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BIOMEDICAL SCIENCES

Synthesizing the connections between environmental disturbances and zoonotic spillover

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Abstract: Zoonotic spillover is a phenomenon characterized by the transfer of pathogens between different animal species. Most human emerging infectious diseases originate from non-human animals, and human-related environmental disturbances are the driving forces of the emergence of new human pathogens. Synthesizing the sequence of basic events involved in the emergence of new human pathogens is important for guiding the understanding, identification, and description of key aspects of human activities that can be changed to prevent new outbreaks, epidemics, and pandemics. This review synthesizes the connections between environmental disturbances and increased risk of spillover events based on the One Health perspective. Anthropogenic disturbances in the environment (e.g., deforestation, habitat fragmentation, biodiversity loss, wildlife exploitation) lead to changes in ecological niches, reduction of the dilution effect, increased contact between humans and other animals, changes in the incidence and load of pathogens in animal populations, and alterations in the abiotic factors of landscapes. These phenomena can increase the risk of spillover events and, potentially, facilitate new infectious disease outbreaks. Using Brazil as a study model, this review brings a discussion concerning anthropogenic activities in the Amazon region and their potential impacts on spillover risk and spread of emerging diseases in this region.

Key words: Amazon Forest, biodiversity, disease ecology, outbreak, spillover, zoonosis.

INTRODUCTION

A robust set of evidence shows that conservation of biodiversity and of balance in ecosystems and food webs reduces the risk of emergence and spread of infectious diseases of zoonotic origin, in addition to contributing to human well-being in general (Ostfeld 2009, Keesing et al. 2010, Pecl et al. 2017, IPBES 2020). From a practical point of view, limiting anthropogenic activity in environments with high abundance

and diversity of species contributes to the maintenance of human and environmental health, containing emerging infectious diseases by multiple ecological mechanisms. On the other hand, anthropogenic disturbances (e.g., deforestation, habitat fragmentation, intensive agricultural practices, unplanned urbanization) indeed affect this balance, facilitating the emergence of new pathogens and the spread of diseases (Ellwanger et al. 2020, IPBES 2020). On a global scale, land-use change was the

major driver of more than 30% of new emerging infectious-disease events since 1960 (IPBES 2020).

Currently, there are more than 7.7 billion humans on Earth. Projections indicate that the world population will reach 9.4 to 10.2 billion people by 2050 (Boretti & Rosa 2019). Economic, political, social, and cultural factors dictate human activities in the natural environment, many of which cause damage and disturbances to the environment and to animal populations. The food, water, and consumption demands of the global population are putting great pressure on nature and triggering a range of environmental problems, with expected exacerbation of this scenario in the near future due to the growing world population (Conijn et al. 2018, Boretti & Rosa 2019, Pastor et al. 2019).

The connections between environmental disturbances and infectious diseases are increasingly worrying because efforts to contain deforestation, climate change, and other environmental impacts are still very modest. Globally, habitat loss and extinction rates are on the rise (Ceballos et al. 2015, Newbold et al. 2016, Powers & Jetz 2019), and the detrimental effects of climate change on the human population and other species are increasingly evident (Beyer et al. 2021, Ma & Yuan 2021). Concomitant with this scenario of environmental neglect, the number of emerging infectious disease events per decade is increasing (Jones et al. 2008). Table I shows several examples of infectious disease outbreaks associated with anthropogenic pressures on the environment and animal populations. Also, the economic impacts and losses of human lives related to Coronavirus Disease 19 (COVID-19), which is a zoonotic disease, make clear the magnitude and severity of the situation and the need to understand how to reduce the risks of new pandemics (Dobson et al. 2020, Holmes et al. 2021). As of February 2, 2022, COVID-19 had

caused more than 381 million infection cases and 5,688,009 deaths worldwide (Dong et al. 2020, Johns Hopkins University 2022). It is increasingly clear that when a pathogen emerges in a given human population after an event of zoonotic spillover, even in a remote location, the pathogen can quickly spread globally by international air travel and other transport systems, especially in situations of high connectivity between remote regions and large urban centers.

Zoonotic spillover is a phenomenon characterized by the transfer of pathogens between different species (usually non-human animals to humans), which may result in new infectious diseases if biological and demographic conditions are conducive to the adaptation of the pathogen in the new species population. Spillover events are among the initial steps towards the emergence of new human infectious diseases, outbreaks, and epidemics (Plowright et al. 2017, Ellwanger et al. 2019). Most of the pathogens (~60%) that affect humans are derived from microbial strains that previously circulated only in non-human animals (Jones et al. 2008), such as HIV (Keele et al. 2006), influenza A viruses (Krammer et al. 2018), Zika virus (Wikan & Smith 2016), Ebola virus (Leroy et al. 2005, Saéz et al. 2015), rubella virus (Bennett et al. 2020), *Echinococcus multilocularis*, *Trypanosoma cruzi* (Thompson 2013), hepatitis B virus (Rasche et al. 2016), MERS-CoV, SARS-CoV (Cui et al. 2019) and SARS-CoV-2 (Andersen et al. 2020), among many others (Montgomery & Macdonald 2020). Considering adenoviruses, phylogenetic analyses indicate that at least 16 B-type human adenoviruses (HAdV) had their original reservoir in great apes, some of them causing severe human disease. Also, it was proposed that the HAdV-B76 strain, which is associated with a human fatality in 1965, arose from recombination of a virus that infected humans, chimpanzees, and bonobos

Table I. Examples of connections among human-related environmental disturbance, animal populations and infectious diseases.

Anthropogenic pressures on the environment and animal populations*	Effect or association with disease emergence or dissemination	References
Habitat loss, deforestation, industrial agriculture, monoculture practices, mining, and other types of land-use changes	Forest fragmentation, fires and other disruptions of natural habitats of bats resulted in outbreaks of Nipah and Hendra viruses in Australasia	Field et al. (2001), Chua (2003), Epstein et al. (2006)
	Deforestation and road expansion were associated with increased human-biting rate of <i>Anopheles darlingi</i> (primary malaria vector) in the Peruvian Amazon	Vittor et al. (2006)
	Habitat fragmentation and biodiversity loss were associated with a higher prevalence of <i>Trypanosoma cruzi</i> infection among small mammals in an Atlantic Rain Forest landscape of Brazil	Vaz et al. (2007)
	Increasing of land cultivated for sugarcane and high annual mean temperature were associated with hantavirus pulmonary syndrome incidence in the Neotropics	Prist et al. (2016)
	Forest loss triggered increased risk of Kyasanur Forest disease (tick-borne viral hemorrhagic fever) in India	Walsh et al. (2019a)
	Habitat changes of putative wild rodent reservoirs and agriculture-related activities were associated with fatalities from Sabiã virus infection (two in 1990 decade and one in 2020), São Paulo State, Brazil	Ellwanger & Chies (2017), Malta et al. (2020)
	Land-use (e.g., habitat degradation) was associated with changes in parasite richness and prevalence, as well as co-infection patterns, of avian parasites	Reis et al. (2021)
	Agricultural and irrigation practices were associated with mosquito proliferation, with increases in Japanese encephalitis cases	Keiser et al. (2005)
	Deforestation for agriculture and cattle pasture was associated with development and dissemination of antibiotic resistance in the Amazonian soil microbiome	Lemos et al. (2021)
	Anthropogenic deforestation associated with the shortage of fruiting due to drought-triggered movement of fruit bats to livestock areas, infecting pigs and then humans with Nipah virus in Malaysia	Chua et al. (2002), Looi & Chua (2007)
	Colonial practices in Indigenous areas had a major impact on the health of Indigenous populations, who were exposed to various infectious diseases transmitted by European colonizers and explorers in American and African continents, for example	Valeggia & Snodgrass (2015), Owers et al. (2017)
	Mining, logging, illegal land grabbing and other types of land-use changes in Indigenous lands favors the transmission of SARS-CoV-2, malaria, sexually transmitted infections, and other infectious diseases in Amazonian Indigenous populations	Ellwanger et al. (2020), Vittor et al. (2021)
	In Brazil, political changes permissible to illegal activities (e.g., logging, mining, fires, weakening of Indigenous leaders) on Indigenous Lands (<i>Terras Indígenas</i>) exposed Indigenous and traditional communities to multiple infectious diseases, including COVID-19	Brançalion et al. (2020), Ferrante et al. (2020)
	Mining and other types of land-use changes were associated with Buruli ulcer (caused by <i>Mycobacterium ulcerans</i> infection) in southwestern Ghana	Wu et al. (2015)
	Agricultural practices exacerbated the risks of many infectious and parasitic diseases (hookworm, malaria, scrub typhus, spotted fever group diseases, schistosomiasis, <i>Trichuris trichuria</i> infection) in Southeast Asia	Shah et al. (2019)
	Mining related practices favored emerging infectious disease events in Africa, including Ebola outbreaks, with mining-associated political interests exacerbating such outbreaks	Wallace et al. (2016), Guègan et al. (2020), Ostergard Jr (2021)
	Monoculture and other current food systems practices expose populations to various health issues, including infectious and parasitic diseases (in some cases derived from malnutrition) and multi-resistant microbes at a global scale	Pradyumna et al. (2019), Everard et al. (2020)
	Gold mine workers are highly exposed to hantavirus infection, malaria and leishmaniasis in South America	Rotureau et al. (2006), Terças-Trettel et al. (2019)
	Agricultural systems bring some bat species (e.g., <i>Desmodus rotundus</i> vampire bat) closer to humans and domestic animals, increasing the risk of bat-borne infections, including rabies outbreaks	Rosa et al. (2006), Kuzmin et al. (2011)
	Infectious diseases events were associated with changes in forest cover and oil palm expansion at a global scale	Morand & Lajaunie (2021)
	Sugar cane monoculture favors some opportunistic rodents, favoring hantavirus infection in humans	Figueiredo et al. (2010)
	Gold mining-associated activities and settlements favor the spread of infectious diseases (e.g., tuberculosis, HIV/AIDS and other sexually transmitted infections, rabies, vector-borne diseases) in Australia, Africa, North America, and South America	Ogola et al. (2002), Eisler (2003)
	Anthropogenic disturbances (e.g., crop plantation, removal of vegetation cover for cattle raising) lead to simplification of ecosystems (biodiversity loss) and thus favor populations of opportunistic/generalist animal species that can transmit hemorrhagic fever viruses to humans	Mills (2006)
Co-circulation of Araraquara and Juquitiba hantaviruses in rodents was detected in the Brazilian Cerrado biome, with agricultural practices increasing the risk of human hantavirus infection	Guterres et al. (2018)	

Table I. Continuation.

Climate change and extreme weather events	Climatic anomalies (with heavy rainfall and eventually flooding after periods of drought) and increase in air and sea surface temperatures triggered outbreaks of Rift Valley Fever in Africa	Anyamba et al. (2001), Martin et al. (2008)
	Fossil fuel-related climate change associated with air pollution favor the occurrence of respiratory infections (e.g. pneumonia, fungal infection, Hantavirus respiratory disease), especially in children	Mirsaeidi et al. (2016), Brugha & Grigg (2014)
	An increase in coccidioidomycosis cases in Arizona from 1998 to 2001 was associated with climatic and environmental changes such as wind, mean temperature, dust and rainfall because these factors affect the abundance of fungal arthrospores of <i>Coccidioides</i> species in the air	Park et al. (2005)
	Extreme weather events, in association with de-urbanization, were associated with higher risk of flood-related non-cholera diarrhea in lower hygiene and sanitation groups in a post-flood period in Dhaka, Bangladesh. Rotavirus, <i>Escherichia coli</i> , <i>Campylobacter</i> and <i>Aeromonas</i> were the most common pathogens causing non-cholera diarrhea episodes	Hashizume et al. (2008)
	Climate change was associated with increased human cases of Lyme disease	Germain et al. (2019)
	Fossil fuel-related climate change will change the distribution patterns of zoonotic and vector-borne diseases in the world in a way difficult to accurately predict, but in general favoring the spread of these diseases on a global scale	Wilkinson et al. (2007), Greer et al. (2008), Dantas-Torres (2015), Wilke et al. (2019b)
	Climate change and land-use change were associated with an increased risk of acute gastrointestinal diseases	Brubacher et al. (2020)
	Climate abnormalities and melting of permafrost released <i>Bacillus anthracis</i> , the etiological agent of the anthrax disease, infecting reindeer, cattle, and humans	Timofeev et al. (2019), Maksimović et al. (2017), Stella et al. (2020)
	Temperature rise alters the distribution, optimal conditions for breeding, growth and survival of <i>Schistosoma</i> -related snails, and such conditions were associated with increased risk of spread and transmission of schistosomiasis	Kalinda et al. (2017)
	Hunting, industrial livestock production, bushmeat practices, and other types of wildlife exploitation	Bushmeat-related practices triggered the SARS-CoV emergence and outbreak in Asia in 2003 and 2004
Pervasive contact with wildlife (e.g., hunting, bushmeat-related practices), in association with forest fragmentation and loss, triggered Ebola virus disease outbreaks in Africa		Judson et al. (2016), Olivero et al. (2017), Rulli et al. (2017)
Coccidiomycosis cases resulted from armadillo hunting		Costa et al. (2001), Brillhante et al. (2012), Capellão et al. (2015)
Poultry and livestock are sources of multiresistant <i>E. coli</i> isolates with clinical importance in China		Yassin et al. (2017)
Livestock and poultry are sources of antimicrobial resistance genes of <i>Enterococcus</i> spp. isolates in Lithuania		Ruzauskas et al. (2009)
An animal-based agriculture river system was associated with antimicrobial resistance of <i>Salmonella</i> sp. in Brazil, with multi-resistance found in 18% of isolates		Palhares et al. (2014)
Poultry and food products (e.g., retail meat, sushi, ready-to-eat foods) are sources of multi-resistant and methicillin-resistant <i>Staphylococcus aureus</i> isolates in Europe		Nemati et al. (2008), Li et al. (2019)
A swine production system was associated with anti-microbial resistance in <i>Campylobacter</i> spp., <i>E. coli</i> and <i>Enterococcus</i> spp. in Australia		Hart et al. (2004)
Antimicrobial resistance and virulence genes of <i>Streptococcus</i> and <i>Salmonella enterica</i> were detected in isolates obtained from dairy cows in Asian countries		Chuanchuen et al. (2010), Ding et al. (2016)
Animals raised for consumption (e.g., chickens, pigs, cattle) use the majority (73%) of antimicrobials sold in the world, and these animals are major sources of multiple multi-resistant microbes, especially in developing countries and emerging economies, such as India, China, Brazil and Iran		Van Boeckel et al. (2019)
Hunting, cleaning and eating of armadillos were associated with the development of Hansen's disease (<i>Mycobacterium leprae</i> infection) in humans		Capellão et al. (2015), Van Vliet et al. (2017), da Silva et al. (2018)
Human-promoted elephant-livestock interface increased anthrax transmission risk in India		Walsh et al. (2019b)
The wildlife exploitation through hunting and trade of threatened wildlife species favors close contact between humans and wildlife, which are contributing factors of spillover events		Johnson et al. (2020)
Human interaction with animal species (wildlife exploitation, animal trade, livestock industry?) triggered the SARS-CoV-2 emergence and the related COVID-19 pandemic		Lam et al. (2020), Zhang & Holmes (2020), Zhang et al. (2020), Holmes et al. (2021)
Livestock/agro-pastoral activities were associated with occurrence of zoonotic diseases, such as brucellosis, Q-fever, and Rift Valley fever, affecting both humans and livestock in Ethiopia		Ibrahim et al. (2021)
Hunting, bushmeat and related activities caused the HIV spillover from wild primates to humans in Africa (around 1920 or before), later (around 1960) spreading around the world as a result of road expansion and globalization, among other social and economic factors		Hahn et al. (2000), Gray et al. (2009), Faria et al. (2014), Gryseels et al. (2020)
Reassortment of different influenza viruses in swine creates new subtypes of influenza, the causative agent of the Spanish flu (1918) and the swine flu (2009); Influenza reassortment events are facilitated by livestock practices	Tomley & Shirley (2009), Shi et al. (2014)	

Table I. Continuation.

Urbanization, de-urbanization, and environmental changes due to infrastructure expansion	The construction of the Binational Itaipu Reservoir contributed to the proliferation of <i>Anopheles</i> mosquitoes and the increase in <i>Plasmodium vivax</i> malaria cases in the region of the Paraná River (Brazil)	Falavigna-Guilherme et al. (2005), Leandro et al. (2021)
	In Fiji, the presence of <i>Leptospira</i> antibodies was associated with different environmental and socio-demographic variables such as living in villages, lack of access to treated water, working outdoors, living in rural areas, high poverty rates, contact with animals, among other factors	Lau et al. (2016)
	The construction of dams was associated with malaria transmission in sub-Saharan Africa	Lautze et al. (2007), Kibret et al. (2019)
	Poorly planned urbanization, presence of waste, and precarious sanitation conditions were linked to the proliferation of <i>Aedes aegypti</i> mosquitoes and circulation of urban arboviruses (e.g., dengue, chikungunya and zika)	Almeida et al. (2020)
	Poor housing conditions in association with loss of habitat and food sources favor the infestation of human dwellings by triatomine bugs, transmitters of <i>T. cruzi</i> (Chagas disease agent)	Starr et al. (1991), Schofield et al. (1999), Lima et al. (2012), Crocco et al. (2019)
	Human contact with wildlife that resulted from mining and entering caves promoted Marburg virus outbreaks in Africa (infection source linked to bats in caves and mines)	Bausch et al. (2003), Pawęska et al. (2018), Amman et al. (2020)
	Higher risk of schistosomiasis infection due to the construction of dams (water blockage) in Africa	Sokolow et al. (2017)
	Overcrowding, environmental contamination, exposure to disease vectors and lack of public health infrastructure favors the transmission of infectious and parasitic diseases in Indigenous populations in many countries	Gracey & King (2009)
	Marginalized and Indigenous peoples in the United States and Brazil experience disproportionate burdens of COVID-19 (both morbidity and mortality) due to social injustice, lack of vaccines and public health infrastructure, and political weakening of Indigenous leaders	Santos et al. (2020), Costa et al. (2021), Hiraldo et al. (2021)
	Infrastructure problems, water contamination and poverty favor infectious and parasitic diseases in Indigenous populations of the Arctic	Hotez (2010)

***Many types of anthropogenic pressures on the environment and on animal populations have been grouped by categories for better organization of the table. However, we stress that in many examples, different categories of anthropogenic actions are acting in association to favor the emergence or spread of disease. At the global level, intensive causes/practices of land-use changes (e.g., logging, mining, industrial livestock production, fossil fuel extraction, deforestation) certainly have a much greater impact as drivers of spillover and emerging infectious disease events than individual practices of consumption and behavior.**

(Hoppe et al. 2015, Dehghan et al. 2019, Kremer 2021).

In this article, the expression ‘zoonotic spillover’ will be used to refer to the introduction of a pathogen into the human population from a different animal species. However, it is essential to emphasize that spillover is a complex phenomenon. There are different pathways of spillover events. For example, a pathogen can be transmitted from one species (source host) to another (recipient host) directly, without an intermediate species. Alternatively, some spillover events involve an intermediate species (intermediary host) that acts as a ‘bridge’ for the transmission of the pathogen between the source host and the recipient host. The intermediary host can be a vertebrate species or an invertebrate animal (e.g., mosquito,

tick). More than one intermediate host may be involved in the spillover event. Also, the spillover can involve the environment. In this case, the recipient host is infected by the pathogen that has been released into the environment by the source or intermediate host (Borremans et al. 2019, Ellwanger & Chies 2021).

The association between anthropogenic activity and emerging infectious diseases has been increasingly recognized by the scientific community and by the general population since the beginning of the COVID-19 pandemic, with some positive impact on public concern and awareness about nature and environmental issues (Rousseau & Deschacht 2020, Severo et al. 2021). A search on the PubMed database using in association the terms “environmental change” and “pandemic” resulted in 1974

documents published in 2021, a huge increase compared to the 64 documents published in 2019 (<https://pubmed.ncbi.nlm.nih.gov/>; search performed on February 2, 2022). However, the connections and ecological mechanisms linking environmental disturbance and increased risk of zoonotic spillover events are not always explored in scientific publications. Synthesizing the sequence of basic events involved in the emergence of new human pathogens is important to guide the understanding, identification, and description of key aspects of human activities that can be changed to prevent new outbreaks, epidemics, and pandemics. This knowledge is critical for researchers from different fields. Thus, the main aim of this review is to synthesize the principal connections between environmental disturbances and increased risk of spillover events. In this article, 'environmental disturbance' refers to disturbance, damage or imbalance caused by human activity on natural landscapes, urban and rural areas, animal populations, or ecosystems.

Considering the multiple dimensions surrounding the association between anthropogenic activity and infectious diseases, this article was written with the collaboration of authors from multiple fields, a strategy aligned with the One Health perspective. In the first part of this article, we briefly discussed the relationship between biodiversity and spillover risk. Subsequently, the connections between environmental disturbances and spillover events are reviewed. Considering the authors' expertise on tropical ecosystems in the Brazilian context, this review also brings a discussion concerning anthropogenic activities in the Amazon region and their potential impacts on spillover risk and spread of emerging infectious diseases in this region. This article therefore differs from the literature on emerging diseases because it brings together basic information on

anthropogenic activities that facilitate zoonotic spillover events in different contexts and countries, and it provides an analysis focused on a specific highly biodiverse biome - the Amazon Forest.

BIODIVERSITY AND SPILLOVER RISK

Biodiversity can be associated with an increased risk of infectious diseases in some situations. For example, this can occur by adding new infectious agents or carriers to the environment (biodiversity as a 'source' of pathogens), or through the incorporation of new (host) species into a given environment, or by increasing food sources for disease vectors and thus contributing to their proliferation (Keesing et al. 2006). A good discussion regarding the complex influences of biodiversity on infectious diseases can be found in Rohr et al. (2020). Although on some occasions biodiverse environments can be associated with increased risk of infectious diseases, biodiversity *per se* is not the cause of emerging infectious diseases. On the contrary, biodiversity usually confers protection to human health.

High-biodiversity ecosystems 'dilute' the density of reservoir hosts and competent vectors, minimizing the contact between reservoir hosts and vectors and reducing the prevalence or load of pathogens in these hosts and vectors, thus decreasing the risk of zoonotic infections. Greater richness and diversity of predators and competitors can also contribute to the control of species that are both adapted to human-modified environments and have the potential to transmit zoonotic pathogens (Schmidt & Ostfeld 2001, Keesing et al. 2006, Ostfeld 2009, Pongsiri et al. 2009, Civitello et al. 2015, Kilpatrick et al. 2017). The phenomenon in which high species diversity reduces the risk of

infectious diseases is called the 'dilution effect' (Keasing et al. 2006).

A good example of the dilution effect can be found in Lyme disease, which is caused by the *Borrelia burgdorferi* infection and is transmitted by ticks in the genus *Ixodes*. Different mammals are natural hosts of *B. burgdorferi* in nature, including the white-footed mouse (*Peromyscus leucopus*), a highly competent reservoir. The disease affects human populations living in the USA, Canada, and European nations, among other countries. In the presence of a great diversity of reservoir hosts in nature (white-footed mouse plus other hosts), ticks feed on the blood of different hosts with varied competence for *Borrelia* transmission (many with a low reservoir competence), thus 'diluting' the number of infected ticks and consequently the risk of Lyme disease (LoGiudice et al. 2003, Ozdenrol 2015, Keasing & Ostfeld 2021). In brief, high host diversity including poor competent hosts dilutes the infection risk exerted by the few highly competent hosts. On the other hand, the risk of disease increases as the diversity of *Borrelia* hosts declines and the density of competent reservoir hosts increases in a particular area (LoGiudice et al. 2003, Keasing & Ostfeld 2021).

The impact of host diversity on the disease risk was observed in other models beyond Lyme diseases. The risk of human infection by West Nile virus and Hantavirus decreases as the diversity of their hosts (wild birds and rodents, respectively) increases. The opposite correlation can also occur, with the risk of human infection increasing as host diversity decreases (Mills 2006, Allan et al. 2009, Ostfeld 2009). These two additional examples highlight the dilution effect, indicating how biodiversity can 'dilute' the risk of zoonotic spillover events, protecting human health.

The dilution effect is strongly related to the number and relative abundance of taxa, namely taxonomic diversity (Naeem et al. 2012), which is the kind of "biodiversity" discussed above. However, it is essential to consider that other forms of biodiversity exist, with varied impacts on disease risk. According to Naeem et al. (2012), biodiversity can be classified on the basis of several dimensions, including taxonomic, phylogenetic, genetic, functional, spatial or temporal, interaction, and landscape diversities. These other dimensions of biodiversity can also affect spillover events and the spread of pathogens. For example, genetic diversity has contributed to the emergence of new pathogens or variants, as observed in the SARS-CoV-2 and HIV pandemics, facilitating the transmission and spread of the viruses to different countries (Faria et al. 2014, Andersen et al. 2020). Also, interaction diversity (e.g., competition, predation, parasitism) has an important influence on the risk of emergence and spread of zoonotic diseases (Vourc'h et al. 2012) because it modulates the contact between species, host immunity, transmission of pathogens and food webs.

It is also fundamental to stress that the dilution effect does not apply to all types of zoonotic diseases, being more closely related to diseases borne by vectors such as arthropods and rodents, as indicated by the examples mentioned above. Furthermore, the dilution effect may be scale dependent. The protective role of biodiversity on disease risk observed at the local scale may not be observed when the effect of biodiversity is analyzed at the global scale. Also, the ecological history of each disease is different and, in some cases, is either weakly dependent on the degree or dimension of biodiversity or its effect is only indirect (Rohr et al. 2020). Some diseases of zoonotic origin, but that are currently highly specialized

on the human host (e.g., measles, tuberculosis, pneumonia), have a weak relation with measures of biodiversity (Rohr et al. 2020).

Other factors (e.g., demography, social issues) also increase the complexity of the relation between biodiversity and zoonotic risk. Globally, countries with high biodiversity are often precisely those where the burden of zoonotic diseases can be observed most intensely. For example, Brazil is classically affected by multiple types of zoonotic vector-borne diseases (Magalhaes et al. 2020), despite being one of the most biodiverse countries in the world. Inadequate sanitary conditions and precarious public health systems, which are frequently observed in tropical developing countries, can override the dilution effect associated with high biodiversity, facilitating the emergence and spread of diseases in these countries (Ellwanger et al. 2021). In brief, the connections between biodiversity and zoonotic spillover are multiple and complex. Although some generalizations are possible, such as the dilution effect and the connections that will be discussed later in this article, each pathogen and spillover event must be analyzed according to its natural history and the context of its occurrence.

ALIGNMENT OF CONDITIONS CONDUCTIVE TO ZOOONOTIC SPILLOVER

Role of animal groups

An increased risk of spillover events is usually associated with particular animal orders, including Chiroptera and Rodentia, which are composed of species with supposed high 'zoonotic potential'. Also, anthropogenic modifications in landscapes favoring human contact with rodents and bats are usually associated with increased risk of zoonotic infection. However, some criticism concerning

these aspects is needed. Some animal species can indeed host a high load or diversity of zoonotic pathogens due to intrinsic biological characteristics (e.g., immune system factors, genetic proximity to humans) or due to ecological characteristics, such as the sharing of a habitat with humans or livestock. However, a greater load and variety of pathogens in certain reservoir hosts can be circumstantial and is not necessarily an intrinsic characteristic of a specific animal group. Bats and rodents are often considered highly competent in transmitting pathogens to humans because they harbor a great diversity of zoonotic pathogens, reproduce quickly and often inhabit human-related environments. Chiroptera and Rodentia are the most numerous orders of placental animals, which can increase the opportunity for the emergence of potential zoonotic agents from these animals (Luis et al. 2013, Han et al. 2016). Canidae and Felidae are families in the order Carnivora that also pose risks to the human population in terms of zoonotic spillover because their members (e.g., dogs, foxes, cats) host different zoonotic pathogens and frequently circulate in human-dominated areas (Han et al. 2021).

Stray dogs and cats find favorable conditions to proliferate in areas where urbanization has taken place in a disorderly way, and these animals are transmitters of zoonotic diseases in urban centers, especially due to soil contamination with the eggs and oocysts of parasites (*Toxocara*, *Trichuris*, *Toxoplasma*, *Cystoisospora* and *Taenia* genera, among others) released into the environment through animal feces. This is a particularly important problem for children because they come into greater contact with the soil in public squares and parks; this affects populations in China, South America, highly developed European nations, and elsewhere (Szwabe & Błaszowska 2017, Montoya et al. 2018, Fu et al. 2019, Saldanha-Elias

et al. 2019). Moreover, leishmaniasis is a major zoonotic disease in several Latin American countries. This disease is caused by *Leishmania* parasites, which have dogs as common reservoirs. The disease is transmitted by phlebotomine sandflies that proliferate in areas with a lack of environmental sanitation and an abundance of domestic animals, thus affecting people living in urban and peri-urban areas (Teodoro et al. 1999, Marcondes & Day 2019). These cases exemplify the role of the order Carnivora as an additional source of zoonotic pathogens.

Mammals in the order Rodentia were initially classified as the animal group with the highest number of zoonotic hosts, with ~11% of species having zoonotic potential. Highly competent rodent reservoirs show a fast life history profile, reaching sexual maturity and producing offspring at higher rates earlier in life as compared to non-reservoir rodents. Also, highly competent rodent reservoirs usually thrive in areas with high human population densities (Han et al. 2015, 2016). Similar to rodents, bats are usually considered to be of special zoonotic concern because they have high longevity, the colonies are numerous, and the share of viruses between different bat species is increased due to sympatry (Luis et al. 2013). Bats have immune systems with unique adaptations that allow these animals to harbor many viruses without themselves becoming sick, which contributes to making these animals of special concern regarding zoonotic risk (Hayman 2019, Subudhi et al. 2019).

However, it is necessary to consider some points regarding the role of the orders Rodentia and Chiroptera (especially bats) as disproportionate zoonotic reservoirs. Limited inflammatory responses, high population densities and gregarious social behaviors observed in some bat species may indeed facilitate pathogen transmission among bats,

especially viruses, contributing to the zoonotic potential of this group (Brook & Dobson 2015, Streicker & Gilbert 2020). On the other hand, the lack of knowledge about the immunity of other animal groups, including their ability to harbor pathogens asymptotically, may currently be biasing the conclusion that bats or rodents are especially competent in harboring and transmitting zoonotic pathogens. There is also high immunological variation among bat species, making generalizations about the ability of bats to transmit zoonosis a complicated task. Beyond bats and rodents, other animal groups can be of great importance for the transmission of zoonotic pathogens to humans, although they have been less considered and sampled in studies involving zoonotic diseases (Streicker & Gilbert 2020). A recent study by Mollentze & Streicker (2020) reported that the viral zoonotic risk was homogenous among mammalian and avian species when reservoir hosts of 415 RNA and DNA viruses were considered, this being the largest dataset to date. Bats and rodents were considered unexceptional zoonotic hosts, with the proportion of zoonotic viruses varying minimally across the taxonomic orders of the reservoirs that were analyzed (Mollentze & Streicker 2020).

Still concerning bats, human activity has effects beyond those expected from human-triggered changes in the sizes and population structures of these animals. Bats are highly sensitive to anthropogenic activity, which generates physiological stress in these animals. These physiological changes impact infection severity and pathogen shedding in bats, affecting their associated viral populations and risk of spillover events. For example, Plowright et al. (2008) observed that reproduction and nutritional stress in little red flying foxes (*Pteropus scapulatus*) increases the risk of Hendra virus infection in

these animals, potentially increasing the risk of human infection when these conditions occur. Pregnant and lactating female bats showed higher Hendra virus infection rates, and animals under nutritional stress showed higher infection prevalence, a result potentially derived from factors such as poor immune defense or greater contact with other animals while sharing food (Plowright et al. 2008). Furthermore, recent data have shown that the ecological conditions of the flying fox hosts of Hendra virus influence the timing, magnitude, and cumulative intensity of virus shedding, thus affecting the spillover risk (Becker et al. 2021). Based on these findings, changes in bat immunity derived from human-associated environmental disturbances (e.g., habitat loss, food shortages) can be considered a mechanism by which human activity can increase the risk of spillover events and zoonotic diseases, since these immunological changes can increase infection severity, viral shedding and infection rate in reservoir host populations. Moreover, this information indicates that the zoonotic risk attributed to a given host is *circumstantial* and not necessarily *intrinsic* to a specific animal group, with human-related interference on these hosts influencing the circumstantial zoonotic risk.

Host-associated factors, pathogen characteristics and the environmental context

Several host-associated factors can increase or reduce the risks of spillover events, including pathogen load in the source or intermediate host, immunity or nutritional status of recipient host, similarity of pathogen receptors in the different hosts, and genetic/evolutionary distance between species. Spillover risk is also modulated by ecological conditions (e.g., habitat sharing by different species, changing patterns disease in reservoir populations, changing reservoir species behavior) and environmental

factors (e.g., landscape characteristics, environmental sanitary conditions, abiotic factors: temperature, humidity, rainfall). Adding more complexity to spillover risk, characteristics of the pathogens (e.g., virulence, transmissibility, viral family, host range) and human behavior (e.g., interaction with other species, invasion of habitats) also affect the spillover risk. The dose and route of human exposure to pathogens also determine the chances of a pathogen crossing the species barrier. After a pathogen successfully reaches a new host, other factors will affect the outcome of the spillover. Not all spillover events result in an epidemic outbreak, and many spillover events go unnoticed, without medical or epidemiological importance. An outbreak or epidemic only occurs when the pathogen, after crossing the barriers between species, finds favorable conditions for its dissemination in the new population. These conditions are usually population agglomeration, unplanned urbanization, and a large number of susceptible hosts (Plowright et al. 2017, Becker et al. 2019, Borremans et al. 2019, Ellwanger & Chies 2021, Grange et al. 2021, Nandi & Allen 2021).

The human immunological status at the time of contact with a new zoonotic pathogen influences the outcome of a spillover event. Immunosuppressed individuals can be infected by viruses, fungi, parasites, and bacteria much more easily than individuals with fully competent immune systems (Raychaudhuri et al. 2009, Vanichanan et al. 2018). Both the maintenance of a pandemic status and the raising of new pathogenic variants are conditions affected by the human immunological status, as can be seen in the current COVID-19 pandemic dynamics. Similarly, HLA alleles and variants in immune-system genes (e.g., single nucleotide polymorphisms in Toll-like receptor, cytokine and chemokine receptor genes, complement system) can either increase or decrease the

risk of infection by different pathogens in human populations, in addition to affecting the progression of infection and the host's pathogen load, and, consequently, disease spread in the population (Burgner et al. 2006, Chang et al. 2008, Pine et al. 2009, Ferguson et al. 2011, Adriani et al. 2013, van den Broek et al. 2020, de Vries et al. 2020, Sánchez-Luquez et al. 2021), indicating the importance of host genetics as a determinant of spillover risk and outcome. Therefore, this information makes it clear that when a new pathogen reaches a human being due to favorable ecological conditions (e.g., contact between species sharing the same habitat, land-use changes), the outcome of the spillover event will also be conditioned to a series of other biological factors.

CONNECTIONS BETWEEN ENVIRONMENTAL DISTURBANCES AND ZOOONOTIC SPILLOVER

Human behavior and demography

Human behavior and demographic changes are critical modulators of risk and outcome of spillover events. Keeping animals in captivity for decorative or entertainment purposes, the frequent and close contact with wild species, as well as human entry into wild environments, facilitate spillover events because they put humans in close contact with different species. For example, tourist activities involving cave exploration in Africa facilitated Marburg infection cases in past years. Caves are usually visited by numerous animals, including fruit bats (*Rousettus aegyptiacus*) that act as Marburg reservoir hosts; caves are places where animal defecate and associated pathogens are found in abundance (Johnson et al. 1996, CDC 2009, Amman et al. 2012). Also related to human behavior, the use of wild or exotic animals as pets can facilitate the introduction of new

pathogens into the human population (Chomel et al. 2007), in addition to being a conservation problem affecting wild species.

Human migratory flows can also change the epidemiology of infectious diseases through the introduction of known and unknown pathogens into new areas, by overburdening health systems, or by exposing non-vaccinated migrants to new pathogens and precarious health conditions. These problems are particularly important in cases of forced migration due to war, political instability and climate change. This indicates that the global political instability associated with the disparity in terms of access to healthcare directly or indirectly affects populations worldwide concerning control and prevention of infectious diseases (Gushulak & MacPherson 2004, Castelli & Sulis 2017, Berry et al. 2020, Ibáñez et al. 2021). Recent measles outbreaks in Brazil and Colombia due to Venezuelan migration demonstrated failures in the vaccination and access to health services by Venezuelans (Hotez et al. 2020). The number of 'climate refugees' will increase as climate change intensifies, contributing to both the exposure of migrants to new reservoir hosts and related pathogens, and to the change in the profile of infectious diseases in many countries (McMichael 2015). However, we stress that the effect of migratory flows on infectious disease burden on migrants and refugees is greater than the effect on the population of the country that receives the immigrants, especially in Europe (Castelli & Sulis 2017).

Exploitation of wildlife

Hunting, wildlife trafficking, animal trade in 'wet markets,' and 'bushmeat' consumption are classic driving forces of spillover events, since these practices put humans in close contact with pathogens in the meat, blood and other biofluids from a wide range of animal species (Karesh et al. 2005, Smith et al. 2012, Johnson et al. 2020,

Magouras et al. 2020, Zhang & Holmes 2020). The expression 'wet markets' refers to places where different live animal species are sold in close contact, sometimes sharing a same cage. Some wet markets sell endangered species (Zhang & Holmes 2020, Peros et al. 2021). Wet markets are frequently associated with bushmeat. The expression 'bushmeat' refers to the meat of hunted wild animals sold in popular or wet markets (Pangau-Adam et al. 2012), in some situations in the absence of adequate sanitary standards according to regulatory agencies (Naguib et al. 2021, Peros et al. 2021, Saylor et al. 2021, WHO 2021). Sanitary requirements may vary depending on the sanitary regulations of each country, and traditional food markets can be considered safe when operating in accordance with health regulations (WHO 2021).

Different from 'bushmeat' (hunted meat for income purposes), 'wild meat' refers to the meat of wild animals killed for consumption by hunters and their families. As bushmeat products usually come from systematic hunting activities, including frequent handling of animal carcasses, blood and viscera without sanitary control or inspection, bushmeat is associated with increased spillover risk (Wolfe et al. 2005, Pangau-Adam et al. 2012, Peros et al. 2021). For these reasons, wet markets and bushmeat consumption are recognized as important drivers of zoonotic spillover, unlike markets or fairs where meat products are sold under sanitary inspection, which reduces the risk of transmission of pathogens to humans (Wolfe et al. 2005, Karesh & Noble 2009, Zhang & Holmes 2020, Naguib et al. 2021, Peros et al. 2021). In these places, spillover risk also exists [as indicated by human outbreaks of food-borne diseases in high-income nations like the UK (Public Health England 2018)], but the risk is lower due to sanitary control.

Land-use changes and exploitation of Indigenous lands

Other human-mediated activities also facilitate spillover events, including deforestation, industrial livestock, monoculture farming, and mining, among other types of human alterations on land. These changes are commonly unified in the expression 'land-use changes.' Land-use changes lead to host exposure to a new array of pathogens (Murray & Daszak 2013). The construction of roads in wild landscapes (e.g., Amazon rainforest), besides causing damage to ecosystems (Ferrante & Fearnside 2020a), increases the contact of humans with forest-associated animal species and the risk of spillover. Although the human presence can scare away some animal species, when humans invade forest environments to build roads or to perform mining and logging activities, among other reasons, the contact with animal species increases, especially contact with mosquitoes and other blood-sucking insects that benefit from the human presence that provides an additional food source. This closer and more frequent interaction between humans and anthropophilic insects favors spillover events mediated by invertebrate intermediate hosts (Ellwanger et al. 2020).

Extensive land-use changes and associated spillover risk are also a major issue for Indigenous populations. Due to limited contact with non-indigenous populations, indigenous peoples have weak or no natural/protective immunity to pathogens that emerged outside Indigenous areas. Such populations also have limited access to vaccines and healthcare facilities. These factors exacerbate the burden related to emerging pathogens in Indigenous populations. This is a problem observed in several situations and in various parts of the world, from the colonization of the Americas and Africa by Europeans to the ongoing COVID-19 pandemic

in Brazil, among other situations (Valeggia & Snodgrass 2015, Ferrante & Fearnside 2020b). Of particular concern is a proposed law in Brazil (PL191/2020) opening Indigenous lands to mining, logging, agriculture and other activities by non-indigenous people (Villén-Pérez et al. 2021). The risk is clear in a project that is already moving ahead to grow corn (maize) to feed pigs in an Indigenous area in association with a food and biofuel company (Ferrante et al. 2021). Land-use activities in the Indigenous areas expose both Indigenous peoples and workers to a new range of potential exotic pathogens.

Similarly, human contact with other animal species is facilitated by habitat fragmentation (Wilkinson et al. 2018). For example, the transmission of zoonotic parasitic diseases such as leishmaniasis and Chagas disease is facilitated in areas with fragmented vegetation due to the increased human contact with the vectors of *Leishmania* and *Trypanosoma* parasites (phlebotomine sandflies and triatomine bugs, respectively), and changes in the composition and infectious status of wild hosts (Vaz et al. 2007, Roque et al. 2008, Curi et al. 2014, Zaidi et al. 2017, Cardozo et al. 2021). In a general sense, the maintenance of habitat core/solidity reduces the habitat perimeter, diminishing the human contact with other species and, consequently, the spillover risk. On the other hand, habitat fragmentation increases the habitat perimeter and contact zones where pathogen transmissions may occur between non-human animals and humans (Wilkinson et al. 2018, Borremans et al. 2019, Bloomfield et al. 2020). Specifically, there are examples showing that habitat fragmentation in Africa was associated with increased human contact with non-human primates, bats, and potentially the zoonotic pathogens found in these animals (Rulli et al. 2017, Bloomfield et al. 2020). A recent study reported that the risk of SARS-related

coronavirus outbreaks in China is higher in areas with forest fragmentation and concentrations of livestock and humans (Rulli et al. 2021). Habitat fragmentation is strongly associated with loss of ecosystem functions, reduced landscape connectivity, and biodiversity loss (Haddad et al. 2015), which impairs the dilution effect and increases the risk of zoonotic diseases through this additional mechanism (Allan et al. 2003, Keesing et al. 2006). These factors act in synergy with the proliferation of species adapted to human-modified environments and an increase in the load of pathogens hosted by these species, thus creating favorable conditions for the transmission of relatively new zoonotic pathogens to humans.

Livestock industry and antimicrobial resistance

The large scale of the livestock industry for the production of meat and other animal products leads to the confinement of a large number of animals in small areas, usually with frequent contact with humans and other species. As previously described, environments with low species richness can limit the dilution effect, favoring the spread of pathogens. In addition, the movement of livestock within and between countries with little or no sanitary inspection poses a threat to the dissemination of infectious diseases if these animals carry pathogens with zoonotic potential, such as Rift Valley fever virus, as seen in East-African countries that export livestock (Anyamba et al. 2001, Martin et al. 2008, Taylor et al. 2016).

Animals from livestock production also act as intermediate hosts for the adaptation of pathogens from wildlife before they are introduced into the human population. For example, swine (e.g., domestic pigs) are considered to be 'mixing vessels' where strains of influenza A viruses from wild birds can undergo

genetic recombination or reassortment with other viruses present in pigs, originating new influenza strains that will then be transmitted to the human population. This occurs because pigs have cell receptors recognized by avian and human influenza viruses, in addition to sharing the environment with different species of birds and humans (Ma et al. 2008, Ellwanger & Chies 2021). The role of pigs as mixing vessels for the reassortment of influenza viruses has already been shown by various studies, confirming that pigs can act as intermediate hosts for the adaptation of animal influenza viruses before being introduced into the human population (Zhou et al. 1999, Urbaniak et al. 2017, Zell et al. 2020). In a study performed in Egypt, Gomaa et al. (2018) found evidence of infection with avian (H9N2, H5N1), human (pandemic H1N1), and swine influenza viruses in pigs. Ganti et al. (2021) recently showed that mallard ducks also have the potential to act as mixing vessels for the reassortment of influenza A viruses.

Animals from livestock production (e.g., cattle, swine, poultry) also pose a zoonotic risk to human populations considering diseases caused by parasites, especially when these animals are raised in inadequate facilities and with poor hygiene conditions. Infection by *Fasciola hepatica*, *Schistosoma japonicum*, *Trichinella spiralis*, among other parasitic infections, can affect humans due to problems in the practices of breeding, confinement and sanitary inspection of livestock animals and derived products (Gortázar et al. 2007, Rist et al. 2015). Livestock can act as bridges (intermediate hosts) for the transmission of parasites from wild hosts to humans (Gortázar et al. 2007, Wiethoelter et al. 2015).

Finally, it is possible that the introduction (spillover) of SARS-related viruses (SARS-CoV, MERS-CoV) to the human population from bats, source hosts for both SARS-related viruses,

has the participation of intermediate hosts, specifically palm civets for SARS-CoV and camels for MERS-CoV. However, the direct bat-human transmission of these viruses cannot be ruled out (Letko et al. 2020). Some farmed species such as minks, red foxes, and raccoon dogs, potentially acted as intermediary hosts in the SARS-CoV-2 spillover into the human population, but this represents an open question (Koopmans et al. 2021, Lytras et al. 2021). The large number of animals observed in industrial livestock production and the frequent contact with other animal species create numerous opportunities for the adaptation of new pathogens before reaching the human population.

The intensive use of antimicrobial drugs in the livestock industry creates ideal conditions for the selection of microorganisms resistant to multiple drugs and for the emergence of new pathogenic microbial strains, reinforcing opportunities for spillover events (Ye et al. 2016, He et al. 2020, Magouras et al. 2020). Drug-resistant pathogens were responsible for ~20% of all emerging infectious-disease events reported since 1940, a phenomenon stemming from the pervasive use of antimicrobial drugs (Jones et al. 2008). Inappropriate intensive use of antimicrobials in human medicine (e.g., azithromycin as a supposed COVID-19 treatment) will contribute to the emergence of multiresistant strains (Afshinnkoo et al. 2021). The role of drug resistance in the emergence of outbreaks and epidemics is expected to gain greater attention in the coming decades, along with anthropogenic pressures on the environment and animal species.

Fires and other drivers of unusual movement pattern of animals

Fires, deforestation, and habitat loss induce wild animals to assume unusual movement patterns and alternative spatial distributions because

these animals need to leave their natural habitats to obtain food, water and shelter, or to escape fire, among other reasons (Johnson et al. 1992, Hadley & Betts 2009, Niebuhr et al. 2015, Nimmo et al. 2019, Ramos et al. 2020). In response to such events, animals often supply their needs in forest-city borders and in urban and peri-urban areas (e.g., migration of non-human primates from wild areas to cities), especially when urban settings are established in areas previously occupied by forests. For instance, in the Brazilian cities of Rio de Janeiro and Porto Alegre, non-human primates share forest fragments with the human population (Cunha et al. 2006, Corrêa et al. 2018). Also in Brazil, non-human primates (howler monkeys) and forest-dwelling mosquitoes found in city-forest interfaces (as a consequence of urbanization, habitat loss and forest fragmentation) can act as bridges between the sylvatic and urban cycles of yellow fever, as well as bridges for the spillover of new human pathogens from wildlife (Cardoso et al. 2010, Almeida et al. 2012, Couto-Lima et al. 2017).

In addition to inducing animals to explore new environments due to habitat loss, fires can favor the occurrence of arboviral diseases. In Brazil, studies have associated fires with outbreaks of Dengue, Zika, Chikungunya and Yellow fever, especially in areas where fires have an anthropogenic origin and are associated with the expansion of agriculture and livestock production (Torres et al. 2019, Moreno et al. 2021). The increase in fire outbreaks recently observed in Brazil and other countries (Pivello et al. 2021) will potentially increase the risk of spillover events involving arboviruses.

Animal trafficking and the domestication of wild animals also contribute to changes in the geographical distribution of animal species and pathogens with zoonotic potential. These processes can put human populations into contact with new pathogens from exotic animals

that have been artificially moved to new areas and environments. For example, zoonotic *Salmonella* outbreaks were associated to animal trafficking and exotic pets (e.g., Amazon parrots) (Marietto-Gonçalves et al. 2010, Saidenberg et al. 2021). Also, Kovalev & Mazurina (2022) recently evaluated Omsk hemorrhagic fever, an endemic disease from Western Siberia and associated with muskrats (*Ondatra zibethicus*). Since the Omsk hemorrhagic fever virus (OHFV) is closely related to the tick-borne encephalitis virus (TBEV), considering genetic and ecological characteristics, the authors suggested that the OHFV originated directly from the TBEV (Far Eastern subtype) in a spillover event involving the transmission of the virus from *Ixodes persulcatus* ticks to muskrats after the human introduction of *O. zibethicus* to Western Siberia in the second half of the 1930s. The introduction of *O. zibethicus* in this new region was motivated by the potential use of muskrat's valuable fur (Kovalev & Mazurina 2022).

Unusual animal movement patterns are also of epidemiological concern when they involve domestic animals with competence for the transmission of zoonoses, potentially increasing the risks of zoonotic spillover or creating conditions for these animals to act as bridges to pathogen hosts. Dogs that circulate between urban and forest areas can facilitate the spillover and spillback (human-to-animal transmission) of many pathogens, increasing the infectious-disease risk for both human and animal populations (Martinez et al. 2013, Ellwanger & Chies 2019).

Biotic and abiotic environmental changes

Studies performed with mosquitoes are critical to comprehend how human disturbance of the environment can lead to an increased risk of spillover events mediated by vectors (as intermediary hosts). Environments with high

biodiversity tend to have a greater variety and abundance of predators of disease vectors. These predators include bats, birds, amphibians and larvivorous fishes that feed on mosquitoes at different stages of development. Reduction of the diversity of predators due to anthropic action can benefit the survival and proliferation of mosquitoes. Also, abiotic factors (e.g., sunlight, wind patterns, temperature, moisture, and the pH of water in breeding sites) are altered in degraded landscapes and can affect vector distribution and proliferation (Burkett-Cadena & Vittor 2018, Almeida et al. 2019, Franklinos et al. 2019). For example, lower temperatures in the forest can slow the larval development of mosquitoes while the opposite can occur when forests are cleared, resulting in warmer temperatures, greater light intensities, and increased availability of nutrients in water pools, thus benefitting the larvae of some mosquito species (Burkett-Cadena & Vittor 2018, Franklinos et al. 2019). Consequently, these ecological and abiotic changes benefit mosquito populations and increase the risk of spillover events mediated by vectors (Burkett-Cadena & Vittor 2018, Ellwanger & Chies 2018, Almeida et al. 2019, Franklinos et al. 2019). From a global perspective, it is very likely that climate change in the coming decades, including a 1.0–3.5°C increase of global temperature and more frequent climatic anomalies (e.g., El Niño, droughts, floods), will lead to an increased burden of vector-borne diseases and more zoonotic spillover events mediated by arthropod vectors (Githeko et al. 2000, Watts et al. 2019, Wilke et al. 2019b).

Finally, it is essential to consider that disease cycles are often complex, being influenced by factors that go beyond the abiotic sphere, such as biological aspects of vertebrate hosts (immunity, genetics, and other characteristics, as discussed previously), arthropod resistance to insecticides, and stresses on communities of vectors (Guedes et al. 2017, Pavlidi et al. 2018).

Therefore, the impact of climate change on vector-borne and other zoonotic diseases will be affected by these other factors, making it difficult to accurately predict the intensity of impacts and distribution of pathogens and diseases in a changing world. Considering these uncertainties, the precautionary principle must be considered (Mahrenholz 2008) and anthropogenic changes in the environment must be controlled in order to reduce zoonotic risks to the human population.

ANTHROPOGENIC ACTIVITIES IN THE AMAZON REGION AND THEIR POTENTIAL IMPACTS ON SPILLOVER EVENTS

The Amazon Forest is one of the most biodiverse regions in the world, with 70% of the Amazon basin located within Brazil (Kirby et al. 2006). Due to its high biodiversity combined with a diversity of anthropogenic activities in the region, the Amazon Forest is a hotspot for the emergence of new pathogens (Val 2020). Indeed, there are numerous potential new pathogens in the Amazon Forest that could pose a risk to human populations. However, it is the intense human activity in the region that is the main driver of potential spillover events in the Amazon Forest, not the biodiversity *per se*.

Degradation of tropical forests, including the Amazon Forest, is strongly derived from economic activities linked to the exploitation of minerals, oil, and timber, in addition to industrial livestock and monoculture production. Globalization and economic connections between developed and developing countries mean that the triggers of environmental degradation in any given part of the world can be derived from demands of distant countries or even other continents. For instance, land-use changes in the Amazon Forest, including the increasing deforestation rate in the region (see Figure 1, panel a, for more data), are partially triggered by the demand for

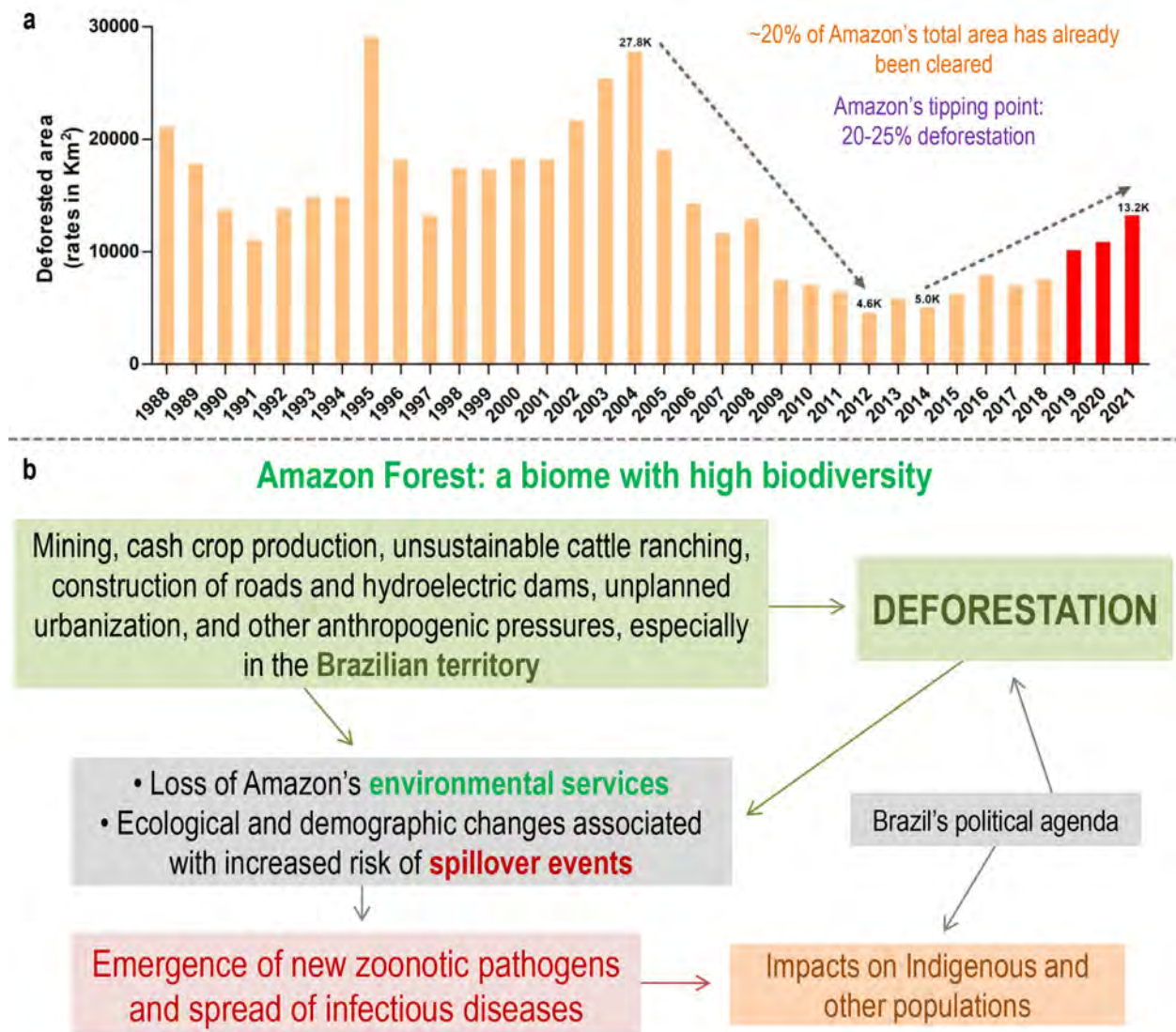


Figure 1. Deforestation rate in Brazilian Amazon Forest (Legal Amazon) between 1988 and 2021 and connections between anthropogenic pressures on Amazon Forest and spillover risk. Panel a: between 2004 and 2012, deforestation in the Amazon underwent a significant reduction, partly as a result of the strengthening of policies for controlling illegal activities. From 2014 onwards there have been increases in deforestation rates, with alarming results in 2019, 2020 and 2021, reflecting the weakening of the regulation of illegal activities in the region. Tipping point: the point at which the Amazon Forest stops properly providing its environmental services (e.g., hydrological cycle, maintenance of carbon stocks), losing many rainforest characteristics and enters into a self-perpetuating decline. Data (deforestation rate by year collected on February 1st, 2022) obtained from TerraBrasilis - *Programa de Cálculo do Desflorestamento da Amazônia* (PRODES), Instituto Nacional de Pesquisas Espaciais (INPE); data under CC BY-SA 4.0 license (INPE 2022). The graph was plotted using GraphPad Prism. Additional information was obtained from Aguiar et al. (2016), Lovejoy & Nobre (2018), and Ferrante & Fearnside (2019). Panel b: deforestation and other anthropogenic pressures on Amazon Forest are closely connected activities. These pressures facilitate spillover events, the emergence of pathogens and the spread of infectious diseases, affecting populations living inside and outside the Amazon region.

beef and agricultural commodities by China and European countries (Fearnside et al. 2013, Fuchs et al. 2019, Pendrill et al. 2019), by the bovine leather industry in Europe (Mammadova et al. 2020), among other economic drivers. These human activities in the Amazon region facilitate the risk of zoonotic spillover events and the spread of infectious diseases in multiple ways (Figure 1, panel b).

A recent study performed in the Amazon rainforest showed that anthropogenic pressure on the natural landscape, specifically forest fragmentation, decreases mosquito diversity and increases the abundance of malaria vectors such as *Anopheles (Nyssorhynchus) darlingi* mosquitoes (Chaves et al. 2021). Human occupation in forest areas causes loss and fragmentation of habitat. In association with this, there is an increase in the availability of human hosts and a blockage of water flow, thus facilitating the dispersion and proliferation of human-associated mosquito species with medical importance, like *An. (Ny.) darlingi* (Chaves et al. 2021). These data reinforce the concept that diversity of species is important for the prevention of vector-borne diseases. Furthermore, the same study (Chaves et al. 2021) demonstrates that anthropogenic actions favor the abundance of medically important mosquitoes not only in urban environments but also in tropical forests. In accordance with the information described above, Prist et al. (2022) recently showed that the construction of roads and the associated increase in forest fragmentation and forest edges facilitate yellow fever virus dispersion. Road construction and associated environmental degradation have been a threat to the Amazon biome from the 1970s to the present (Barni et al. 2015, Ferrante & Fearnside 2020a).

The construction of hydroelectric dams in tropical forest areas can result in population

explosions of some mosquito species, as occurred in Brazil's Tucuruí Dam for *Mansonia* species (Tadei et al. 1991, Fearnside 1999) and at the Samuel Dam for *Culex* species (Fearnside 2005). In the first years after dam construction, large areas of the reservoirs were covered by aquatic plants (macrophytes) that provide breeding grounds for *Mansonia* mosquitoes (Fearnside 2001). Potential spillover events involving mosquito-borne pathogens are therefore a major concern in the Amazon region.

Hunting and commercialization of wild animals in the Amazon region is very intense, with a bushmeat market reaching up to 6.49 kg per person/year in the central Amazon (quantity varies by Amazon region) (van Vliet et al. 2014, El Bizri et al., 2020). These data suggest that spillover events derived from bushmeat practices are a recurrent possibility in the Amazon region, similar to what happens in other countries with high biodiversity (Ellwanger & Chies 2021).

In addition to habitat fragmentation, construction of water reservoirs and bushmeat practices, logging, mining, and other exploitative (and often illegal) economic activities in the Amazon region trigger a number of ecological and demographic changes, including migratory flows, habitat loss, unplanned urbanization, prostitution, pollution, climate change, and extreme weather events (Ellwanger et al. 2020). As discussed earlier in this article, these conditions directly or indirectly favor the occurrence of spillover events and the spread of emerging pathogens. For this reason, deforestation in the Amazon Forest and other anthropogenic activities in the region create the "perfect storm" of infectious diseases in the Amazon region (reviewed in Ellwanger et al. 2020).

The potential emergence of pathogens in the Amazon Forest may affect populations living in the region as well as people living outside the Amazon region. As exemplified by the COVID-19

pandemic, emerging pathogens can spread across the world very easily and quickly. Thus, conserving the Amazon Forest is critical not only to protect biodiversity and associated ecosystem services (e.g., water cycling, carbon stock maintenance); protecting the Amazon biome is a global public health measure (Fearnside 2008, Ellwanger et al., 2020).

Combating deforestation, mining and other types of land-use change is difficult to achieve, but this is not an impossible task. In Brazil, deforestation in the Amazon region declined greatly (~70%) between 2005 and 2012 (Figure 1, panel a), in part due to government policies (West et al. 2019, Dobson et al. 2020, West & Fearnside 2021). These policies have ended under Brazil's presidential administration that took office in January 2019 (Ferrante & Fearnside 2019, 2020b), but the potential for controlling deforestation through government policies remains an essential lesson. A recent study (Dobson et al. 2020) pointed out that the costs of mitigating a pandemic such as the COVID-19 are much greater (estimated at US\$8.1 to US\$15.8 trillion) than the amount that would have to be invested to prevent the main drivers of emerging infectious disease events, estimated at US\$17.7 to US\$26.9 billion per year. Of note, the prevention costs for 10 years would represent ~2% of the costs of the COVID-19 pandemic (Dobson et al. 2020). In other words, conservation actions protect the environment, limit the spread of infectious diseases, and are cheaper than bearing the burden of emerging infectious disease events. Also, in Brazil, the demarcation of Indigenous lands (*Terras Indígenas*) is an effective way of limiting the exploitation of natural resources and land-use changes while protecting traditional communities. The contribution of protected areas governed by local communities and Indigenous peoples in the field of biodiversity conservation is widely recognized (Corrigan et al.

2018). Considering that Brazil holds most of the territory of the Amazon Forest and has strong political and economic powers, the country needs to take the lead in the conservation of the region, contributing to the reduction of the risks of potential spillover events in the Amazon Forest.

CONCLUSION

This article synthesized the main connections between human-related environmental disturbances, ecological modifications, and increased risk of spillover events (Figure 2), primarily based on examples and models from different world regions. In brief, anthropogenic disturbances in the environment lead to changes in ecological niches, reduction of the dilution effect, increased contact between humans and other animals, changes in the incidence and load of pathogens in animal populations, and alterations in the abiotic factors of landscapes, among other ecological changes. These alterations can increase the risk of spillover events, facilitating new infectious disease outbreaks. In addition to our interpretation of the issues addressed in this paper, we emphasize that other models also explain the relationship between human activity, environmental disturbances, and emerging infectious diseases (e.g., Wolfe et al. 2007, Parrish et al. 2008, Karesh et al. 2012, Morse et al. 2012, Murray & Daszak 2013, Faust et al. 2018, Glidden et al. 2021). These interpretations are generally not mutually exclusive, and in most cases are complementary. Above all, it is important to keep in mind that generalist explanations for the emergence of infectious diseases will always be incomplete (Jones et al. 2013). Each outbreak, epidemic, pandemic, or small-scale zoonotic event has its specific characteristics and triggers that are inherent to the place and

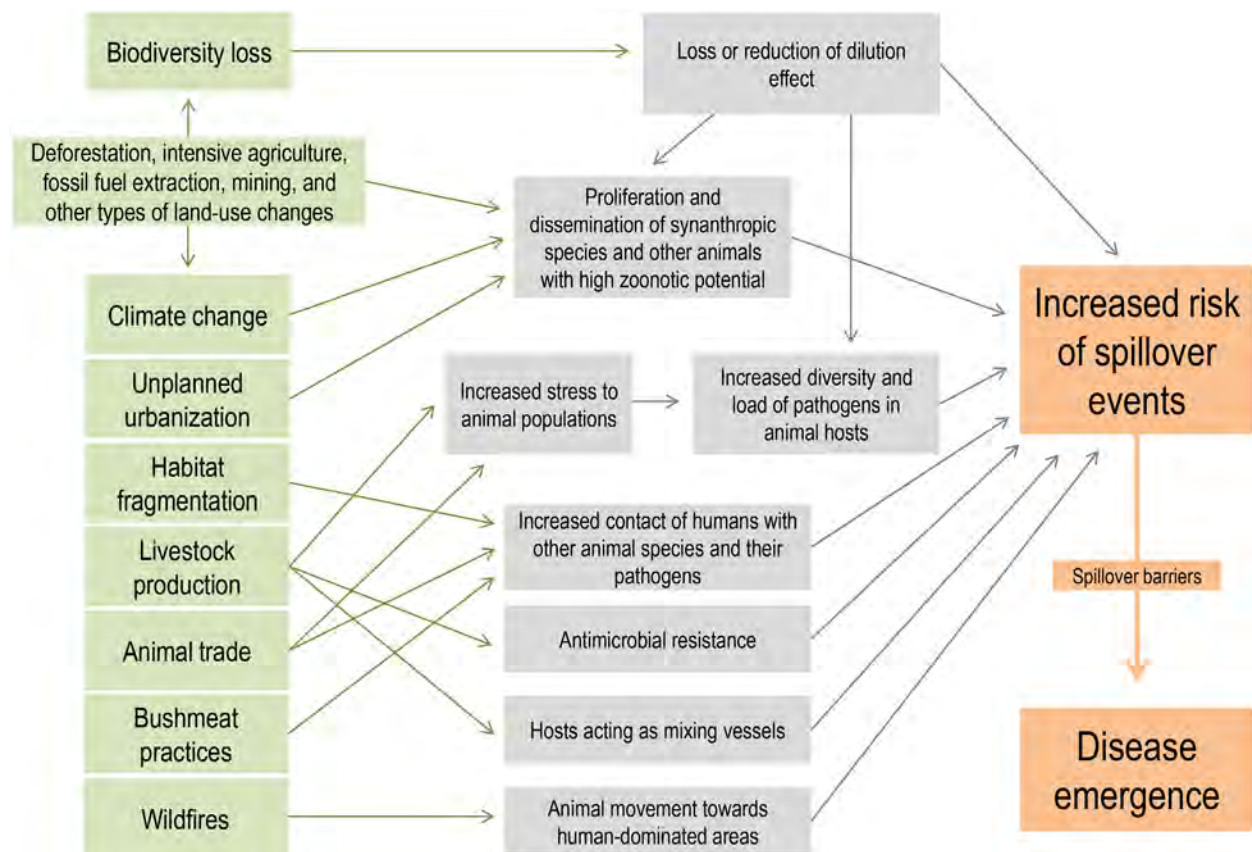


Figure 2. Connections between human-related environmental disturbances, ecological modifications and increased risk of zoonotic spillover events. Spillover barriers are factors that facilitate or hinder the transmission of pathogens between different species/populations. They can be biological (e.g., genetic proximity between hosts, immunological and genetic factors), demographic (e.g., overcrowding), ecological (e.g., habitat sharing), cultural (e.g., bushmeat practices), and associated with pathogens (e.g., virulence, survival in the environment). These barriers affect both spillover risk and the outcome of spillover events. More information concerning spillover barriers can be found in Plowright et al. (2017) and Ellwanger & Chies (2021).

context in which it occurred. Considering the specificities of each environment, our review brought a discussion specifically focused on the Amazon rainforest, showing that increasing anthropogenic damage in the region may also increase the risk of zoonotic spillover events and spread of infectious diseases, impacting the Amazon populations and potentially populations elsewhere (Figure 1). Finally, conservation efforts lead to benefits to different global spheres in an integrated manner, as they help to contain anthropic activities on the environment and to reduce the risk of zoonotic spillover events.

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