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Perspective

Looking beyond land-use and land-cover change: Zoonoses emerge in the agricultural matrix

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SUMMARY

Emerging zoonoses (new infectious diseases where pathogens circulate between humans and domestic and wild animals) follow ecological and evolutionary processes that are becoming more common, undermining our ability to achieve the sustainable development goal of good health and well-being. Agriculture has been implied as a major force promoting emerging zoonoses. However, agricultural systems are variable, with some agricultural modes of production expressing social formations that condition biological interactions that can promote (or protect us from) the emergence of new zoonoses in the same way they destroy (or protect) species biodiversity. Consequently, the socioecological characteristics of the agricultural system influence the probability of zoonosis emergence. Here, we propose an approach to examining the relationship between agriculture and zoonoses that suggests that the agricultural matrix, within which other elements of the landscape are positioned, confers various degrees of landscape immunity. Highly simplified, homogeneous, and chemically intensive agricultural landscapes are unlikely to provide such immunity, while diverse agroecological matrices populated by small-/medium-scale farmers and a robust local food system likely will; i.e., they will decrease the probability of zoonosis emergence. In addition, such a landscape is also expected to enhance food sovereignty and security, mitigate climate change, reduce poverty, and protect biodiversity.

INTRODUCTION

By the middle of the 20th century, the transient success of antibiotics, vaccines, and general improvements in sanitation, especially in high- and middle-income nations, gave a general impression that human societies had conquered infectious diseases. However, this triumphalist attitude, mainly held in the Global North, began to fade in the mid-1970s with outbreaks of Lyme disease, Legionnaires' disease, HIV-AIDS, hantavirus, and other diseases.[1] Over the past 20 years, the world has seen notable human outbreaks of H5Nx avian influenza, SARS-CoV-1, MERS-CoV-1, Ebola virus, Zika virus, chikungunya virus, West Nile virus, and, most recently, SARS-CoV-2, the agent that causes COVID-19. Around two-thirds of these emerging diseases have been reported to be zoonotic (i.e., originating in non-human animals) and, of those, nearly three-quarters are thought to have originated in wildlife before spilling over either directly to humans or via livestock.[2–4] Indeed, recent major epidemics, such as those caused by MERS-CoV-1 and SARS-CoV-1, and the current COVID-19 pandemic, have wildlife origins.[5–7]

Various studies have shown that land-use change, along with changes in the agricultural mode of production, are major drivers of pathogen spillovers from wildlife to humans.[6,8–10]

The narrative emerging from many disease ecology-land-use change studies is that deforestation, landscape fragmentation, and agricultural conversion are accelerating zoonotic spillover by reducing biodiversity, increasing the likelihood of reservoir host species (i.e., species in which disease is endemic and that can act as sources for transmission to humans) becoming infected and transmitting pathogens and increasing human contact with reservoir hosts.[11,12] These studies often assume that agriculture is always in conflict with biodiversity conservation, favoring the dominance of reservoir species that can infect and live alongside people.[9,12,13] As part of the narrative, Indigenous and local peasant populations, through their agricultural and other cultural practices,[14] are commonly blamed for disease emergence (e.g., Wolfe et al.[11]). Solutions to prevent disease emergence often include higher levels of surveillance (not only epidemiological), population control, and tighter restrictions on people's interactions with wildlife.[15–17] These solutions often

promote the separation of humans and nature (e.g., the protected areas approach; Obura et al.[18]) and are neocolonialist in essence,[14] as they also undermine the ability of poorer Global South nations to work in their best interest, instead favoring the interests of wealthier, and geopolitically powerful, countries of the Global North.[19–21] These solutions are often based on the premise that tropical regions of the Global South present a higher risk for disease emergence,[4,11,12] not acknowledging the role that investments and commodity demands from the Global North have in shaping such emerging risk patterns.[22–24]

From an ecological perspective, there are two main problems with these perspectives and solutions that increasingly separate humans from nature. First, there is an underlying assumption that unregulated human population growth is the most pressing driver of environmental degradation (e.g., Pianka and Vitt[25]; Cafaro et al. [26]). Although this argument has become more nuanced since the publication of Ehrlich's *The Population Bomb* and now considers, for example, levels of consumption, the assumption that the number of people is the most significant factor is still common in the conservation literature.[25,26] However, this assumption does not reflect current demographic trends and projections.[27] Global fertility rates have been decreasing over the past six decades in response to reductions in mortality and concomitant social change, and population growth has been decoupled from food production; these trends are expected to continue.[28] Second, and more critical to the argument we present here, not all agriculture has the same impact on biodiversity.[29] Many diverse agroecological systems maintain wildlife diversity at local and landscape levels.[30–33] Conservation biologists increasingly recognize that the areas between habitat patches are just as important for species' persistence as the patches themselves.[34–37] Nonetheless, even when researchers recognize the heterogeneity of agriculture conceptually, it often remains undifferentiated or simplistically categorized in analyses of land-use change and biodiversity. With respect to pathogens in particular, an understanding of spillover processes requires a nuanced and well-informed framework that recognizes the impact of different kinds of agricultural systems. Pathogens have complex and scale-dependent responses to environmental change, and consequently, zoonotic disease emergence is a complex phenomenon influenced by many processes. Pathogen dynamics in reservoir hosts, transmission outside reservoir hosts, and the susceptibility and behavior of the recipient hosts, including those of humans, together complicate successful spillover.[38–40]

These complexities make it difficult to generalize the effects of land-use change on the likelihood that (1) a pathogen will infect or evolve the capacity to be more infectious or pathogenic to humans or livestock and (2) subsequent pathogen transmission will result in an outbreak with a broad geographic impact on humans. Yet frequently, land-use change is compressed into simplified categories of land conversion to agriculture, regardless of the type of agriculture and the socioeconomic relations associated with it.[4,9,11–13] In other words, past studies often ignore the characteristics of the agricultural matrix and its impacts on biodiversity. The agricultural matrix refers to the human-managed areas within which natural habitats and centers of human populations are embedded.[29,34] Here, we use "agricultural matrix" to describe all land uses for the production of food, fiber, and wood, including managed rangelands and forests, which constitute most of the earth's surface. In Box 1, we provide an example of the 2014 West Africa Ebola epidemic and its emergence from changes in the agricultural matrix.

In an attempt to consider the complexities associated with zoonoses and land-use change, Plowright et al.[40] called for an integrated concept of "landscape immunity" that combines landscape ecology, wildlife immunology, and disease ecology to analyze how land-use change affects: (1) the abundance and distribution of wildlife, (2) the dynamics of wildlife exposure to pathogens and susceptibility to pathogen infection, (3) the pathogen shedding from wildlife hosts, and (4) the contact opportunities between reservoir hosts and humans, in what they call the "infect-shed-spill-spread" cascade.

Here, we build upon this analysis by presenting a novel approach to the land-use change-zoonoses emergence relationship that, first, focuses on how characteristics of the agricultural matrix modulate its role in the evolution of wildlife pathogens and their subsequent transmission to, and spread among, humans and, second, places pathogen transmission within a socioeconomic and political context.[23] We argue that ecological, socioeconomic, and political factors all play dynamic, critical, and intertwining roles in defining the landscape immunity against a zoonotic epidemic, with the agricultural matrix mediating these processes. In doing so, we argue for the need to study the influence of agricultural matrices on landscape immunity.

THE AGRICULTURAL MATRIX AND LANDSCAPE IMMUNITY

Some anthropogenic land uses negatively affect ecological integrity and biodiversity and facilitate zoonotic pathogen transmission.[10,12,48] However, this is not always the case. In a review of over 300 empirical studies, Gottdenker et al.[10] found that 10.4% of the studies observed decreased pathogen transmission in response to anthropogenic change, and another 30.4% had variable pathogen responses. Land-use changes examined in these studies included deforestation, fragmentation, agricultural development, and urbanization. This suggests a complex response of pathogens to environmental change across spatial and temporal scales.[49] Non-linearities between pathogen transmission risk, human behavior, and environmental factors can lead to unexpected complexities.[38] Given the complicated interactions involved in most pathogen-host systems, it is likely that the relationship between biodiversity and zoonoses is idiosyncratic, contextual, and scale dependent.[50–52] However, such complexity does not obviate either the need for or the possibility of developing a general framework to understand the relationship between land use, particularly agriculture, and zoonoses. Instead, it suggests that such a framework must be nuanced. It must acknowledge the variety of agricultural matrices within which pathogens evolve, are transmitted, and spread, particularly to centers of critical human population densities (i.e., cities), where rapid human-to-human spread of the pathogen becomes possible.

Within this context, we develop a novel agricultural matrix framework for the analysis of zoonoses from recent spillovers. Since most natural/little-disturbed habitats are fragmented to some degree[53] or are separated from cities by agriculture or other human-managed areas, this matrix framework applies to most areas of the world. From the perspective of biodiversity

Box 1. Changes in matrix quality and the Ebola virus epidemic in West Africa

Wallace et al.[41] illustrate how the quality of the matrix interacts with the sociopolitical context to affect the emergence and spread of the virus. The Ebola virus disease (EVD) experienced several small outbreaks in remote regions of Central Africa during and after the 1970s. But in 2014, the Ebola virus spread to Guinea, Sierra Leone, Liberia, and Nigeria. It went from an intermittent infection (killing people in isolated villages and then fading away) to an epidemic that infected 28,000 and killed 11,000 in the region.[41,42] Farmers had been harvesting natural and semi-wild groves of several oil palm types for generations in the Guinean forest. As international palm oil demand increased, traditional oil palm groves were intensified by increasing plant densities. Semi-wild production was replaced by intensive plantations of hybrids, and red oil was replaced or mixed with industrial or kernel oils. In the 2000s, milling capacity quadrupled with European Investment Bank funding. This triggered a transformation of the agricultural matrix, from a mixed matrix of agroforestry systems (including semi-wild palm groves, coffee, and cocoa) and diverse annual shifting cultivation systems to one dominated by monocultures of oil palm where forest patches were embedded.[43] These plantations favor disturbance-associated fruit bats, key reservoirs of Ebola, because they provide abundant food and shelter from heat.[44] Similarly, the insectivorous free-tailed bats, also Ebola hosts implicated in the initiation of the 2014 outbreak,[45] are attracted to cash crops and intensive agricultural systems.[46,47] As oil palm monocultural plantations replaced forests and a diverse agricultural matrix, more bat species shifted their foraging to these plantations and other agricultural areas within the matrix, increasing human-bat contact. The transformed agricultural matrix in the Guinean forest region enhanced the probability of pathogen evolution, since the reservoir host proliferated in this new habitat. The transformed matrix also promoted transmission, since the partially proletarianized pickers now interacted more with one another. Land appropriation resulted in displacement and migration outside the region to areas in the city with higher employment prospects.

conservation, agricultural matrices have been described as ranging from high to low quality based on the degree to which they resemble natural habitats and maintain biodiversity.[29] Exemplary systems include organic shaded coffee contrasted with intensive-sun coffee,[54] multistoried agroforestry systems contrasted with monocultural forestry plantations or annual monocultures,[55] and diverse milpa systems for staple grain and vegetable production in Mesoamerica contrasted with grain monocultures,[56] among others.

In the context of zoonoses, it is helpful to conceive the matrix as having characteristics that mediate the probability of (1) a pathogen evolving the capacity to infect humans, (2) a pathogen infecting humans when the appropriate contact occurs, and (3) subsequent transmission among humans. The current land-use change-zoonoses paradigm assumes that agriculture lowers biodiversity, favoring reservoir hosts, and pushes people farther into uncultivated areas, increasing interactions with wildlife. These processes then increase the probability of a pathogen infecting humans and spreading through the human population (Figure 1A). The agricultural matrix framework distinguishes between different types of agriculture. It examines how characteristics of the matrix modulate species abundance and diversity, as well as species interactions, that facilitate or inhibit the evolution of a pathogen capable of infecting humans and the subsequent spread of that pathogen to cities (Figure 1B). Our framework identifies two distinct roles by which the agricultural matrix influences landscape immunity. First, the matrix can act as an incubator of novel zoonotic pathogens (facilitating the evolution of a human-capable pathogen genotype). Second, the matrix can act as a barrier to the transmission of zoonotic pathogens (both reservoir-human and human-human transmission).

CONCEPTUAL FRAMEWORK

Landscape immunity has been defined as the ecological conditions that maintain and strengthen the immune function of wildlife species while preventing the conditions that lead to high pathogen prevalence and shedding.[40] To express zoonotic emergence potential as part of a broader idea of landscape immunity, we propose a framing that conceptualizes how the different elements of the agricultural matrix mediate pathogen evolution and transmission as two dynamic rules. We presume that the landscape contains a gradient between two extremes, "natural" (areas of natural vegetation without significant human intervention and no human population) and "city" (areas with no undisturbed wildlife habitat and high human density, referred to as cities for simplicity), as suggested by Faust et al.[39] Most terrestrial landscapes include elements that are neither natural vegetation nor cities, this we term "matrix." Different combinations of human density, agricultural production, and natural vegetation create a diversity of agricultural matrices. Indeed, at a very large scale, most "natural" areas, such as undisturbed forests, and most cities are embedded in an agricultural matrix, or what some call the countryside or rural landscape.[57]

Both evolutionary and ecological changes contribute to infectious disease emergence.[58] The probability of the evolution of a human-capable variant of a pathogen with a non-human host(s) is one of the dynamic rules in our conceptualization. However, many pathogens with non-human hosts do not have to change to be capable of infecting humans.[59] A high density of the host population or behavioral traits that increase interactions among potential hosts, like crowding and co-mingling with different host species, increase this probability.[22,58] At this point, the pathogen might be potentially zoonotic, i.e., affecting non-human animal species, with pathogens circulating among many different species of hosts, as is the case in Chagas disease,[60] or it may be a recognizable problem.

Once the pathogen infects humans, the second dynamic process becomes relevant: the continued spread through some fraction of the human population. This spread is associated with various ecological factors, but socioeconomic and political factors, such as commodity market circuits, wealth distribution, and

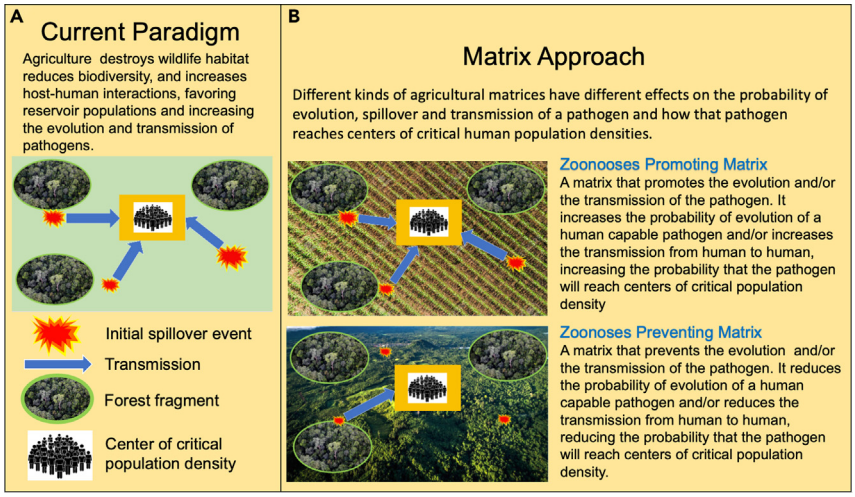

Figure 1. Contrasting paradigms
(A and B) Contrast of the current paradigm (A) and the matrix approach (B) to understanding the impacts of land-use change on zoonosis evolution and transmission.

associated equity in health and well-being, inevitably play a role. All of these factors are connected to the "transmission" potential of a landscape.

Graphically, we summarize the basic idea in Figure 2. We conceive the probability of the evolution of a human-capable pathogen as highly flexible, ranging from a simple monotonic relationship (not shown) to a variety of forms that adjust to the particulars of a given situation. For example, the dashed curve with the high hump at intermediate landscape values (Figure 2A) would be some potential pathogen that rarely emerges in the natural areas because its host (a mouse, say) is very rare, being mainly held in check by competitors or predators. But it is also rare in cities due to efficient public health procedures, often led by organized communities, that keep the mouse population at very low levels. In between, however, both competition from other biodiversity elements and control from urban public health procedures are reduced, and the probability of zoonotic pathogen evolution increases. Alternatively, the dot-dashed curve might represent a situation in which a dominant species (a bat, perhaps) takes advantage of the dense vegetation in the natural habitat and the abundant attic space in the city extreme, with both of those factors reduced in the matrix (Figure 2A). Many other scenarios can be imagined (e.g., Figure 2A, solid line).

The second dynamic, describing how landscape elements affect human-to-human transmission, is illustrated in Figure 2B. Here we present a two-dimensional form for simplicity. The relationship can take a variety of forms, but due to low human population density in natural habitats and high density in cities, it will always go from low levels of human-to-human transmission in the natural habitat to high human-to-human transmission in cities. For this reason, it is likely that this relationship (human-to-human transmission along the landscape element gradient) will take one of two forms, with different degrees of distortion depending on conditions. The conditions are primarily associated with human sociocultural and political organization but also with the inherent transmissibility of whatever pathogen is under consideration.

Given the basic framework summarized in Figures 2A and 2B, the two dynamic rules can be combined to view the probability of zoonosis emergence in a more general framing (Figures 2C–2E). Since both dynamic rules are formulated as probabilities, we can also assume they are independent and compute the probability of a successful zoonosis emergence as the product of the two, as shown by the gray area in Figures 2C–2E. This area can be taken as a measure of the fundamental probability of successful zoonosis emergence. Since the focus of this framework is on the agricultural matrix, we can say that a matrix that is a poor incubator and a good barrier for a particular zoonotic pathogen will increase landscape immunity to that pathogen. Figure 2C presents an example of a landscape comprising a low-quality matrix, with consequent low landscape immunity (with a high probability of evolution of a human-capable genotype and high probability of human-to-human transmission; in other words, the matrix is a good incubator and poor barrier), while Figures 2D and 2E illustrate examples of high-immunity landscapes associated with matrices of two different qualities. Here, for brevity, we focus on a zoonotic disease with a single wildlife reservoir host species. However, this modeling approach can be easily extended to consider pathogens with complex multiple host species life cycles and different modes of transmission, for example, including vectors. Similarly, the probabilities presented in Figures 2A and 2B can be mechanistically linked to the ecological and evolutionary aspects of specific pathogens across a widely defined matrix that considers diverse aspects of the landscape, from its geomorphology and patchiness to the dominant political economy of the larger socioecological context where a disease emerges.

AGRICULTURAL MATRICES AND LANDSCAPE IMMUNITY

Given the above conceptual framework, it is clear that whether the agricultural matrix contributes to a landscape that promotes, or inhibits, the emergence of a zoonotic pathogen depends on the particular disease complex and how it interacts with the socioecological characteristics of the matrix. This conclusion suggests the need for a conceptual shift in the study of zoonoses from a focus on the pathogen, its evolution, and its transmission, to an examination of the matrix as the playing field where zoonotic disease emergence is ultimately the expression of the totality of interactions—physiological, immunological, ecological, socioeconomic, and political—that contribute to the incubation and barrier characterizations of the matrix. Examples of matrices composed of various levels of agricultural intensifications are illustrated in Figure 3. By agricultural intensification we mean conventional intensification,[61] including landscape simplification, monocultures, and increased application of external chemical inputs.

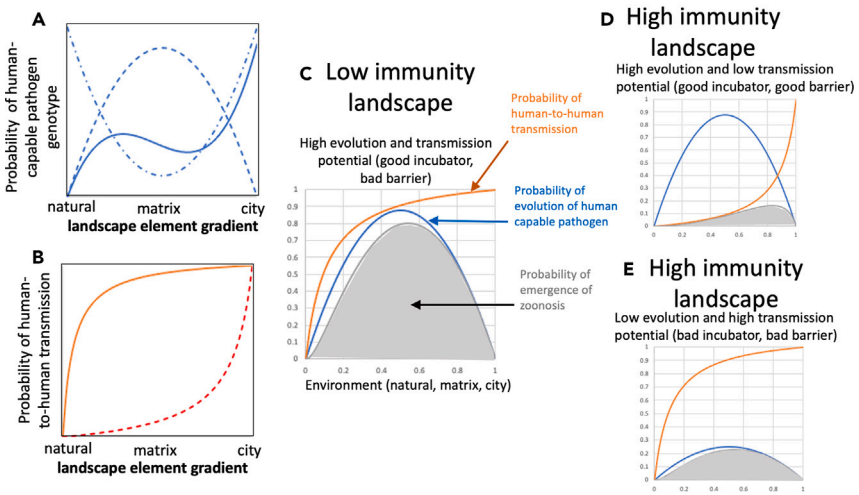

Figure 2. Conceptual framework

(A) The conceptual framework relates landscape elements to probabilities of pathogen evolution, transmission, and zoonosis emergence. The probability of evolution of a human-capable pathogen genotype is described over the landscape element gradient, illustrating three of a myriad of potential patterns.

(B) Over this same gradient, there can be varying probabilities of human-to-human transmission, generally thought to be of two qualitatively distinct types.

(C–E) Combined, as products of the two probabilities, these two dynamic rules describe the overall landscape immunity (the gray area in C–E). A high landscape immunity may emerge from the matrix with a low transmission potential, as in (D), or by having a low probability of evolution, as in (E).

The agricultural matrix mediates biodiversity-disease patterns

The potential of a landscape to promote the emergence of zoonotic pathogens is frequently cited as being related to host species diversity.[50–52] Because all animal species may host multiple pathogens, some of which have a high degree of host specificity, higher parasite and pathogen diversity generally occurs in communities with higher host diversity.[62] A naive assumption might be that each parasite or pathogen species has some roughly equal chance of spilling over to humans; in this scenario, the risk of zoonotic spillover should relate positively to host species diversity. This amplification effect of biodiversity has been documented at the global level.[4]

In reality, hosts often vary dramatically in their competence as pathogen reservoirs; if the population of more-competent hosts is regulated by the presence of less-competent hosts or non-hosts, we can expect a dilution effect of biodiversity on pathogen transmission.[63] Indeed, working at regional scales, some studies have documented an increase in the prevalence of zoonoses with the loss of biodiversity, consistent with the dilution-effect hypothesis.[63–65] Yet even at regional scales, the dilution effect does not always occur.[50,51,66] This suggests consideration of other attributes of both the original host species involved and the matrix in which organismal interactions occur, within a broader context that places biodiversity and disease patterns as an expression of fundamental ecological and evolutionary processes shaped by matrix characteristics.

For example, we can think of zoonoses whose transmission includes synanthropic host species (i.e., undomesticated species living in close association with humans, such as mice, raccoons, etc.), which are common reservoir hosts of zoonotic pathogens.[60] Population density of synanthropic reservoir species is often highest in landscapes dominated by a low-quality matrix, due to a combination of (1) release from predation and/or competition,[67] which might be an expression of reduced biodiversity in these landscapes,[50] and (2) access to abundant food from crop monocultures.[68] However, outbreaks of synanthropic hosts, such as rodents, are often seen as an external liability in monocultures,[69] ignoring the role that monocultures might have had in rendering rodent species prone to extreme changes in population abundance resulting from changes in their interspecific and intraspecific interactions across a landscape gradient with different matrix quality. This highlights the need to further contextualize evolutionary and ecological phenomena at the population and community level, driving associations of disease with diversity patterns over the agricultural matrix.

The agricultural matrix mediates pathogen evolution

The first step in zoonosis emergence is the transmission of a wildlife pathogen into humans. This step is often linked to the evolution of a pathogen genotype that can infect humans, whose pathogenicity, ancestral or recently evolved, raises concern among affected communities and public health authorities. The incubator potential of the agricultural matrix influences the likelihood of this evolution by shaping the population size and structure of reservoir hosts. Assuming a fixed mutation rate, the larger the reservoir population size, the greater the chance of the evolution of a human-capable genotype, as the effective population size of the pathogen increases.[70] Thus, landscapes that support high numbers of reservoir hosts are more likely sites for zoonotic pathogen evolution.

At the same time, the probability of a novel mutation that confers or increases a given pathogen's ability to infect humans may arise in a landscape that maintains high pathogen genetic diversity. Maintenance of high genetic diversity will occur where the reservoir host and pathogen populations are spatially structured and composed of metapopulations with low levels of immigration.[70] However, increased habitat fragmentation creates separate evolutionary trajectories in isolated reservoir host-pathogen subpopulations, creating genetic bottlenecks at the patch scale but increasing pathogen genetic diversity at the landscape scale, which may increase the probability of the emergence of a human-competent strain of the pathogen.[71] For host species that thrive in intensified agroecosystems, such metapopulation structure is likely to occur where farms are separated from one

Pathogen incubation	**Wildlife host distribution and density**	Maintains high biodiversity and low wildlife host numbers and densities [b]. Dynamics of infection among hosts like that of natural forest.		Reduced biodiversity of wild species (due to habitat destruction and pesticide use). Reduced competition and predation, and abundance of resources may benefit reservoir host and may lead to high host numbers and density [c]. Monocultural plantations that produce food that host can use will further increase host numbers and density.		
	Wildlife infect-to-shed cascade	New cultivation of land may lead to proliferation of hosts and vectors [d].	Low stress on wildlife; therefore, host susceptibility and shedding, and pathogen prevalence and intensity like that of natural habitat.	Low stress on host due to abundance of resources may make hosts less susceptible and reduce pathogen shedding; but high host population numbers and density may increase transmission from host to host and mean more overall pathogen being shed. These systems also have host populations with a reduced genetic diversity that eases the selection and spread of virulent pathogens [e].		
Pathogen barrier	**Wildlife-human interactions**	Possible exposure following land clearing and invasion of human-associated animal hosts [d].	Relatively little host-human interaction, dependent on human activity and intensity, as well as landscape context of agroforests.	Increased host-human interaction possible, especially at habitat edge [f], depending on land use configuration and human activities.	Humans may be exposed to high populations of generalist hosts that thrive in monoculture conditions [g] (or through high-density livestock operations).	High host population, though mechanization reduce labor force, along with the possibility for human exposure.
	Human-human interactions	Limited human-to-human interactions outside of the local community.	Dependent on the socio-economic systems in place [h]. Systems based on exploitation and migrant labor can create vulnerable, denser, and/or shifting human populations, increasing potential for pathogen exposure and transmission. Access to healthcare, education, and resource security can improve health outcomes and reduce susceptibility and spread.			Alienation of the wider human population [i] from wildlife and food production could reduce appreciation for biodiversity and associated benefits

[a] Adapted from Plowright et al. [40]; [b] Perfecto et al. [29]; [c] Tesh et al. [68]; [d] Wilson [79]; [e] Wallace et al. [22]; [f] Faust et al. [39]; [g] Wallace et al. [84]; [h] Santos [20]; [i] Kremen and Merenlender [35].

Figure 3. Agricultural matrices as barriers or incubators
Examples of agricultural matrices along an intensification gradient and their potential impacts as pathogen barriers or incubation.

another by natural barriers (e.g., rivers or patches of semi-natural habitat) or anthropogenic ones (e.g., highways or areas of dense human population). Thus, a matrix that supports high numbers of likely reservoir hosts, separated into isolated subpopulations, will be a particularly good incubator of novel pathogens that can become zoonotic. On the other hand, matrices that maintain high biodiversity may regulate potential reservoir hosts at low density and also provide habitat connectivity, facilitating gene flow and reducing the evolution of genetically differentiated pathogen subpopulations. Such matrices will serve as particularly poor incubators.

This is illustrated, for example, by cutaneous leishmaniasis transmission risk in the Americas, where both extremely high and extremely low mammal and vector diversity has been associated with reduced pathogen transmission.[72,73] Indeed, the number of cases is highest in areas where forest cover is intermediate (Figure 4), which are areas known to host an intermediate species diversity.[74,75]

At the other extreme, pathogen evolution may also accelerate when genetic diversity in the host population is extremely low through another evolutionary mechanism. In high-quality matrices a "red queen" dynamics, where hosts and pathogens co-evolve,[76] likely regulates the selection of mutations that allow the infection of a new host species. However, in low-quality matrices, such as those dominated by monocultural plantations[77] or industrial animal farms,[58] species are composed of genetically depauperate populations grown at high densities, conditions that are ideal for the selection of highly virulent and transmissible pathogens able to infect any host species within the matrix, i.e., the occurrence of a pathogen spillover event.

The agricultural matrix mediates pathogen spillover

The likelihood and frequency of pathogen spillover from a reservoir to a novel host (including humans) will depend on the reservoir host's interactions with the novel host, which are intimately linked to the nature of the agricultural matrix and its intensification. In principle, pathogen spillover, as an ecological event with evolutionary causes and consequences, requires some "ecological fitting," where traits relevant for interaction with the novel host evolved with a different host or under different environmental conditions. Yet, the specific colonization of a novel host is ultimately limited by the co-occurrence of the reservoir and that novel host.[78] This co-occurrence is modulated by the transmission mode, as vectors or environmental pathogen reservoirs, e.g., cholera and other water-borne diseases, can dramatically increase the potential area where spillovers can occur.[79] For example, a recent and comprehensive study about novel host species colonization by *Blastocystis* spp. suggests that host switching is more likely to be driven by ecological fitting than phylogenetic relatedness. In other words, a shared environment is more important than a common evolutionary ancestry among host species for predicting host species switching.[80]

In terms of specific organismal interactions, or the ecological fitting conditions promoting pathogen spillover, we can expect that a heterogeneous agricultural matrix composed primarily of diverse perennial systems that are structurally similar to undisturbed habitat will encourage the movement of predators and other wildlife species key to the regulation of pathogen reservoir host species.[30,36,81] By maintaining the reservoir host population at low density, this type of matrix may pose barriers to pathogen transmission among hosts and between host species and

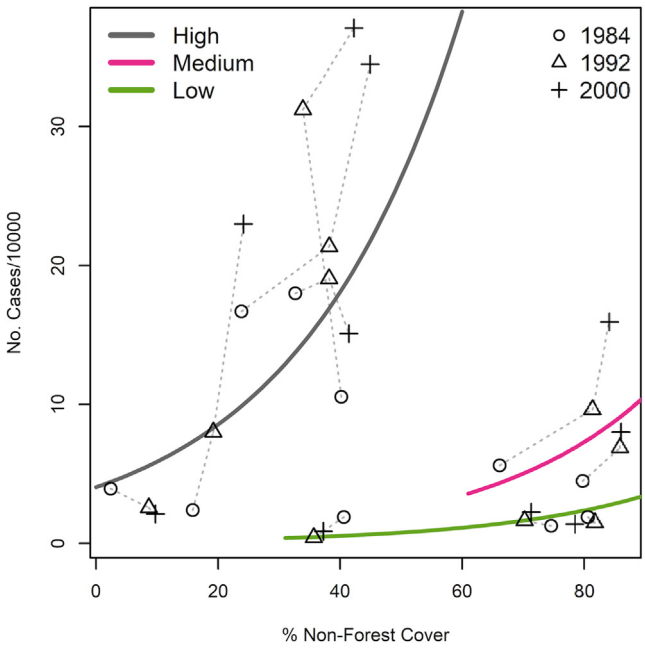

Figure 4. Incidence of American cutaneous leishmaniasis as a function of land use in Panamá

On the x axis, low values correspond to a predominantly natural, or forested, landscape, while high values represent deforested landscapes (including cities and monoculture agriculture). Gray dashed lines indicate the trajectory of change in the different health areas of Panamá, where years are indicated by different symbols (see inset key). Solid lines represent estimates at which disease incidence increases with the percentage of non-forested land; color indicates clusters of health areas with different baseline transmission risks that are conditional on forest cover (high, medium, and low). All the curves share a common exponential rate of incidence increase (mean ± SE = 0.04 ± 0.01) per percentage unit of increase in non-forest cover. This figure is modified from Yamada et al.[74]

humans, thereby preventing pathogen spillover. Thus, we can expect that a heterogeneous agricultural matrix will likely reduce the risk of pathogen spillover. By contrast, a low-quality matrix of crop monocultures, especially in cases where the reservoir host is supported by the crop (for example, grains for mice or oil palm for bats), may enhance reservoir and novel host contact, thus promoting pathogen spillover. However, there may be particular situations in which a heterogeneous matrix facilitates, or is not a barrier for, the movement of infected reservoirs and can increase pathogen transmission. This has been observed for zoonoses with avian reservoirs in urban environments, where reservoir bird species cluster at patches with vegetation appropriate for their nesting, which become transmission hotspots.[82]

The probability of an infected host encountering humans is mediated by the sociocultural milieu of the agroecological system. For instance, in agriculture of subsistence or shifting cultivation, we might expect reservoir host-human interactions to be low, since the intensity of human activities in that matrix is low, despite higher per-capita rates of human-wildlife encounters. In a more intensive agricultural matrix, the interaction between reservoir hosts and humans will be greater if monocultural conditions allow reservoir hosts to thrive. On the other hand, some monocultural systems (like soybean plantations) are highly mechanized and have a reduced human labor input. In these systems, human-wildlife encounters will also be minimized due to the low human population density, but the mobility of infected humans is likely increased in these contexts as farm size scales up, increasing the need for migration related to labor that is seasonal.[83]

Further, specific landscape compositions and configurations will influence the transmission of a zoonotic pathogen within a region through the contact and interaction of its hosts, human or non-human. Often, effects might be related to the movement of hosts or an increased probability of interaction derived from an increased density of hosts per area. The pathogen's mode of transmission adds another layer of complexity that should be considered in this analysis. For instance, water-borne pathogens can be transferred miles from the infectious host; it is on the scale of tens to hundreds of meters for vector-borne, a meter or two for airborne, and immediate physical contact for directly transmitted pathogens.[79]

In monoculture or high-density livestock operations, whether infected humans transmit the pathogen to more human hosts may depend on economic and social labor conditions that mediate human interactions and movement among agricultural areas and from agricultural areas to cities. For example, to explain the initial emergence of influenza A H5N1, i.e., bird flu, a coupled phylogeographic and political economy analysis suggests this virus jumped from its original host, wild waterfowl, to chickens and ducks grown as industrial poultry and released in paddy fields. In Guangdong province, China, where this host switch appears to have occurred, waterfowl have been domesticated as a protein source since the Qing dynasty in the middle of the 17th century, but this host switch coincided with a transformation of the region's agricultural matrix, which shifted from traditional to industrialized agriculture, creating conditions more conducive to the evolution and spillover of novel pathogens.[84,85]

The agricultural matrix mediates pathogen transmission among humans

For human-to-human transmission, the socioeconomic and ecological conditions of the matrix are of prime importance. In a matrix populated by small-scale farmers who rarely interact physically with individuals from distant populations, even highly transmissible pathogens are constrained to affect few people and to be geographically limited. Although the impact on those individuals should not be underestimated, we think the probability of pathogen spread in that situation is small. In contrast, a system of large-scale monocultural plantations with migrant workers moving regularly from plantation to plantation or from the city to the countryside is more likely to create conditions of community spread locally within a plantation, among plantations, or even between plantations and villages or cities from which the migrant farmworkers originated. Such a scenario is more likely to occur when a neoliberal political economy promotes land ownership consolidation, a phenomenon referred as latifundia formation[86] or land grabbing,[87] which is coupled with the generation of vulnerable populations of landless peasants.[88] In a highly industrialized agroecosystem, if migrant workers move from city to plantation and back, the matrix cannot be thought of as much of a barrier. In general, the sociopolitical conditions of production in the agricultural matrix dictate the degree to which the matrix will be a barrier to transmission.

When pathogen transmission is dependent on human-to-human contact, such contacts are not random but shaped by a host of socioeconomic factors.[89] Marginalized populations with low nutrition levels are more vulnerable to pathogens and can increase community transmission.[90] We are just beginning to understand how practices of community self-governance, including water and food sovereignty and agroecology, can influence the well-being of individuals and farming communities, including their health conditions and ability to fight pathogens.[91–93] We elaborate on this theme in the next section.

SOCIOECONOMIC AND POLITICAL REALITIES THROUGH THE LENS OF HORIZONTALITIES AND VERTICALITIES

Our framework recognizes that the agricultural matrix, and the landscape more broadly, includes more than just the biophysical. Political economy and social relations within and beyond the local agricultural landscape vary and influence the emergence and transmission potential of the matrix, as indicated above. To understand pathogen evolution, spillover, and spread, it is imperative that we also consider how human interactions with nature depend on the structure of food production systems and broader social norms, which in turn are shaped by the socioecological geographic space structured by global capitalism.[19,57] Here, the concept of space as a totality of integrated co-evolving horizontalities and verticalities, developed by the geographer Milton Santos[89] and recently employed to study pandemic spread,[24] is useful.

Horizontalities are interactions that occur within a spatially contiguous domain. For example, deforestation driven by the expansion of commercial mango plantations and the intensification of pig farming next to those plantations led to a spillover of the Nipah virus (NiV) from the *Pteropus* spp. fruit bats to pigs and from pigs to humans, initiating an outbreak of the Nipah virus in Malaysia and Singapore between 1998 and 1999.[3,64,94] These horizontalities align with how spatial processes tend to be analyzed in ecology and evolutionary biology. However, the eco-evolutionary conditions of any matrix are primarily created as a by-product of the social, political, and economic relations of the humans within those spaces. These are factors that do not necessarily emerge within a spatially contiguous domain, but instead entail connections among geographically distant entities that nevertheless can affect interactions among organisms, including humans, within the landscape. These forces are what Santos refers to as verticalities. These include economic systems that structure the global movement of capital, goods, and people, which influence local decision-making related to agricultural management. In the Nipah virus example, attending to verticalities would lead us to ask what led to the intensification of pig farming in Malaysia in the decades preceding the virus outbreak.[94]

In a second example, Venezuelan hemorrhagic fever (VHF) emerged in a landscape where all elements associated with the virus causing the disease had been present for a long time without causing an outbreak. It was not until a neoliberal development agenda promoted economic specialization[95] through the expansion and intensification of maize monocultures[96] that an outbreak of VHF was documented, potentially because agricultural intensification contributed to a growing reservoir of rodent hosts and crowding of a vulnerable migrant human population.[68] A similar case occurred with Argentine hemorrhagic fever, caused by Junin virus, which re-emerged after 50 years of epidemiological dormancy in increasingly mechanized and deforested maize monocultural landscapes, where machinery lethal to rodents increased viral transmission among human workers in the field.[97]

As these examples illustrate, considering verticalities helps unveil processes at expanded spatial (e.g., regional or global) and temporal (e.g., historical) scales that are as important as local processes (i.e., horizontalities) for determining the likelihood and trajectory of zoonotic diseases. Thus, the interpenetration of horizontalities and verticalities is central to disease emergence and re-emergence. However, verticalities can have contrasting effects, either increasing or reducing transmission, depending on the context of their internal relations with horizontalities. This is illustrated in Box 2, where we analyze different impacts of verticalities on malaria transmission.

MERGING THE ECOLOGICAL AND THE SOCIOPOLITICAL

The agricultural matrix creates biophysical conditions that either promote or hinder pathogens, their animal hosts, their interactions, and the probability of spillover events to the human population. The type of agricultural matrix also determines the interactions of humans with wild and domestic animals, but also among humans themselves. But the matrix is also created through human agency and decision-making, and those decisions are driven by sociopolitical and economic factors, both local and distant, as horizontalities and verticalities. A comprehensive framework for disease emergence and associated landscape immunity must incorporate both the ecological characteristics of the agricultural matrix, where the pathogen evolves and moves, and the historical and sociopolitical conditions that shape the agricultural matrix and the interactions occurring within it. Box 1 illustrates, using the West Africa Ebola epidemic as a case study, how merging the ecological and sociopolitical can lead to a more nuanced understanding of disease emergence.

PROMOTING DIVERSE AGROECOLOGICAL MATRICES TO ACHIEVE LANDSCAPE IMMUNITY

It seems self-evident that more human interactions with wildlife and human-to-human contact contribute to the emergence of zoonotic diseases. While these conditions are generally factual and useful, their utility is marred by a failure to acknowledge certain complexities. In the context of land-use change, especially in tropical and low-income regions, these conditions, taken in a vacuum, lend themselves to neo-Malthusian interpretations and oversimplifications[27]: human population growth leads to agricultural expansion and deforestation, which destroys wildlife habitat, reduces biodiversity, and provides opportunities for pathogen reservoirs to flourish, increasing the probability of animal-human interactions and spillover events that can lead to zoonotic epidemics and pandemics. While there are elements of truth to this standard zoonotic disease emergence paradigm,

Box 2. Interpenetration of horizontalities and verticalities in the transmission, emergence, and control of disease: Malaria across different local contexts

Malaria is a major global infectious disease with a likely zoonotic origin thousands of years ago.[98] Areas in the Caribbean basin of Costa Rica, which the United Fruit Company historically exploited for the production of bananas to satisfy markets in North America, became endemic for malaria soon after the establishment and expansion, as horizontalities, of large banana plantations. This situation was remediated only after housing quality and health-care access improvement reached most of the population in this area.[99] Currently, a major impediment to malaria elimination in Costa Rica is the development of pineapple plantations and open-field mining operations along the border with Nicaragua, both initiated as verticalities by foreign direct investment[100,101] and associated with recent malaria outbreaks among impoverished migrants and local, often landless, peasants.[99,102] However, verticalities such as technology transfers in agricultural matrices can also improve the health and well-being of local populations. For example, in Africa, Ijumba and Lindsay[103] have described the "paddies paradox," a phenomenon where the introduction of irrigated rice did not increase malaria transmission. A rise in malaria transmission was expected, because rice paddies are productive mosquito habitats, and mosquito abundance is a significant risk factor in malaria transmission. Yet the introduction of irrigation, in this case, was associated with increased food sovereignty, with technology transfer coupled with land reform and other organized efforts to reduce political and socioeconomic inequity, ultimately leading to a landscape that reduced transmission. Similarly, declining trends in malaria transmission have been linked to housing improvement. Malaria-infective mosquito bites are less likely to happen in houses that cannot be infested by mosquito vectors, and housing improvement is a significant contributor to well-being in sub-Saharan Africa[104] and Mesoamerica.[105]

we propose a different approach that better characterizes disease emergence and offers a broader array of potential interventions. Our approach allows for a more nuanced understanding of the intersection of zoonoses, disease emergence, and land use. Our focus is on the role of the agricultural matrix in promoting or preventing zoonoses. We argue that the structure of the agricultural matrix, both ecological and social, strongly influences the evolution, spillover, and transmission of pathogens that eventually cause epidemics and pandemics. While that structure is complicated and cannot be summarized easily, thinking of the interdependence of these factors in shaping the emergence of diseases should be the focus of a new kind of science that fully couples knowledge and research efforts from the natural and social sciences,[22] as a guide to changing the web of factors that have been driving the "pandemicity" of new and old diseases.

This framework suggests a new program that goes beyond ecological issues associated with hosts and pathogens, placing zoonotic disease emergence as a predictable yet malleable feature of the structure of agricultural matrices and societies,[106,107] a strategy also proposed for global climate change mitigation.[108] This approach can lead to coherent, practical, and effective actions that address interconnected problems of food security and sovereignty, biodiversity conservation, disease emergence, climate change, and poverty. These problems seem to have common roots in unquestioned and commonly accepted tenets of neoliberal political economy, which promotes specialization in all realms of human action[95] and threatens diversity, including agrobiodiversity, as illustrated by the global push for large-scale monocultures and their impact destroying mature forest ecosystems[109,110] and increasing climate-change-causing greenhouse gas emissions.[108,111] Neoliberal political economies also promote the dissociation between the location of economic production and social reproduction,[112] which erodes food sovereignty and generates food insecurity, as locally produced food is displaced by food from global supply market chains,[113,114] whose monocultures create niches for disease emergence. Ultimately, disease and food insecurity interact, exacerbated by poverty,[86] in a perfect storm that is often only strengthened by neoliberal-inspired "structural adjustment" programs that destroy the ability of political governance to address any of these life and death-threatening challenges.[90]

The implications for disease and agricultural management are profound. Local decisions about management style, i.e., the mode of production, and the ubiquity of different agricultural strategies are vital in shaping disease dynamics.[115] This integrative framework highlights the role of distant economic interactions (i.e., verticalities) in shaping agricultural opportunities and norms and acknowledges how disease dynamics might differ among common agricultural management styles. Untangling the ecology of disease emergence then requires widening the scope of our understanding of the human/nature interplay. Focusing on the agricultural matrix is key to this critical project.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

I.P. is on the board of directors of the Institute for Research and Action in Agroecology-Puerto Rico, which advocates for the agroecological transformation of agriculture. J.V. is on the advisory board of the Institute for Research

and Action in Agroecology-Puerto Rico, which advocates for the agroecological transformation of agriculture.

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