effects of environmental change on zoonotic disease risk: an ecological primer

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Impacts of environmental changes on zoonotic disease risk are the subject of speculation, but lack a coherent framework for understanding environmental drivers of pathogen transmission from animal hosts to humans. We review how environmental factors affect the distributions of zoonotic agents and their transmission to humans, exploring the roles they play in zoonotic systems. We demonstrate the importance of capturing the distributional ecology of any species involved in pathogen transmission, defining the environmental conditions required, and the projection of that niche onto geography. We further review how environmental changes may alter the dispersal behaviour of populations of any component of zoonotic disease systems. Such changes can modify relative importance of different host species for pathogens, modifying contact rates with humans.

The players and the stage for zoonotic diseases

Disease transmission systems are, at heart, sets of interacting species. In the simplest cases, the system involves a single host species such as humans and the particular pathogen that causes a disease; in more complex cases, multiple pathogens and/or hosts, as well as arthropod vectors, may be involved. Pathogenic agents can circulate among one or many species of wild hosts (i.e., zoonotic circulation); they may occasionally 'jump' the species barrier and infect humans, and in a subset of these cases, go on to manifest as disease transmissible between humans. Environmental changes, including changes in climate, landscape characteristics, and communities of zoonotic hosts and vectors, have all been implicated as factors potentially involved in initiating such jumps.

Effects of environmental changes on zoonotic pathogens can take many forms. First, changing climate can affect pathogen burdens in host individuals directly, such as by altering immunocompetence [1]. Second, densities or species composition of host or vector communities can be affected by changes in landscape characteristics or climate [2–7]. Third, contact rates (see Glossary) between zoonotic hosts, humans, and vectors can respond to changes in landscape or climate [8,9]; for instance, Dearing and Dizney [10] showed that habitat changes that reduce mammalian diversity increase hantavirus infection prevalence in deer mice (*Peromyscus maniculatus*) by increasing intraspecific and decreasing interspecific contact rates. Changes in contact rates that accompany environmental changes can occur both within and between populations. Fourth, changes in landscape and climate can affect contact rates between developmental stages of pathogen life cycles and hosts (zoonotic or humans); for instance, environmental stressors can change longevity or movement patterns of environmental stages of vectors or hosts and thereby affect contact rates. It is, however, difficult to discern differential effects of environmental factors on pathogens, vectors, or hosts. Many studies have assessed effects of climate on spatial distributions or life cycles of arthropod vectors [11–13] or subsets of hosts [14]. Others have described the biotic distribution limits of zoonotic agents – their host range – but much uncertainty remains about how specific abiotic variables, acting directly or indirectly, affect zoonotic agents [15–18] (Box 1).

Most zoonotic pathogens are transmitted to humans either directly from zoonotic hosts or indirectly via vectors that acquire infections from the reservoir host and transmit them to humans [11]. In some cases, pathogens can persist in the environment outside of either zoonotic hosts or vectors: for instance, some zoonotic helminths, protozoans, fungi, bacteria, and viruses can persist in soils and water bodies, and can later be transmitted to humans. For most of these pathogens, population growth and reproduction occur

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Glossary

Abiotic niche: the set of physical conditions (e.g., temperature, moisture) that permit a positive turnover of the population of an organism. Very generally, it is the set of features of the weather that allow the persistence of populations of living organisms. Geographic features, such as altitude, are not part of the abiotic niche of an organism.

Allopatry: two or more species (or populations of the same species) are in allopatry when they occur in separate, not overlapping geographic areas (the opposite term is sympatry). In the context of this review, one species may be the vector of a pathogen under laboratory conditions. However, if they occur in allopatry there is not the possibility of contact, and therefore the transmission of the pathogen by the vector is not possible.

Anthropogenic: the term refers to the human impact on the environment and includes impacts on the environment and biodiversity. In a wider sense, the term refers to everything that is originated from human actions.

BAM diagram: a Venn diagram in which the interactions among the Biotic niche, the Abiotic niche, and the Mobility are expressed. This diagram has profound implications for distributional ecology, but it summarises the zones where populations of an organism can have positive turnover, where the relationships with organisms allow the survival of the focus species, and that area reachable from areas where permanent populations exist. Vectors, reservoir hosts, pathogens, and humans are a transmission system that responds to the BAM diagram; the disease is transmitted only where the BAM conditions of all component species are fulfilled.

Biotic niche: the collection of species in an ecosystem that either inhibit (e.g., predators, competitors) or facilitate (mutualists) the focal species. In this review, the focal species may be a pathogen, its vector(s), or its reservoir(s). Therefore, the biotic niche implies a large cluster of connections that may change over time or be altered by human actions or climate.

Contact rates: the number of potentially infectious contacts made per infected host per unit time. In the context of vectors transmitting zoonotic pathogens, a potentially infectious contact is one that is capable of resulting in infection if contact is with an infected vector. The assumption is that the contact rate is directly proportional to density of the reservoir host, vector, and humans.

Dilution effect: the disruption of parasite transmission in a natural ecosystem because the low suitability as hosts of the species added as diversity increases. It is not a universal effect because new species in a community may be very suitable hosts for existing parasites, having positive impacts on their dynamics, creating a 'spillback' effect on the original hosts, which suffer from higher infection rates as a consequence.

Ecological niche modelling: the process of using computer algorithms to capture the niche of a species and project such preferences into the prediction of its distribution in the geographic space on the basis of a mathematical representation of its known distribution in the environmental space. The environment is in most cases represented by climate data (such as temperature and precipitation), but other variables such as soil type, water depth, and land cover can also be used. The concept may be alternatively known as environmental niche modelling, species distribution modelling, ecological niche modelling, predictive habitat distribution modelling, and climate envelope modelling.

Eltonian Noise Hypothesis: an ecological hypothesis in which the biotic factors become much less relevant than the abiotic ones in the definition of the niche of organisms.

Environmental change: from the point of view of zoonotic pathogens, it refers to any variation in the environment, which includes changes in climate, in the characteristics of the landscape, and communities of animals, plants, vectors, or reservoirs of a pathogen. The simple trends or changes of climate are not the only factor in an environmental change, which is a richer and broader concept.

Focal species: the species that is in focus, the species of interest.

Interspecific and instraspecific: the terms are antagonists and refer to individuals of the same or different species.

Interspecies barrier: in the terminology of zoonotic pathogens, the lack of phylogenetic similarity may be a barrier that determines the inability of a pathogen to adapt to a new host.

Metapopulation: a group of spatially separated populations of the same species that interact at some level. The concept has been mostly applied to species in fragmented habitats.

Persistence (of a population): a population may persist in a landscape if the reproductive rates are higher than the mortality rates. In other words, a population may persist if the number of offspring is higher than the losses because of the various factors regulating the mortality through the complete cycle of the species.

Phylogenetic similarity: pathogens are more likely to colonise new host species that present conditions similar to those associated with their current hosts; therefore, they spread more readily among closely related hosts.

Scenopoetic niche: a set of ecological variables (a niche) that change very slowly.

Spatial resolution: the geographic scale at which an analysis is carried out. For example, the presence of a vector may be analysed at a local or regional scale, which is a fine spatial resolution. However, the presence of such a vector may be reported for a large area, such as a country, ignoring the variety of environmental factors that may impact on its distribution.

Sympatry: two or more species or populations are considered sympatric when they exist in the same geographic area and thus regularly encounter one another (the opposite term is allopatry).

exclusively within hosts, so environmental conditions are likely to affect only their persistence (mortality) and transmission (movement) [19]. Beyond mostly rudimentary information on residence times of some of these pathogens in the environment, little is known concerning abiotic factors affecting persistence. Because abiotic factors may affect reproduction, development, and mortality of pathogens, hosts, and vectors, describing their specific actions across all species participating in a disease transmission system becomes a crucial research need.

Here, we review environmental factors affecting distributions of zoonotic agents and their transmission to humans. We begin by discussing the abiotic requirements of species for maintenance of populations, and go on to explore biotic interactions and the special roles that they play in disease transmission systems. In the end, we focus on the question of factors affecting how pathogens may or may not jump from reservoir hosts to humans, as a function of spatial scale and the biotic and molecular interactions that occur at each distinct scale.

Basic framework for distributional ecology

Ecologists use the idea of a scenopoetic ecological niche, often termed a 'climate envelope' or 'abiotic niche' for simplicity, to refer to environmental tolerances that delimit geographic ranges of species. In disease systems, these niches are occupied by pathogens, vectors, and hosts, and are defined in terms of non-interactive, largely abiotic variables such as temperature, precipitation, and vapour pressure (Figure 1) [15]. Within these climate envelopes, species may vary in abundance along environmental gradients that together correspond to optimal and less optimal conditions [20,21]. Effects of climate change on distributions of species have typically been assessed via correlative ecological niche modelling approaches at coarse spatial resolutions such that population processes and biotic interactions are subsumed [22,23]. For many elements of biodiversity, the idea that species interactions, such as competition, predation, and parasitism, may not determine the major features of geographic distributions of species, and rather may work at finer spatial resolutions, has been termed the Eltonian Noise Hypothesis [24]. By ignoring that hypothesis, an implicit assumption is that responses of species to climate change are 'individualistic' [25]; however, interspecific interactions may structure biotic communities even at coarse spatial scales [26,27], and such effects are probably particularly frequent in disease transmission systems [28]. Hence, the 'individualistic response' assumption fails to account for key interdependencies between species. Recent studies on the issue have stressed the evidence of how biotic interactions shape species distributions beyond local extents, highlighting emerging methods to quantify relationships among interacting species from spatially explicit data [29,30].

Box 1. Important gaps in current knowledge: zoonotic pathogens

Drivers of (re)emergence of zoonotic pathogens as human disease

- Changes in climate altering the fitness and the phenology of vectors and density and phenology of hosts.
- Factors affecting the relative composition of the community of hosts and influencing the circulation of pathogens depending on specific reservoirs.
- Human or natural actions on the landscape that modify (increase) the fragmentation of habitats.
- Changes in human habits because of social (e.g., tourism) or natural (e.g., climate) factors, increasing the contact rates of humans with pathogens in either space (e.g., urbanisation near areas of transmission risk) or time (e.g., changing seasonality in areas where the pathogen circulates).
- Major human actions increasing the density of livestock or wild animals, allowing increased circulation of pathogens.

Eco-epidemiology of zoonotic pathogens: gaps to fill

- A harmonised framework to analyse and compare the abiotic niches of pathogens.
- Studies on natural (regional) communities of hosts comparing species composition and rates of pathogen circulation.
- Studies capturing the genetic variability of pathogens in the field according to host features (density, richness of species).
- Understanding linking incidence rates in humans with prevalence rates of pathogens circulating in ecosystems.
- Linking the physiology of vectors to climate.
- Knowledge of the 'genetic fingerprint' of vectors and their ability to transmit a pathogen.
- Defining the immunological and genetic factors and molecular interactions at the host–vector–pathogen interface involved in pathogen transmission and infection.

Very generally, geographic distributions of species can be conceptualised as manifesting combined actions of three factors (Figure 1): (i) abiotic conditions that permit persistence, for example, temperature or moisture, the 'A' portion of the niche; (ii) impacts of other species that either inhibit or facilitate the focal species, predators and competitors, or mutualists, respectively, that is, the biotic niche or 'B' portion; and (iii) the ability of the species to colonise favourable areas, for example, the dispersal ability or presence of barriers, which represents the 'M' portion of the niche. Geographic distributions of species, then, can be seen as the interaction of B, A, and M; this constitutes a Venn diagram that has been termed the BAM diagram [24,31]. BAM diagrams can take numerous configurations, with profound implications for geographic distributions, distributional ecology, and the ability of researchers to reconstruct either of the two [32]. A universal characteristic of species is that they do not typically inhabit the entire spatial footprint of their ecological niches, that is, some effect of M generally limits species to only a subset of A or A∩B (A intersecting B), leaving suitable areas for species uninhabited [33].

One can conceive the distributional potential of each interacting species of vectors, reservoir hosts, pathogens, and humans as a BAM diagram; that is, each species involved in transmission of a disease responds to its environment, other species, and dispersal barriers in its own way (Figure 1). In these systems, abiotic conditions influence distributions of each pathogen, vector, and/or host, and a complex chain of events thus results in the realised distribution of pathogens. Because of scale effects, however, BAM diagrams may differ among species, regions, and environmental drivers, which increases uncertainty associated with the system of vectors, hosts, and pathogens. In the simplest example, if each species in the transmission system responds to its environment in a particular manner, the disease should be transmitted only where the BAM conditions of all component species are fulfilled.

Hence, for instance, West Nile virus (WNV) can be transmitted only at sites where: (i) a competent vector is present in appreciable numbers; (ii) the pathogen is circulating; and (iii) abundance of susceptible hosts is sufficient. If any of these conditions is lacking, that is, if abiotic

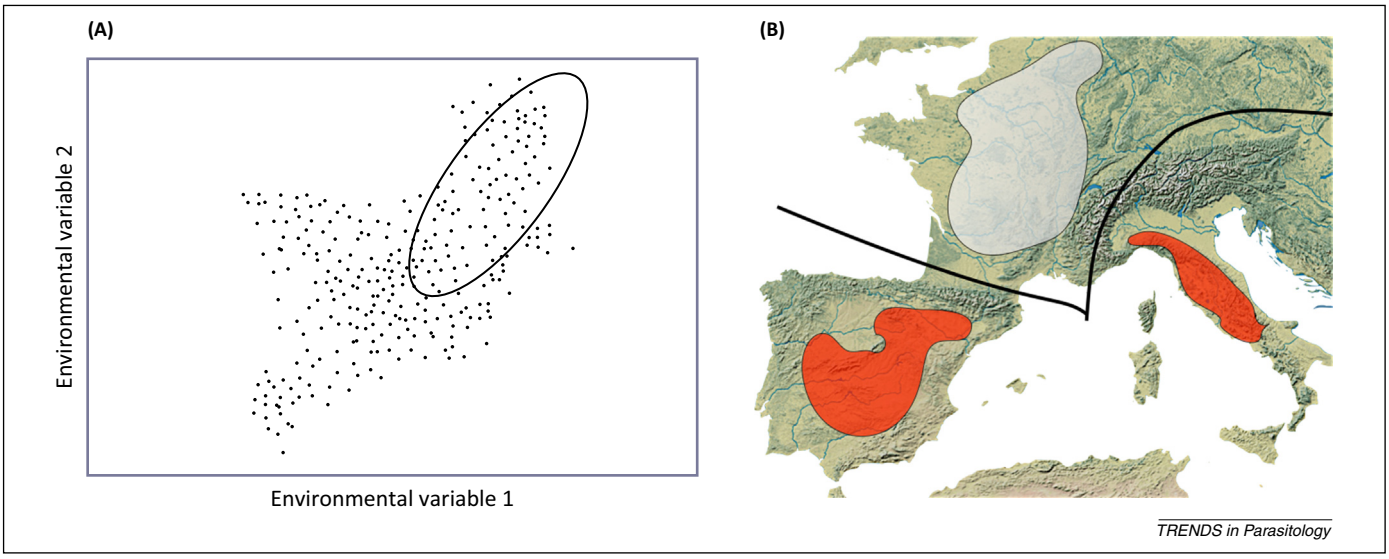


Figure 1. The relationships between abiotic niche and spatial distribution. Consider a large area in which two environmental variables (e.g., average temperature and total rainfall) are measured. The scatterplot **(A)** represents values of two variables at every site across the region of interest. The ellipse shows the abiotic niche of a hypothetical organism; this ellipse encloses the environmental conditions under which the organism can maintain populations. This ecological niche can be translated into the hypothetical spatial domain **(B)**. These conditions may be found in scattered areas. Although in theory different areas are suitable, the organism may be found only in a subset of these (white) because geographic barriers to movement (black lines) prevent spread to other suitable areas (red).

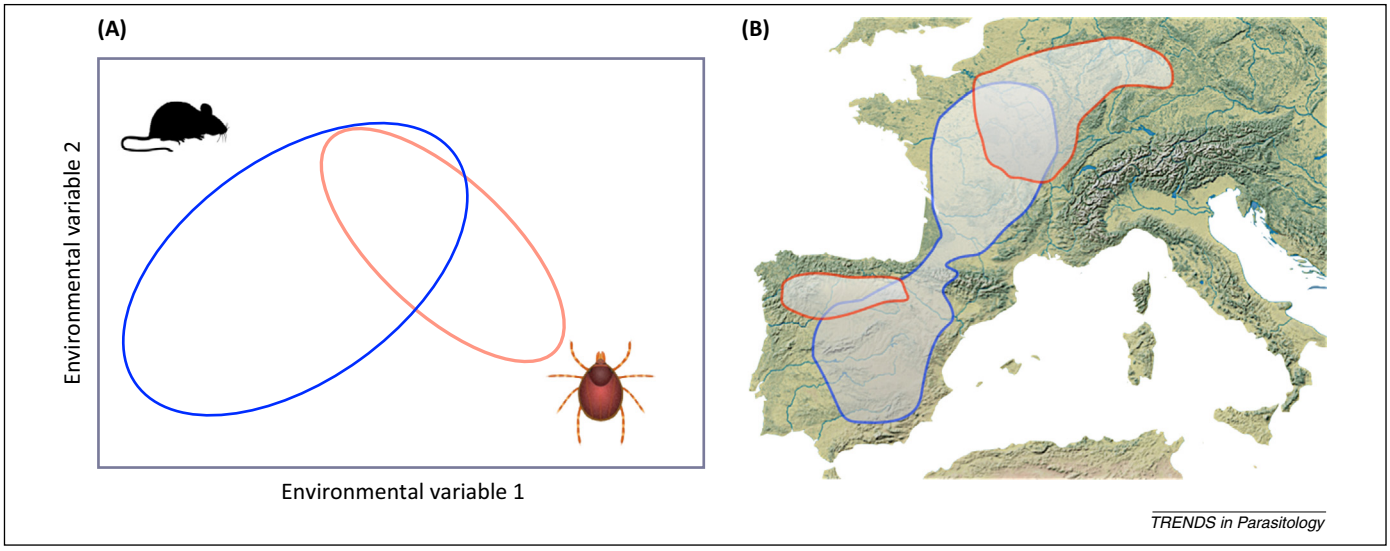


Figure 2. The species relationships in environmental and spatial domains. The space delimited by two environmental variables allows the description of the abiotic niche **(A)**, and ellipses show the positions of both host and vector in the space delimited by these environmental variables. The two niches occupy distinct combinations of the two environmental variables, and their preferences overlap in some portions of the abiotic niche (points representing collection sites have been removed for clarity). When the abiotic niche is translated into a hypothetical spatial domain **(B)**, the host and the vector may have contrasting distributions, resulting in spatial overlap only in some areas. The transmission of the pathogen to humans would be possible only at sites where both the host and the vector co-occur.

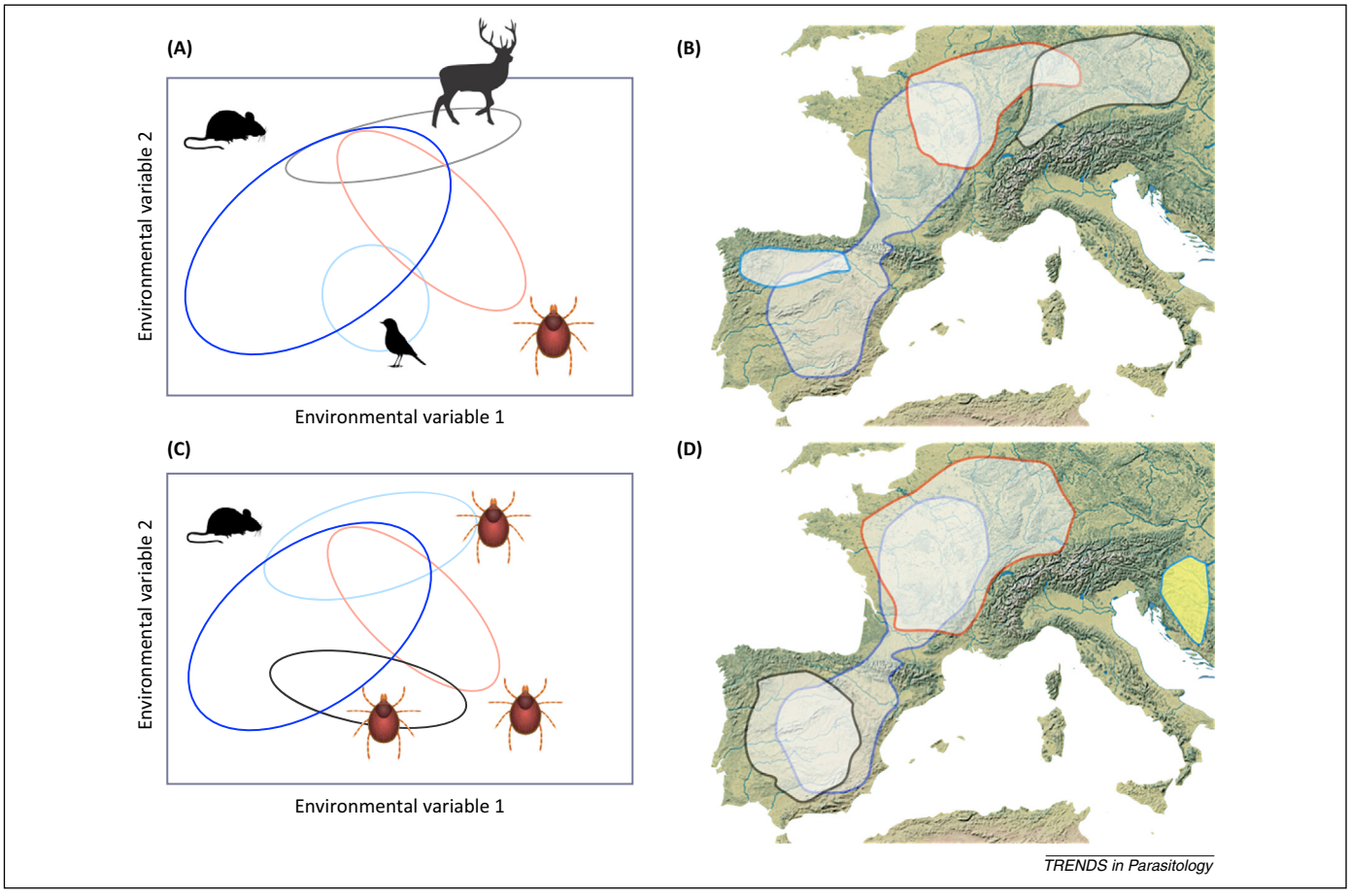


Figure 3. The disease systems with several interacting species. The figure represents a further complication of ideas explained in Figures 1 and 2, when several hosts **(A, B)** or several vectors **(C, D)** are involved in the zoonotic circulation of a pathogen transmitted to humans. In nature, disease systems may be associated with complex sets of host and vector species, and with distinct ecological niches. Several host species overlap in some portions of the environmental space (A). These host species may have a partially overlapping spatial distribution (B) where the potential for transmission of pathogens may be enhanced or diluted. In the same way, several vector species may partially overlap in the environmental niche (C) and hence occupy different areas. This may enhance the transmission of the pathogen at sites where several vector and host species exist (D). However, the translation of the abiotic space into geographic space may reveal the existence of species of vectors that do not overlap with other partners of the system (yellow ellipse in D).

requirements or biotic interaction requirements for the vector, host (birds, in this example), or pathogen is lacking, or if the site is not accessible to any agent in the system, WNV will be not be transmitted (see Figures 2 and 3 for the concept). Such has been the case, for example, in North America: humans, important avian reservoirs, and vectors, mostly *Culex* mosquitoes, are all present, but because the pathogen was unable to cross the Atlantic ocean until 1999, no WNV transmission was sustained there [34]. Similar logic will hold for any disease system, given the particular set of species that make up the transmission system.

As a consequence, an important first step in understanding the distributional ecology of any species is to analyse its BAM configuration. Joseph Grinnell proposed the concept of abiotic niche a century ago, and recent work has clarified that niches are best restricted to variables not affected by populations of the species in question [24], most commonly climatic dimensions. These fundamental abiotic niches determine a basic set of sites where the species can in theory maintain populations. The abiotic niche, however, does not take into account effects of interactions with other species: key interactions may include the presence or absence of particular pathogens, prey, competitors, vectors, or hosts (Figure 3). Dispersal limitations, by contrast, surely determine many or most of the major (coarsest) features of geographic distributions of species: oceans and mountain ranges and other major geographic features limit the broadest features of distributions of species. On finer scales, dispersal and dispersal agents are not crucial determinants of range extension. For example, ticks do not fly, and therefore can disperse long distances only via host movements [35]. However, some tick species are dispersed on highly mobile animals, such as birds or ungulates, which may introduce massive numbers of ticks and the pathogens they carry into new areas [36].

Why disease transmission systems are different

Importance of biotic interactions

We can define the biotic niche of a pathogen as the set of host and vector species that the pathogen inhabits out of those that are available locally, and how each species is used by the pathogen. This point can be applied across the entire cycle of the pathogen or to each life stage individually. Measuring components of this niche amounts to quantifying host or vector specificity using the multifaceted indices now available [37]; in this way, host specificity becomes much more than the mere identities and numbers of host species used. The biotic niche translates into a biotically suitable area, which may or may not reduce the abiotically suitable area to a potential distribution [24].

Environmental changes may alter the behaviour, social structure, or dispersal behaviour of populations of any component of pathogen transmission systems [19,38–44]. Such changes can modify the relative importance of different host species for pathogens, elevating or depressing levels of infection in particular hosts. Anthropogenic changes to landscapes, from fragmentation of previously continuous habitats [45,46] to creation of reserves [47], can concentrate animal populations in small areas at unnaturally high densities. Because host density is a key driver of transmission rates, these changes may create new foci of transmission or novel sources of zoonotic infections because reserves may also attract human visitors. Similarly, changes in food or other key resources, without changes to the habitat itself, can promote clumping of hosts and create foci of intra- or interspecific parasite transmission, for

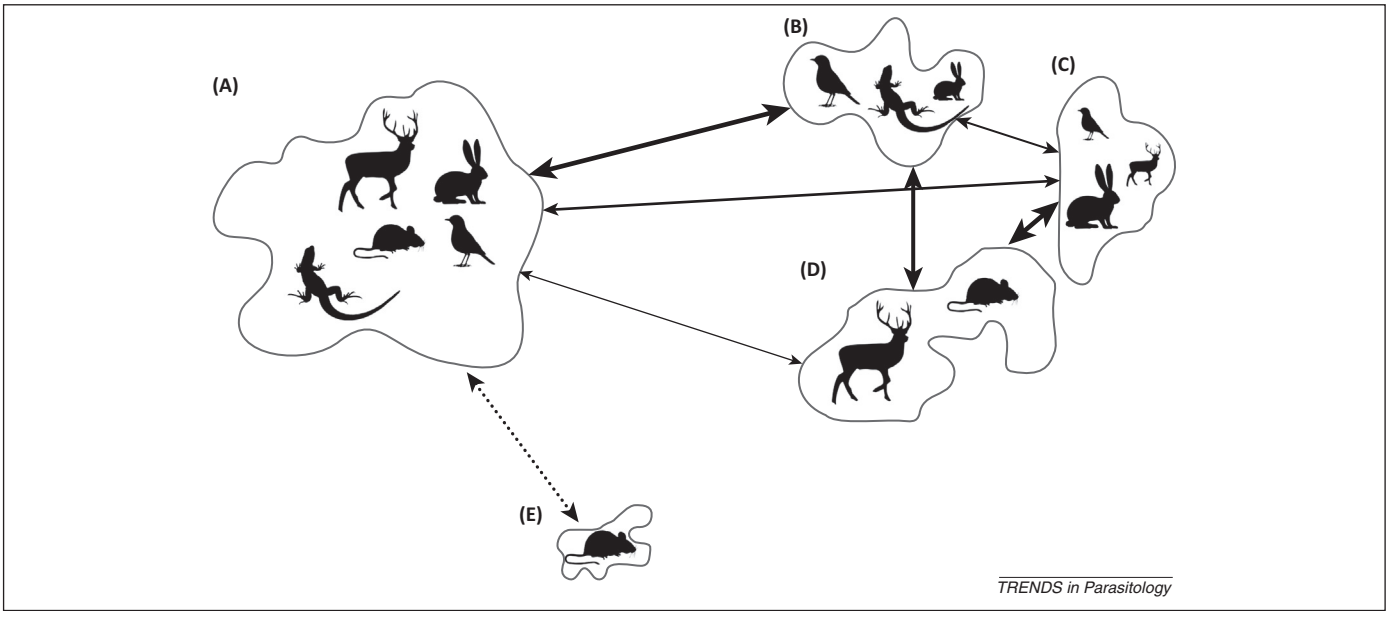


Figure 4. How patchiness hypothetically affects the circulation of hosts. Patches are illustrated by irregular areas, with a diversity of vertebrate species, denoted by the animals illustrated inside each polygon. For this example, we assume that 'rodents' are the best reservoirs of a given pathogen, whereas other animals inadequately support the pathogen. The connectivity is a measure of the exchange of hosts between the patches and is illustrated by black lines of different thickness, or by a broken line indicating negligible communication between two patches. There is an exchange of hosts among the well-connected patches, allowing a hypothetical pathogen to spread, but also to become 'diluted' in a richer assemblage of hosts and vectors. Non-connected, small patches may remain isolated with low host species richness and little or no exchange of hosts among them (broken lines). These small, isolated patches may fuel an intra-patch self-amplified loop of transmission between vectors and reservoirs, in which a large proportion of hosts may be infected because of the lack of exchange of animals with other patches and the lack of intra-patch diversity.

example, aggregations of raccoons induced by human food waste result in enhanced transmission of indirectly transmitted endoparasites and ticks [48].

Changes in habitat or climate may also alter the composition and diversity of local animal communities, including both hosts and non-host species for a particular pathogen or parasite (Figure 4). These changes have diverse repercussions for pathogen transmission and risk of infection. Indeed, just changing the number of animal species in a local community may affect the dynamics and host-to-host transmission of pathogens, either increasing or decreasing risk of disease transmission. Under a wide range of conditions, increased community diversity leads to decreased transmission risk for any particular host species, this is the so-called dilution effect [38]. Although not universal [38,49], dilution occurs because species added as diversity increases are frequently either low quality hosts or non-host species, and can disrupt transmission of the parasite in a range of ways [50,51]. Alternatively, in some cases new species in a community may be suitable hosts for existing parasites, having positive impacts on their dynamics, creating a 'spillback' effect on the original hosts, which suffer from higher infection rates as a consequence [52]. Describing the connections and interaction patterns among the host, vector, and pathogen has proven useful in elucidating key properties of these systems [53].

Changes to the phylogenetic structure of a local community, independent of changes in diversity, may also affect the risk of disease transmission. Invasion by new species into an established community can bring into sympatry closely related species that previously existed only in allopatry. Through phylogenetic inertia, such closely related species tend to be more similar to each other, ecologically and physiologically, than random pairs of species [54]. Pathogens are more likely to colonise new host species that present conditions similar to those associated with their current hosts; therefore, they spread more readily among closely related hosts [55–57]. For example, two of the most virulent pathogens of modern humans, the malaria parasite *Plasmodium falciparum* and the human immunodeficiency virus HIV-1, originated in African great apes [58–60]. However, whether the likelihood of cross-species 'jumps' by pathogens increases with decreasing phylogenetic distance is an open question. On the one hand, the number of major human diseases originating from an animal group, divided by the species richness of that group, is approximately 0.2 for apes, 0.017 for non-human primates other than apes, 0.003 for mammals other than apes, 0.00006 for vertebrates other than primates, and essentially zero for non-vertebrates [61]. These differences indicate that the per-species probability of zoonotic species jumps increases with phylogenetic similarity. By contrast, other studies [62,63] showed that ungulates, rodents, and carnivores host more total zoonotic pathogens than do primates, probably as a result of the higher species richness in the former three orders. Consequently, overall probability of zoonotic species jumps does not increase with phylogenetic similarity. Indeed, most of the zoonotic emergence events worldwide over the past several decades have occurred in temperate areas in which there are no wild non-human primates [64].

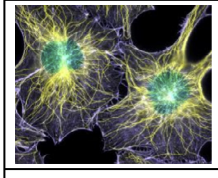
Finally, at the molecular level, ecophysiological processes are among the most important biotic components. For example, tick stress responses are activated in response to temperature change, blood feeding, and pathogen infection to counteract negative effects on questing behaviour and increase tick survival [65]. Pathogens have also evolved strategies to counteract host/vector immune responses to infection and increase transmission [66]. However, under natural host/vector–pathogen relationships, stress responses may not be strongly activated, probably reflecting coevolutionary processes [67]. In fact, some pathogens confer survival advantages to vectors under challenging environmental conditions [68]. An additional dimension of these interactions relay on the immunological status of hosts and vectors, both at the individual and population levels – in many cases, infections may or may not be successful, or disease may or may not manifest, depending on such conditional factors. Prior immunological experience of subjects at risk is certainly a major factor in pathogen infection and disease. For example, in heavily endemic regions for cholera such as Bangladesh, the infection rate is relatively low among adults in comparison with children, whereas in non-endemic areas cholera is more frequent among the working adult population [69]. These changes play important roles in pathogen transmission and adaptation to challenging environmental conditions [65,70], but – importantly – are mediated by biotic interactions: genetic traits, immunological status, and molecular mechanisms in hosts, vectors, and pathogens can affect infection and transmission by pathogens, and thus risk of disease outbreaks under certain conditions.

Human condition and human behaviour

Changes in climate and landscape also affect human condition and behaviour in ways that can affect exposure, infection, and disease manifestation. *Lyme borreliosis* in eastern North America presents one case, where the tick vector, *Ixodes scapularis*, transmits the bacterial pathogen, *Borrelia burgdorferi*, from reservoir hosts to humans. Although several studies show that abundance of infected ticks increases with habitat fragmentation and biodiversity loss [71,72], habitat fragmentation can either increase [73] or decrease [74] human incidence rates. The observation that fragmentation increases ecological risk (density of infected ticks), while simultaneously decreasing Lyme disease incidence, suggests that humans are less likely to enter risky habitats (forests) when forests are highly fragmented [74]. A similar example is tick-borne encephalitis, in which a viral pathogen is transmitted by *Ixodes ricinus* and *Ixodes persulcatus* in Europe and Asia: multiple social drivers affect exposure of humans to infectious foci [75], and socioeconomic changes that increase human activities in risky forest habitats (e.g., collecting supplementary foods such as mushrooms) can increase exposure irrespective of tick and virus abundance [76].

Another example is the changing risk of transmission of zoonoses when human behaviour causes habitat change, such as forest clearing, which may also increase probability of exposure to vectors or hosts. In Western Uganda, forest fragmentation accompanies replacement of native forest with agricultural fields and human settlements; this forest

fragmentation appears to increase encounter rates and overlap between native primates, humans, and domestic animals, and increases transmission of bacterial and viral pathogens via multidirectional transmission among primates, livestock, and people [77]. Similarly, proximity of human settlements to native forest in West Africa appears to facilitate bushmeat hunting and transmission of zoonotic viruses from native wildlife to humans [61]. Both of these factors have been implicated in transmission of viral haemorrhagic fevers, such as Ebola [15]. Modifications of landscapes by human activities also appear to be behind recorded increases in incidence of tick-borne viruses, such

Scale	Description and examples	Drivers	Gaps
	**Continental** – The major divisions of the Earth's surface (e.g., continents) structure many major features of disease distributions. For example, West Nile virus was found only in Europe, Asia, and Africa until the late 1990s, plague was found in Asia until the middle ages and did not reach the Americas until the late nineteenth century.	Earth history	Phylogenetic understanding of pathogen lineages
	**Regional / biogeographic** – Regional distributions of zoonotic pathogens are often structured by broad climatic variation, biogeographic barriers such as mountains, rivers or deserts, etc. This structuring means that only areas with all necessary species (host, vector, pathogen) will see transmission. For example, Lassa Fever is restricted to West Africa, Ebola Zaire to the Congo Basin, and Plague in North America only to the western portion of the continent.	Dispersal barriers, climatic limits, tolerances and requirements in other dimensions	Detailed knowledge of correlates of distributional patterns
	**Local landscape** – On local landscapes, the details of habitat associations and finely-resolved distributions of species in transmission cycles become important. For example, Lyme disease risk in North America is linked to fragmentation of forested landscapes, which exacerbates spatial overlap of reservoir hosts (white-footed mice), vectors (blacklegged ticks), and humans.	Interactions of a species with the living and nonliving factors of its environment, landscape configuration	Dynamics of multiple-vector systems
	**Individual** – Infection and disease cannot—obviously—take place without some sort of physical transfer of the pathogen to the body of the human. For example, Sin Nombre virus is present across much of North America, but infections across more than half of the continent are rare owing to improved living conditions and perhaps environmental conditions associated with infection.	Human condition, behaviour, location of the house (i.e., near forest patches with infected vectors)	Details of individual range of variability in the transfer of pathogens
	**Cell** – Even after a pathogen enters a human body, infection and manifestation as disease may not occur depending on the infection route or if immunological status removes the infection prior to broad replication and spread within the body.	Previous exposure to pathogen or similar pathogens; health and condition; infection route	Knowledge of cell factors affecting pathogen transmission, infection and multiplication
	**Molecular** – In tandem with cell level barriers to infection and disease, some genotypes are resistant to some disease infections, such that molecular (genetic) scales must also be considered. For example, *Mycobacterium bovis* infection in wild boar may be affected by methylmalonyl CoA mutase (*MUT*) genotype.	Resistance of particular genotypes of host, interaction with particular genotypes of pathogen	Knowledge of molecular mechanisms at the host/vector–pathogen interface and genetic factors affecting pathogen infection

TRENDS in Parasitology

Figure 5. The hierarchy of spatial scales in zoonotic systems. The figure illustrates the scales at which contact between pathogen and host is necessary for infection and disease to result in a disease emergence event. Each scale is necessary for transmission, infection, and manifestation of disease to occur, but no scale is sufficient to assure human infection and disease.

as Crimean–Congo haemorrhagic fever virus: abandonment of labour lands and growth of secondary vegetation provides shelter for hosts of the ticks, promoting large vector populations, and is believed to be a driving factor in the ongoing epidemic of Crimean–Congo haemorrhagic fever in Turkey [78,79]. However, because human incidence rates are frequently the only empirical data available, separating the influences of abiotic, biotic, and human effects on pathogen transmission can be challenging.

When and why pathogens switch hosts

The two previous sections outlined basic requirements for pathogen circulation: abiotic requirements of each species involved in the transmission cycle of the pathogen, and biotic interactions among these species that serve to circulate the pathogen through the different species involved. Nonetheless, circulation of a pathogen in the zoonotic realm in a place does not mean that it will necessarily infect humans or cause disease there. Hence, in this section, we discuss what factors are necessary and sufficient to lead from zoonotic transmission to human disease (Figure 5).

A first requirement is that of spatial overlap. That is, if the pathogen is circulating in zoonotic realms on one continent, humans on other continents are unlikely to be affected; consider the example of WNV in North America until 1999. As such, spatial co-occurrence in some sense (i.e., at some spatial resolution) is a requirement. The spatial and temporal resolution of that overlap, however, is highly disease- and situation-specific. At the coarsest extreme, an environmental pathogen, for instance, *Coccidioides*, a fungus that causes coccidiomycosis, may be wind-blown and can infect people hundreds of kilometres away, or a pathogen with a stable spore stage such as anthrax may 'wake up' and resume transmission after decades when the situation is suitable. At finer resolutions, vector-borne diseases such as malaria, dengue, and leishmaniasis may be transmitted within radii of tens to hundreds of meters by mobile arthropods, including mosquitoes and sandflies. Finally, directly transmitted pathogens may require very close proximity or even direct contact, as in the cases of hantavirus, Ebola, Lassa fever, and many others. In this regard, then, spatial overlap, however defined, is a necessary condition, and yet – as will be discussed below – may not be sufficient to assure transmission to humans.

Beyond spatial overlap, diverse phenomena manifested at similarly diverse spatial resolutions also enter the picture. At the finest spatial scales, phylogenetic closeness to the reservoir host species, immunological history, host genotype, or pathogen genotype may determine whether human exposure to a pathogen will lead to infection, and whether infection will lead to disease. In some cases, exposure of a single human to a single pathogen (or a single population of pathogens) suffices to produce a growing pathogen population within the human, which eventually is manifested as human disease. In other cases, however, either chronic exposure to and infection by pathogens is needed to produce human disease (e.g., onchocerciasis), or sufficiently numerous exposures are required to overcome demographic barriers to infection.

The point is that simple spatial and temporal co-occurrence of a pathogen in a zoonotic transmission cycle with humans is necessary, but not sufficient, to assure that human disease will result. Beyond spatial overlap, numerous factors enter the picture: human social structure, living conditions, economic status, and health status; local dispersal ranges of vector populations; habitat fragmentation; and disease aetiology all can promote, diminish, or modify transmission patterns of pathogens to humans and manifestation as human disease. These interactions of disease transmission cycles with scales of time and space are little studied, and yet we suspect drive much of the dynamics of disease emergence.

Concluding remarks and future directions

Zoonotic diseases are complex systems driven by different forces acting alone and in combination. Transmission of zoonotic pathogens is affected by environmental changes, which dictate dynamics of hosts, vectors, and humans. The players in these systems – pathogens, hosts, vectors, habitats, and landscapes – interact, and these interactions are frequently modulated by human condition, status, and activities. Such transmission systems have considerable inherent plasticity, such that their responses to external drivers may be difficult to generalise. Consequently, important research challenges constrain any effort to understand and anticipate zoonotic disease emergence events.

In this review, we have highlighted the broad hierarchy of scales at which species in disease transmission systems interact, pointing out how little is known about the relative importance of each spatial scale and domain. We have further highlighted the fact that spatial co-occurrence is necessary, but not sufficient, for zoonotic transmission and human disease to occur, and have suggested a series of additional factors that may affect transmission. Future research will face the challenges of understanding the biotic and abiotic components of these species and how anthropogenic environmental changes affect their niches. Such evaluation must necessarily include all hosts and vectors involved in transmission of a pathogen within a single framework. Broad geographic studies are necessary, owing to local populations of vectors with large geographic distributions responding differently to the same abiotic variable or to host availability. However, more narrowly focused studies are required to understand whether dynamics vary between, for example, the core of species geographic distributions and the periphery, as well as to capture impacts of key factors, such as genetic diversity of hosts and pathogens, immunocompetence, dispersal characteristics, and local population dynamics, which can vary over small scales.

The complexity of the ecosystems in which zoonotic pathogens circulate has inhibited understanding of interactions between species in transmission systems and key environmental variables that ultimately can influence disease emergence. For a start, biotic interactions need to be considered in a holistic multispecies context, using, for example, analysis of whole interaction networks or multispecies hierarchical models [80]. The current, more reductionist focus on individual components at local spatial scales and short temporal scales has not been adequate

to generate a predictive understanding of disease emergence. We do not expect that all phenomena at all scales from broadest to finest will contribute equally to disease transmission, but that all relevant scales should be assessed empirically, rather than assumed out of existence. Such empirical explorations should include interactions between broad-scale environmental variables and cellular/molecular processes at the pathogen–host–vector interface. A key frontier is assessing the relative importance of environmental drivers of zoonotic risk and human behaviours at both population and individual levels in determining disease transmission patterns. This would aid integration of information relevant to epidemiology that is currently sequestered in sociological and ecological information stovepipes.

More generally, this overview illustrates the complexities that underlie disease emergence events. Environmental, biotic, molecular, and human socioeconomic phenomena combine to produce the broad patterns in disease transmission, but also to produce the unpredictable, seemingly random events that are so common in disease emergence events. Only by appreciating and understanding the complexity of the overall phenomenon can the system become more understandable and less bewildering.

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