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The Risk of Virus Emergence in South America: A Subtle Balance Between Increasingly Favorable Conditions and a Protective Environment

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Abstract

South American ecosystems host astonishing biodiversity, with potentially great richness in viruses. However, these ecosystems have not yet been the source of any widespread, epidemic viruses. Here we explore a set of putative causes that may explain this apparent paradox. We discuss that human presence in South America is recent, beginning around 14,000 years ago; that few domestications of native species have occurred; and that successive immigration events associated with Old World virus introductions reduced the likelihood of spillovers and adaptation of local viruses into humans. Also, the diversity and ecological characteristics of vertebrate hosts might serve as protective factors. Moreover, although forest areas remained well preserved until recently, current brutal, sudden, and large-scale clear cuts through the forest have resulted in nearly no ecotones, which are essential for creating an

adaptive gradient of microbes, hosts, and vectors. This may be temporarily preventing virus emergence. Nevertheless, the mid-term effect of such drastic changes in habitats and landscapes, coupled with explosive urbanization and climate changes, must not be overlooked by health authorities.

Around 1519

> While over a dozen major infectious diseases of Old World origins became established in the New World, perhaps not a single major killer reached Europe from the Americas. The sole possible exception is syphilis, whose area of origin remains controversial. The one-sidedness of that exchange of germs becomes even more striking when we recall that large, dense human populations are a prerequisite for the evolution of our crowd infectious diseases. If recent reappraisals of the pre-Columbian New World population are correct, it was not far below the contemporary population of Eurasia. Some New World cities like Tenochtitlán were among the world's most populous cities at the time. Why didn't Tenochtitlán have awful germs waiting for the Spaniards?
>
> Jared Diamond (1, p. 252)

1. INTRODUCTION

Turbulent history, mega- and still-uncovered biodiversity, multiethnicity, and dramatic increases of pressures on a well-preserved environment shaped and characterize modern South America. The continent has experienced a hectic history since the Miocene (2). The Andes and other higher elevation terrains and the current positioning of the Orinoco, Amazon, Parana, and Uruguay Rivers enabled the formation of humid forest refugia interspersed with dry forest and open grasslands. This led to highly contrasted and diverse biomes beside and in the shadow of Amazonia, from dry savannas to pristine evergreen equatorial forests (3).

This biogeographic region is known for its astonishing biodiversity. This richness results from a combination of diverse ecosystems, environmental and climatic heterogeneity, and a complex evolutionary history. For instance, more species of vascular plants, butterflies, amphibians, and snakes are found in South America than in tropical Africa and Southeast Asia combined (4). However, since the large-scale and brutal displacement of Native American people by European immigrants and enslaved African peoples, anthropogenic factors have seriously eroded this diversity (5). Moreover, in the last 50 years, the South American population has doubled (6) and has shifted from a rural culture to a predominantly urban one, with 80% of the population currently living in cities (7).

South America has also experienced an increased number of outbreaks and epidemics due to zoonotic emerging or re-emerging viruses, especially arboviral diseases, such as the four serotypes of dengue virus (DENV-1 to 4), Zika virus (ZIKV), yellow fever virus (YFV), and chikungunya virus (CHIKV). None of these viruses are indigenous; they were introduced into the region and were able to spread and establish urban and/or peri-urban cycles due to favorable conditions such as climate, competent vector/reservoir species availability, and immunologically naïve populations (8).

The frequency and spread of zoonosis are increasing worldwide (9). Zoonotic viruses can pass directly from natural hosts (e.g., bats, rodents, and primates) to humans, or they can be transmitted through intermediate hosts or vectors (e.g., cattle, equines, mosquitoes, and ticks). Combined virological and ecological methods have estimated a multitude of mammalian and bird viruses with the potential to spill over into humans (10–12).

However, for these spillovers to take place, a favorable environment and close proximity and numerous contacts between species are necessary, allowing for the infectious agent to adapt to the new host (13, 14). Concurrently with entering in and modifying natural habitats, the continuous

human population growth creates new opportunities for species contact and facilitates the emergence of infectious diseases.

A complex variety of genetic, immunological, and ecological barriers must be overcome for successful virus emergence in humans. Nevertheless, climate change and increasing environmental degradation might weaken these barriers, facilitating species contact and viral adaptation to new hosts (13, 15). Moreover, this process can be facilitated by the fast-evolving rate of RNA viruses, leading to genetic variability and increased fitness (16).

In this review, we explore why we have not yet observed the emergence of epidemic/pandemic viruses native to South America despite numerous examples of potential threats circulating in the continent (17–19). We also analyze the changes in local environmental landscapes, focusing on their potential effect on the ecology of arboviruses and rodent-borne viruses (roboviruses).

2. VIRAL DIVERSITY IN SOUTH AMERICA

The process of discovering new viruses is not trivial. It requires infrastructure, technologies, and training of human resources that are achieved only with continuous investment in science and innovation. Thus, it is not surprising that approximately 64% of all animal virus species described by the International Committee on Taxonomy of Viruses (ICTV) were isolated from samples collected in North America, East Asia, and Europe (**Figure 1**). South America, even with its enormous animal biodiversity, ranks fifth in the number of viruses identified from local specimens ($n = 253$), right after sub-Saharan Africa ($n = 324$). This suggests that a significant portion of the virosphere in both regions remains uncharted.

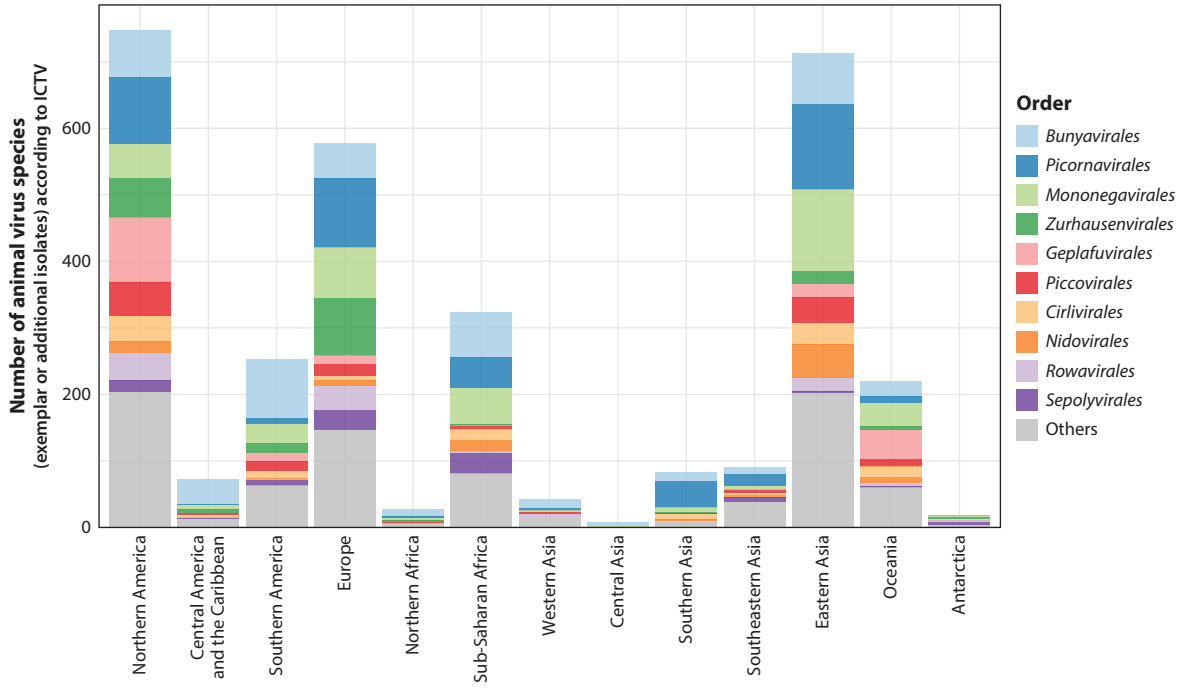

Figure 1

Number of animal virus species registered by the International Committee on Taxonomy of Viruses (ICTV) according to the specimen collection site where the discovery was made. Virus Metadata Resource (153) was used to compile all animal exemplar well-characterized virus isolates and additional isolates that are distinguished from the exemplar isolate of the virus species.

While their usefulness in predicting the emergence of new human pathogens is still up for debate (10, 20), studies aiming to describe viral diversity in animals are of great value for understanding the evolution and ecology of viruses and the history of emergence of human pathogens and for describing sylvatic cycles that can be sources of new variants. Regarding viruses of medical importance, the rate of new species described over the years is closely linked to investments and strategies (21). In Latin America during the 1950s and 1960s, the Rockefeller Foundation (RF) research program on arboviruses promoted the discovery of dozens of new viral agents, many not yet implicated in human disease (22). Among the most relevant for public health were Mayaro virus (MAYV) (genus *Alphavirus*), Oropouche virus (OROV) (genus *Orthobunyavirus*), and Ilheus virus (ILHV) (genus *Orthoflavivirus*), as well as an enormous diversity of arboviruses discovered from forest-fringe dwellers, with most of them being members of the *Orthobunyavirus* genus. Despite the disinvestment of the RF program from the mid-1960s and the slowdown in arbovirus discoveries, the diversity of new viruses isolated from South American local specimens has continued to grow over the years, particularly for the *Mammarenavirus* (23) and *Orthohantavirus* genera (24), which, together with the *Orthobunyavirus* genus, make up the *Bunyavirales* order that has the highest species richness registered by ICTV in South America (**Figure 1**).

With the next-generation sequencing revolution, an explosion in the rate of discovery of new viruses began in the mid-2000s (25). Metagenomics revolutionized virology, enabling the discovery of viromes of animals and environmental samples. Due to their important role in zoonoses, studies investigating the viral diversity in bats (*Chiroptera*) are particularly prevalent worldwide (26) and in South America (27, 28). Rodents (*Rodentia*) are also recognized as important animal reservoirs for human pathogens; however, in contrast with bats, fewer studies have surveyed their virome in South American biomes (29–31). Finally, metagenomics of South American arthropods has already revealed several new viruses, many of them possibly insect specific (32–35) and some with potential fitness to replicate in vertebrate cells, as demonstrated by in vitro experiments (36, 37). It is crucial to acknowledge that metagenomics alone cannot fully ascertain a virus's potential to emerge as a pathogen in animals or humans; hence, ideally, traditional virological methods should complement the genomic identification of new viruses.

Despite this extensive viral diversity described in South American fauna, the main viral agents of public health importance in the region are still of external origin and were introduced in the continent by human population movements (e.g., YFV, DENV, CHIKV, and ZIKV). In the following sections, we highlight several viruses of medical significance that originated in South America and that sporadically cause outbreaks and merit close surveillance for their potential emergence as human pathogens.

2.1. Indigenous Arboviruses of Importance in South America

2.1.1. Oropouche. OROV is the causative agent of Oropouche fever, a febrile disease with clinical manifestations very similar to other arboviruses such as DENV, CHIKV, and ZIKV, and this similarity may be the reason it may go undiagnosed or misdiagnosed (38). OROV's main insect vector is *Culicoides paraensis* (order *Diptera*) (39), which can reproduce in semiurban regions. OROV presents an urban and a sylvatic cycle, where *C. paraensis* is the primary vector in the urban cycle, and several species of vertebrates (sloths, nonhuman primates, and birds) and mosquitoes might play a role in the sylvatic cycle (38). Thus, OROV presents the potential for epidemic spread. The first OROV outbreak, with around 11,000 cases, was reported in 1961 in Belém (state of Pará), the largest city in the Brazilian Amazon forest. In the following two decades, several other large outbreaks were reported mainly in cities of Pará state but also in Manaus (Amazonas state). Then, after a long period of sporadic outbreaks, OROV re-emerged in the mid-2000s,

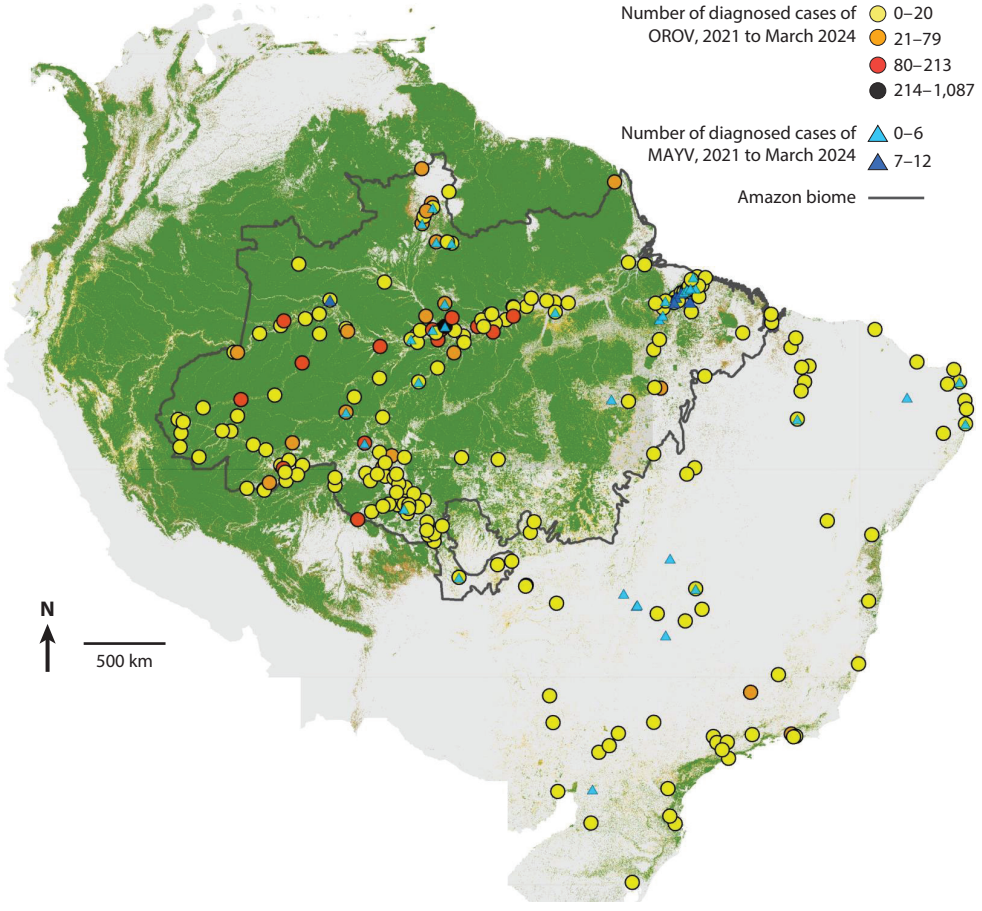

Figure 2

Distribution of Oropouche virus (OROV) and Mayaro virus (MAYV) cases in 2021–2024. Epidemiological data were provided by the General Coordination of Public Health Laboratories and are geolocated by the patient's city of residence, not necessarily representing the location of infection. For the map background, green is the moist forest (tropical rain forest and tropical moist deciduous forest) cover, either pristine and/or with lightly modified canopy height; brown is degraded forest; and white is no forest and forest areas cut before 1990 [updated data extracted from the European Science Hub: **https://forobs.jrc.ec.europa.eu/TMF/data** (for details of forest classes and remote-sensing methodology, see Reference 154)].

causing several outbreaks in different cities in the Amazon region, but with limited spatial spread (40). Nevertheless, we are currently observing the most widespread OROV outbreak ever reported in Brazil (**Figure 2**). In this outbreak that began in 2021 and that is still active, more than 4,000 cases were confirmed by laboratory tests, spread across more than 250 cities and 12 states, 7 of them outside the Amazon region. At the time of writing this work, for the first time, autochthonous cases had been confirmed in four non-Amazonian states, located in the northeast, southeast, and south regions of Brazil (**Figure 2**). As the current outbreak unfolds and new cases are confirmed, the potential for OROV to establish local circulation in other regions and to cause large epidemics becomes more evident. Besides Brazil, OROV cases were also reported in Colombia, Bolivia, and Peru in 2024 (41). Previous to that, only Panamá and Peru had reported cases (40).

2.1.2. Mayaro. MAYV (genus *Alphavirus*) is part of the Semliki complex, the same as CHIKV. Like OROV, MAYV causes a febrile disease that can be misdiagnosed as dengue or chikungunya. But unlike OROV, MAYV presents a sylvatic cycle only where humans are dead-end hosts (42, 43). The main vectors are forest-dwelling *Haemagogus* mosquitoes, and nonhuman primates, rodents, birds, and small mammals can be natural reservoirs for the virus (44). Most MAYV infections occur near rural and forest areas, where the individuals with a higher risk of infection are adult men because they are more likely to enter forest areas (43) (**Figure 2**). MAYV outbreaks are often small, usually not exceeding 100 cases, and were reported autochthonously in several countries from Latin America and the Caribbean (42). The largest reported outbreak was in Pará state, Brazil, in 1977, where more than 800 cases were reported during 7 months (45). Of note, most of the epidemiological data available for MAYV are based on serological tests, which might cross-react with other alphaviruses. With the successful introduction and wide spread of CHIKV in the Americas since 2013, it will be increasingly difficult to diagnose MAYV infections specifically with serological tests. An important point to observe is that with the current epidemiological emergence generated by the OROV outbreak in Brazil, new and better protocols to detect neglected arboviruses, such as OROV and MAYV, are in use. This led to an increase of MAYV cases in 2023 and 2024, suggesting that cases of infection by this virus were being underreported (**Figure 2**). However, we cannot rule out that the same ecological and environmental conditions that led to the re-emergence of OROV in north Brazil and its likely establishment in other Brazilian regions may also be boosting MAYV circulation in the natural reservoirs and more spillovers to humans.

2.1.3. The neurotrophic arboviruses: Ilheus, Rocio, and Venezuelan equine encephalitis. Ilheus (ILHV) is a flavivirus whose infection symptoms also fit in the dengue-like clinical spectrum. A noticeable difference is that progression to encephalitis is much more frequent, although only one death by encephalitis in a patient with a positive test for ILHV has been reported so far (46). There are no records of human outbreaks or epidemics caused by ILHV, and the paucity of clinically well-documented human cases hinders the assessment of its potential to emerge. However, the low but constant seroprevalence among humans through time indicates a sustained circulation of ILHV in Latin America and suggests that most infections are inapparent or misdiagnosed (47). An enzootic cycle between birds and several arboreal mosquitoes is believed to maintain ILHV in nature, but serological data suggest that infections may occur in a wide range of vertebrates, such as rodents, monkeys, sloths, and horses (48). Seropositivity to ILHV in humans is much more frequent in adult men, which is characteristic of a sylvatic cycle where humans are dead-end hosts (47).

Rocio virus (ROCV) is another neurotropic flavivirus indigenous to South America that is classified in the same species as ILHV (i.e., *Orthoflavivirus ilheusense*), although it has genetic divergence of more than 20%. It was first identified in the 1970s during a severe outbreak of encephalitis in the coastal region of Sao Paulo state, southeast Brazil, and virtually disappeared afterward (49). In the following years a few additional ROCV-positive individuals were found in serosurvey or among patients misdiagnosed with dengue fever (50). The transmission cycle of ROCV is not well understood, although ROCV is probably maintained in an enzootic cycle between birds and mosquitoes (49, 51, 52) and is likely widespread in Brazil (53). Nonetheless, the reasons and conditions that caused the periodic emergence of ROCV in the largest viral encephalitis outbreak in Brazil in the 1970s remain a mystery.

Venezuelan equine encephalitis virus (VEEV) is the main species of a group of phylogenetically related alphaviruses called the Venezuelan equine encephalitis (VEE) complex (54). This group includes eight virus species that occur across the Americas, mainly in South America, and

are maintained in enzootic cycles by rodents of several genera (55). Within the VEE complex, only VEEV is able to maintain a transmission cycle in equines, for which several mosquito species are the vectors. VEEV was implicated in severe encephalitis outbreaks in the twentieth century, mainly in northern South America (Colombia, Venezuela, and Ecuador) but also reaching Central American (Guatemala and El Salvador) and North American (Mexico and USA) countries. Many of these outbreaks took several months to be controlled, leading to the deaths of thousands of horses and, in some cases, hundreds of humans (56). With the development of a veterinary vaccine, the severity and size of epizooties in equines, and the resulting human outbreaks, decreased beginning in the 1970s (57), despite the re-emergence of the virus in the 1990s after a long silent period (58).

2.1.4. Rodent-borne hantavirus and arenavirus. Rodents are reservoirs for health-threatening viruses, such as the *Orthohantavirus* genus (*Hantaviridae* family) and the *Arenaviridae* family (59, 60). Hantaviruses and arenaviruses are transmitted to humans through urine, saliva, and feces from infected rodents, and they share a long history of coevolution with their hosts, intertwined with events such as host switch and subsequent adaptation. Although under debate, analysis of reconciled phylogenies between hantaviruses and their hosts (orders *Rodentia*, *Soricidae*, and *Chiroptera*) showed that the observed pattern of phylogenetic congruence is the product of a coevolution process (61). Ultimately, this has been reinforced by recent findings of highly divergent hantaviruses in fish and reptiles (62–64).

New World hantaviruses are the causative agents of hantavirus pulmonary syndrome (HPS), a severe respiratory disease with a case fatality rate ranging from 20% to 50% and with approximately 300 cases annually (65). In South America, pathogenic and nonpathogenic hantaviruses are hosted by *Sigmodontinae* rodents and display great diversity, with at least 20 recognized viral lineages. Between them, Andes virus (ANDV) stands out because it is the only lineage where person-to-person transmission has been reported. The reasons for this unique feature are not completely clear, but specific amino acid signatures are present in the small nonstructural protein and in the glycoprotein of the lineages associated with efficient person-to-person transmission (66, 67). The 2018–2019 ANDV outbreak in Chubut province (Argentina) accounted for 34 confirmed infections and 11 deaths due to person-to-person transmission. A study reported differences in innate immune responses to ANDV in comparison with other hantaviruses such as Lechiguanas, Sin Nombre, or Puumala hantaviruses, for which person-to-person transmission was not documented. Sequence comparison of the Chubut ANDV strains showed a high identity with the strain recovered in the first known person-to-person episode at the El Bolson outbreak (1996), suggesting that these viruses share the genetic traits for successful rodent-human and human-human transmission, without a need for further adaptation to gain viral fitness. Although more studies are needed, the pathogenesis and immune response characteristics, together with high viral loads and certain social behaviors, such as attendance at massive social gatherings or extensive contact among persons, account for a higher likelihood of ANDV person-to-person transmission outbreaks (68).

New World arenaviruses are also hosted by *Cricetidae* rodents and include hemorrhagic fever viruses such as Junin (JUNV), Machupo, Guanarito, Sabia, and Chapare. Hemorrhagic fever viruses were of great concern in the past century due to the severity of the disease and high fatality rates (up to 30%). Several outbreaks were reported in Bolivia, Venezuela, and Argentina. JUNV was endemic in central Argentina, with frequent outbreaks, but the development of an effective vaccine in the 1980s was pivotal to virus control and lowering the fatality rate (69). Chapare virus was the most recently identified *Mammarenavirus* in a fatal hemorrhagic fever case that occurred in 2003, close to Cochabamba, Bolivia. Since then, sporadic outbreaks were reported; the most recent case was in 2019 in the rural area of La Paz city, with evidence of nosocomial transmission.

Hemorrhagic fever arenaviruses are generally restricted to limited outbreaks, probably due to a stricter association with specific rodent species.

3. IMPORTANT FACTORS FOR VIRAL EMERGENCE IN HUMANS AND THE SOUTH AMERICAN CASE

3.1. Human Evolutionary History

Viruses infecting *Homo sapiens* can be divided into those that were acquired vertically from our common ancestor with nonhuman primates and then codiverged with the host species over millions of years and those that were acquired horizontally when there was an interspecies transmission event (70). The emergence of new pathogenic viruses in humans is a phenomenon that intensified with the beginning of agriculture and animal domestication. These two changes in human civilization promoted a large increase in population density and greater contact with other animal species, creating more opportunities for spillover events (71). Moreover, the faster human population growth rate also meant a faster population turnover and a steady availability of susceptible hosts, facilitating pathogen adaptation to humans and endemic circulation. The history of animal domestication is an important factor that paved the way to the emergence of many human pathogens in the Old World but none in the New World. However, the vast majority of livestock species domesticated by humans originate from the Old World; only the llama and alpaca were domesticated in South America. These South American camelids have not yet been described as animal reservoirs or amplifiers of viral zoonosis (72). These deeply divergent scenarios also had a great historical importance, facilitating the conquest of the New World by Europeans when they brought with them diseases much more lethal than their weapons (1) (**Figure 3**).

Phylogenetic proximity of humans and animal species hosting viruses influences the emergence of new viruses in humans, a factor that also sheds light on the scene in South America (73). Phylogenetic proximity reflects the genetic barriers that pathogens must overcome for horizontal transfer and has been demonstrated to be an important predictor of the proportion of zoonotic viruses in several orders of mammals. While primates contribute significantly to this predictive model, it is the continuous variable of phylogenetic proximity, rather than primates as a discrete group, that correlates with a higher proportion of zoonoses. Our most recent common ancestor with New World monkeys dates back 36–50 million years ago (MYA), 20–38 MYA with Old World primates including 13–18 MYA with orangutans (forming the family *Hominidae*), and 6–7 MYA with chimpanzees (74). This closeness between humans and Old World monkeys is reflected in the fact that approximately 20% of the main infectious diseases of humans have their origin in this group of animals (e.g., hepatitis B, AIDS, dengue, yellow fever) (71). Additionally, much more evolutionary time was available for horizontal transfer and adaptation of viruses into humans in the Old World (**Figure 3**), after the split of the *Homo* and *Pan* (chimpanzees) genera, than in the New World, following the first migratory waves into the continent (about 14,000 years ago) (71).

Another important evolutionary event that facilitated the emergence of new viruses was the specialization of the *Aedes aegypti* mosquito to live with and feed on humans. The most-accepted hypothesis currently estimates that this event took place in the Sahel region, West Africa, about 5,000 years ago when the African humid period finished and long periods of drought became seasonal in the region (75). In this scenario, local populations of *Ae. aegypti*, which were once generalists (feeding on a variety of vertebrate animals), were forced to rely on human-stored water for survival, with adaptations to breeding in artificial containers as well as to biting humans (76). This new subspecies, *Aedes aegypti aegypti*, spread efficiently in tropical and subtropical latitudes and became the primary vector of several arboviruses of public health concern, including YFV, DENV,

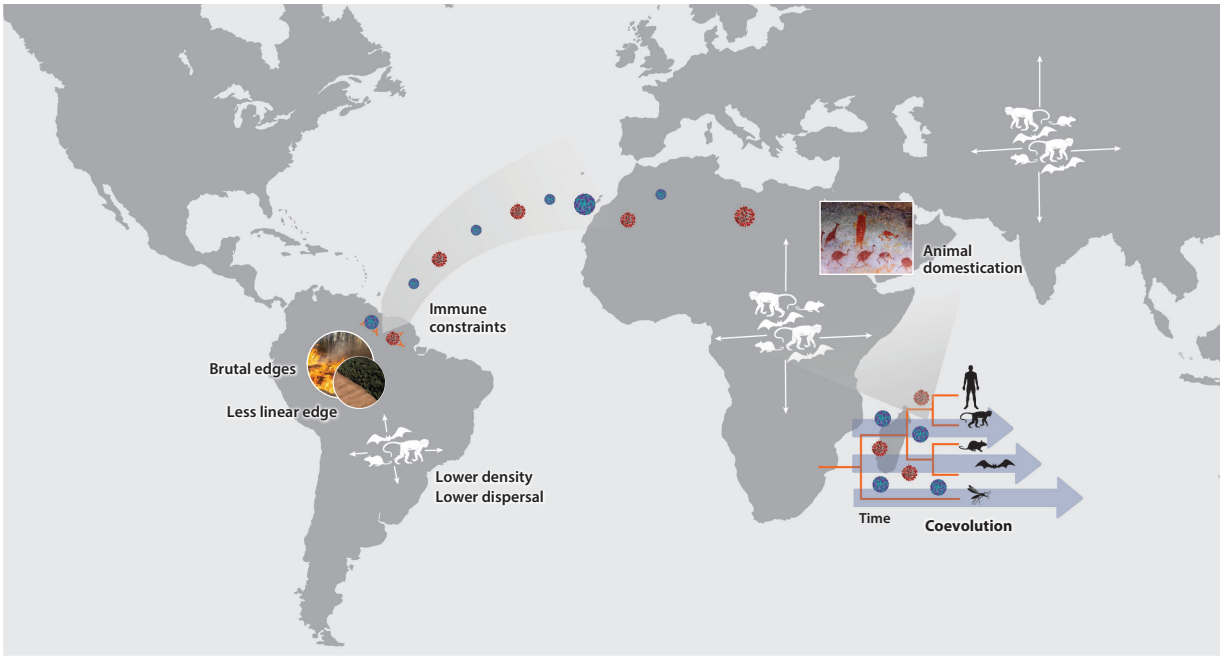

Figure 3

Remarkable differences between Old World and New World with potential effect on the emergence of new viruses. The long presence of humans in the Old World and consequent coevolution with other species of animals generated more opportunities for transmission and adaptation of viruses to humans. Likewise, the domestication of animals in the Old World promoted countless new spillover opportunities in the Old World compared to the New World. The colonization of the New World by European immigrants and the slave trade brought with them Old World viruses that spread successfully throughout the New World, creating possible immune constraints for the emergence of local viruses in humans. Ecological factors such as lower density and dispersal of some important virus reservoir mammals in the New World may also limit dispersion of native viruses by their animal hosts. Finally, rapid deforestation in South America led to two patterns: Brutal edges limit the ecological transition zones where hosts, vectors, and viruses may adapt, and a lower ratio linear edge/forest fragment surface limits contact zones between potential reservoirs and humans. Figure created by Wagner Nagib.

CHIKV, and ZIKV (77). These viruses have African or Asian origins, probably in primates, and their transmission to humans may have occurred numerous times over thousands of years by the action of generalist *Aedes* species. The emergence of *Ae. aegypti aegypti* was probably the missing factor to accelerate the adaptation of these arboviruses to humans and start domestic/urban transmission cycles.

Ae. aegypti aegypti is likely to have been introduced in the Americas during the Atlantic slave trade in the sixteenth century. Along with its vector came YFV, which ravaged the New World for centuries (77). A continental plan for *Ae. aegypti aegypti* eradication (1947–1970) cleared the vector from 18 Latin American countries by 1962 (78). These efforts, together with vaccination campaigns, helped to bring yellow fever under control, and the last urban outbreak in Brazil was reported in 1942 (79). Then followed a long period of sporadic and restricted arbovirus outbreaks in South America (see Section 2.1). By the 1980s, almost all South American countries experienced *Ae. aegypti aegypti* reinfestation, culminating with successive introductions of DENV lineages in the region at the same time, turning the continent into a hyperendemic region (80). Subsequently, the region experienced the introduction and spread of another important anthropophilic mosquito, *Aedes albopictus*, which is also a highly competent vector for many arboviruses

(81). Most recently, CHIKV and ZIKV were introduced in South America in the mid-2010s, expanding the list of exogenous threats that are very efficiently transmitted by one or both vectors (82).

Therefore, in comparison with other hotspots of viral diversity, South America lacks coevolution time between hominids and some of the main sources of horizontally transferred viruses (**Figure 3**). The same seems to be true for a local human-adapted vector that could effectively bridge native viruses and human populations. However, time to adaptation is relative to the rate of exposure (opportunities to new viruses infecting new hosts), and the drastic changes in habitats and landscapes promoted by humans are deeply modifying the ecosystems and accelerating the rate of spillovers (83).

3.2. Immune Constraints

Once a virus enters a cell, success of the infection is determined by the virus's ability to subvert the cellular machinery for its replication. Considering the rapid evolution of host-encoded immune-related genes, these are anticipated to be significant drivers of viral evolution and act as primary constraints on interspecies transmission.

An example of viral immune evasion that determines host range is the degradation of STAT2 by the DENV NS5 protein. In humans, NS5 is able to efficiently degrade STAT2, counteracting type I interferon signaling. In contrast, in mice, a single point mutation in STAT2 can block this degradation, resulting in inefficient viral replication (84, 85).

Vaccinia virus (VACV) also relies on genes such as *C7L* and *K1L* to replicate efficiently in human cells, and the absence of either gene restricts VACV replication to rabbit cells (86, 87). Both proteins appear to function through cell-intrinsic immunity and translational control mechanisms (88–91).

These examples illustrate how viral evasion is crucial for infection establishment in different species. However, coevolution is key to subverting the immune system, which requires both time and opportunity (92). Adaptive immunity also influences pathogen behavior within a population, affecting the extent and frequency of coevolutionary events a virus might undergo with a specific host.

When highly adapted viruses arrive at isolated or previously unexposed communities, they can cause extreme damage. This has been observed several times in Native American populations after first European contact, with viruses such as measles, influenza, and variola, the cause of smallpox (93). Such outbreaks are commonly termed virgin soil epidemics, and they arise from factors that include the absence of protective immunity to related viruses and genetic susceptibility (94). In the late 1800s, the first measles epidemic in Fiji had a mortality rate of nearly 20%; in subsequent years, the mortality rate dropped to that of European societies (95). Although the cause of a high mortality rate is likely multifactorial, the lack of a previous immune response is probably one of the major contributors (95). It is also unlikely that purifying selection, a process by which less-adapted variants are eliminated, occurred within such a brief period in that population.

Some of the most thoroughly studied examples of the adaptive immune system shaping epidemics include the succession of influenza virus variants (96) and DENV serotypes (97–99). However, the influence of the immune system can be seen even with cross-reactions with other species in the same genus. For instance, cross-protection against circulating flaviviruses may be a factor that hinders the spread of West Nile virus in South America (100). Similarly, convalescent sera from chikungunya patients can neutralize MAYV infection in vitro (101). Interestingly, cross-reaction of the immune response between flaviviruses can have varied effects for the hosts; for instance, prior ZIKV infection in certain cohorts appears to elevate the risk of severe dengue (102, 103). However, this risk enhancement seems to be dependent on a variety of factors,

including cross-immunity with other flaviviruses and surveillance ability, and studies on animal models are not always conclusive (104).

Therefore, it is possible to consider that a virus emerging in a given population, where there is immunological cross-reaction with several different viruses of the same family, could have difficulties establishing enough productive infections to overcome other restriction factors, immune or not, as cited above. In this view, the immune system can be seen as an ecological barrier limiting the niches that might be explored by a given virus.

This is especially important to consider when analyzing arbovirus emergence. The Amazon alone harbors dozens of arboviruses that emerged or re-emerged in the last decades. They usually cause self-contained outbreaks, with a few exceptions such as OROV, which is the most frequent native arboviral disease in Brazil (40). One reason is that highly specific ecological niches might be needed to support the vector distribution, thereby delaying further adaptation to new hosts. Furthermore, the vector's distribution is usually broader than that of the virus. An additional layer of virus-host interaction that contributes to the control of arbovirus transmission is the presence of insect-specific viruses. For instance, the insect-specific viruses Phasi Charoen-like virus and Humaita-Tubiacanga virus can downregulate histone 4, a proviral protein, in DENV-infected mosquitoes, inhibiting their transmission (105).

Consequently, the considerable diversity of hosts and viruses, combined with relatively low and isolated human populations in the Amazon, might explain why, along with several other factors, such a variety of viruses have not coevolved with humans sufficiently to overcome immune constraints and hence emerge as global threats.

3.3. Bioecological Factors

The likelihood of zoonotic disease emergence is geographically correlated with animal species richness (106, 107), and South America has one of the richest faunas in the world (**Figure 4**). Notably, *Chiroptera*, *Rodentia*, and *Primates* host a significantly higher viral richness even if other variables (e.g., research effort) are controlled. Rodents and bats are the two most diverse mammalian orders. Moreover, both present peridomestic habits, which increases the likelihood of spillover to humans (108, 109).

The immune system of bats may explain their apparent immune tolerance, which allows them to harbor viruses without an overt disease, and probably affects transmission (110, 111). Rodents develop long-lasting infections without overt pathology and shed virus continuously into the environment. High population rates and sympatry, as well as aggressive behavior for territory and reproduction, may contribute to virus maintenance and dispersal. Finally, primates have phylogenetic proximity with humans, and socioecological and ecological factors (e.g., social organization, sleeping sites, dispersal, density) also make them good candidates to host and disperse viruses (112, 113).

Bioecological traits of hosts are also important driving factors for emergence and spreading of viruses (114, 115). Neotropical terrestrial mammals have higher richness and lower mean range size than communities from other regions (116). The database COMBINE (117) allowed exploration of biological pattern differences among tropical areas (**Figure 4**). For instance, Neotropical primate species have a higher yearly litter size and a shorter generation time than their Afro-Asian counterparts. Some ecological traits also differ in monkeys, with higher richness but lower dispersal capabilities and lower densities. In bats and rodents, female maturity is also reached more quickly in Neotropical species, with a higher number of yearly litters. Lower species densities are also observed in rodents.

Neotropical richness provides a higher number of ecological niches for pathogens, resulting from higher host species isolation that likely promotes their diversity (28, 30) but also restricts viral

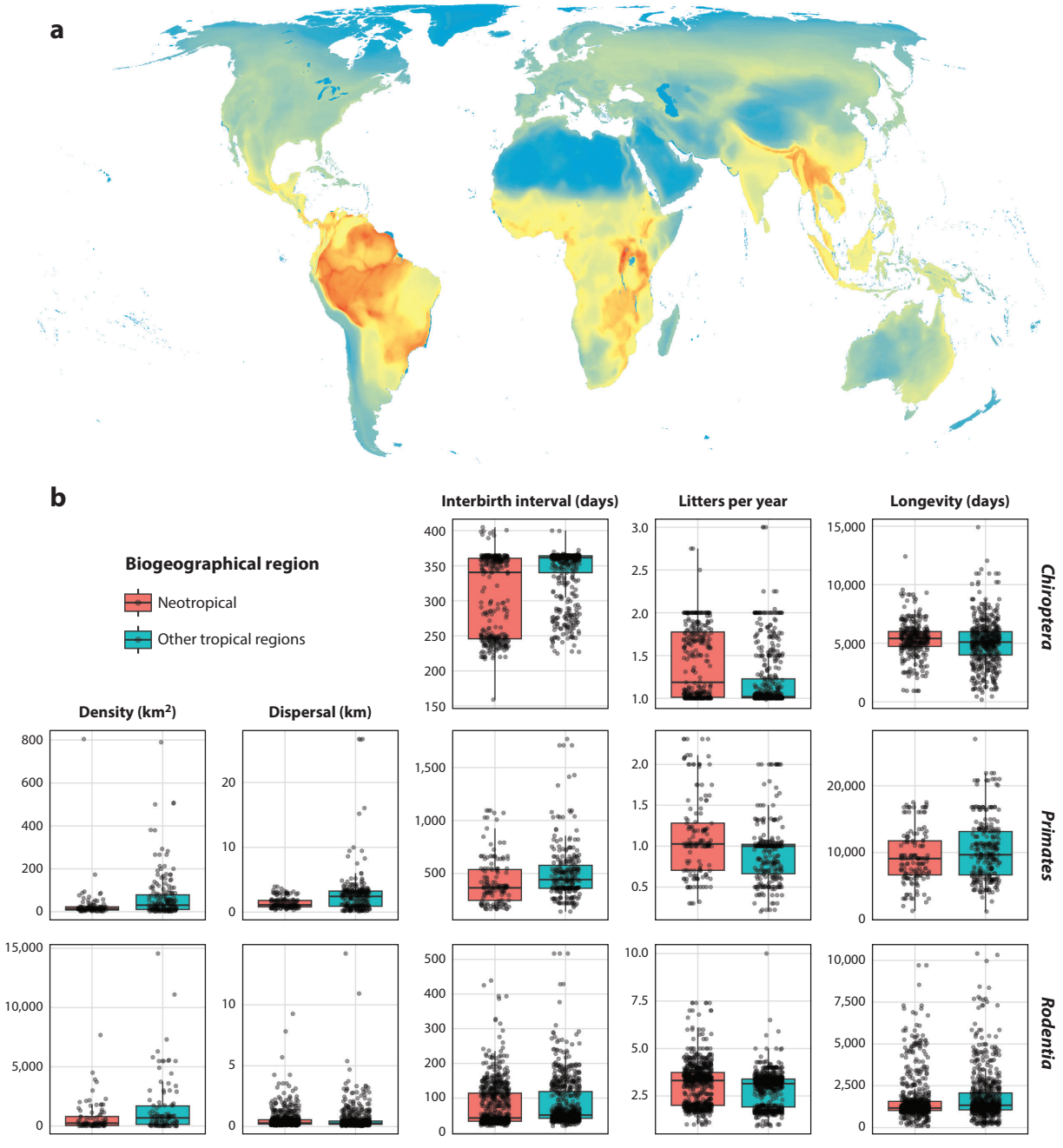

Figure 4

Biological traits comparison between *Chiroptera*, *Primates*, and *Rodentia* mammalian orders from Old and New World tropical regions. (*a*) Map showing the vertebrate richness distribution in the world [data extracted from **https://biodiversitymapping.org/** (for detailed methodology used to construct the map, see Reference 155)]. (*b*) Box plots comparing the distribution of measures of a selection of features for species living in the Neotropics and in other tropical regions. All presented features are significantly different ($p < 0.05$ in Student's t-test) between compared regions. Data were retrieved from the COMBINE database (117). Dispersal data were not available for *Chiroptera*.

spread. Low densities and limited dispersal may also make species less efficient parasite spreaders. Shorter lifespans in the Neotropics may sound counterintuitive to explain a lower spreading efficiency, since higher population dynamics are expected to generate more naïve individuals, likely excreting more viral particles. But one may also argue that a higher mortality rate limits viral release and dissemination. An example of these factors limiting virus spreading in South America's ecology was observed for coronaviruses in bats, where switching of hosts between distantly related species was much more frequent in Asia and Africa than in South America (118).

Together with biological factors at the species level, attention has also been given to the potential regulation of pathogens in ecosystems via a mechanism referred to as the dilution effect (119), which needs to be understood at the community level. Theoretical, laboratory, and field studies suggest that at a local scale, in a community of species differing in their competence for a given pathogen, a dilution effect may occur if the presence of the least competent hosts reduces contact rates between the most competent ones and the pathogen or decreases the density of competent hosts. The main assumption of the dilution effect is that species contributing the most to pathogen transmission dominate in disturbed and less diverse communities. Ecological and evolutionary hypotheses have suggested the existence of such a positive relationship between host competence for pathogens and resilience to disturbance, leading to a general increase of the overall community competence with biodiversity loss (119, 120). Species that are resilient to changing environments are frequently characterized by fast life history strategies, including low investment in adaptive immunity and high reproductive rate, yielding an important influx of susceptible individuals in the population. In addition, pathogens may adapt predominantly to resilient host species because these hosts are generally widespread, mobile, and abundant, therefore constituting the most frequently encountered resource (121, 122). As seen above and in **Figure 4**, Amazonian species have this life history strategy and may then be more competent to spread virus, but they are also highly diverse and specialized, making them bad dispersers. Once more, we highlight here the subtle and fragile equilibria of animal communities and virus spreaders.

In South America, the dilution effect was explored with zoonotic rodent-borne viruses (123, 124). Rodent community species richness may reduce intraspecific encounters among hantavirus hosts, resulting in fewer opportunities for virus transmission. Also, species diversity may reduce the prevalence of a pathogen in a given ecosystem by reducing the density of the reservoir host through predation or competition for resources.

The dilution effect has not been deeply explored for arbovirus emergence. For vector-borne diseases, ecology and feeding habits of arthropod vectors must also be considered: Higher vector density should be associated with more frequent host-pathogen contacts and increased transmission (125). Additionally, when several arthropod species act as vectors for a given pathogen, higher arthropod diversity can result in higher pathogen transmission through an overall increase of vector abundance, or due to functional complementarity between vector species (126, 127). A single in-depth study explored the relationship between mammals, sandflies, and *Leishmania* parasites; it revealed that biodiversity changes may simultaneously dilute and amplify transmission through different opposite mechanisms, implying complex relations between vector and host richness, abundances, and competence (128). Although suggested to explain some outbreaks, more comprehensive case studies are required to fully understand the role of those relationships between biodiversity and viral circulation.

4. HABITAT AND LANDSCAPE MODIFICATIONS

The abrupt demographic and socioeconomic changes in South America have induced important pressures on its ecosystems. Although the 1985–2015 period showed slow evolution of the human footprint—human footprint being a measure of transformation, integrating information

on human access, settlement, transformation of land use/land cover, and development of energy infrastructure—recently human footprint greatly accelerated, with almost 60% of natural vegetation lost in the non-Amazonian ecosystems and 15% of Amazon biome loss (129) (**Figure 2**). Rapid rates in urbanization and increases in populations residing in crowded, low-quality dwellings have created new opportunities for the emergence of infectious diseases (130). Moreover, with the expansion of cities close to almost pristine areas, human activities such as ecotourism, hunting, mining, transport of live wild animals to markets/trafficking, and farming might increase chances of pathogen spillover (131).

Pressures on natural habitats are key drivers of zoonotic disease emergence (132), with multihost parasites with complex life cycles and generalist vectors responding most readily to changes to biodiversity (133). This pattern favors viral cycles involving a set of species, a community, rather than relying on single hosts with too low density to sustain cycles. Such cycles are expected to be more prone to sensitivity to anthropogenically induced changes (133).

Deforestation and edge effects have been deeply explored and theorized as promoters of emergence (132, figure 5). As deforestation increases, cross-species transmission rates in multihost disease systems are disrupted. Habitat changes modify the dynamics and abundance of hosts and vectors, in complex retroactive loops with possible antagonist effects, that may simultaneously have diluting and amplifying effects on vector-borne disease transmission (128). Development of ecotones and marginal areas favors contacts and exposure to potential sylvatic sources of new infection, ultimately influencing cross-species transmission. Despite similar deforestation rates during the last decade, forest fragments remain significantly higher in the Americas, with a lower edge area versus core area fraction, than in African and Asian tropical forests (134). This difference of edge patterns may explain part of the difference in the likelihood of occurrence and spread of emergence.

A second tipping point is not only local conditions, as outlined above and already extensively explored, but also the purpose of modified landscape. Although ecological conditions define the hazard, the reasons for deforestation and the political/economic planning associated with landscape conversion drive the risk of emergence. Amazonia experienced quick and brutal changes. The conversion of forest into agricultural or livestock fields is driven by scaled-up private sector finance due to growing interest in emerging markets in commodities such as beef, soy, sugar, and palm oil (135). Cattle ranching is leading to large-scale forest clearance. Above a deforestation threshold, massive biodiversity loss drastically decreases the contact rates with sylvatic cycles until their extinction (132). Brutal edges in Amazonia, extensive use of fires, and lack of transition zones reduced the timeframe for pathogen evolution along a transitional gradient. Paradoxically, the extent of the deforestation for those demands, due to the almost total associated biodiversity loss, may not be associated with a short-term viral emergence risk because of low exposure and limited and spatially restricted human colonization along those converted landscapes (**Figure 3**). Yet, it is crucial not to overlook or underplay the mid-term consequences of these landscape alterations. The erosion of ecosystem services, including forests' vital role in mitigating global warming effects, will have a delayed impact on global health issues. This is exemplified by the recent YFV outbreaks in South America. YFV is maintained in enzootic cycles involving arboreal *Aedes* species and nonhuman primates, and historically transmission occurs within this sylvatic cycle in the Amazonian region. In the extra-Amazonian region, YFV re-emerges from the forest every 7–8 years, causing outbreaks with an average duration of 21 weeks (136). However, since 2016, Brazil has observed an unprecedented uninterrupted circulation of YFV in the extra-Amazonian environment, which coincides with ongoing anthropogenic-related ecological changes, such as disturbed native biomes and deforested riparian forests. Relaxation in forestry legislation has allowed and fomented forest degradation, leading to recurrent epizootics with spillover outbreaks into human

populations nearby highly populated urban areas (137). This situation highlights the risk of YFV reurbanization due to the possibility of virus spill back to the human/*Ae. aegypti* urban cycle.

5. CLIMATE CHANGE AND ITS POTENTIAL EFFECT ON VIRAL EMERGENCE

Climate change resulting from the gradual increase of global temperatures may alter the range of global pathogens, particularly vector-borne infections, to expand into new locations and target new hosts. Temperature changes affect both host and virus biology and impact the enzootic transmission cycle dynamics.

Insects have body temperatures that depend on ambient temperature, and so the increasing global temperature influences all biological processes such as blood feeding and mating behaviors, vector competence, and life cycle characteristics of immature stages and adult vectors. Moreover, favorable temperatures allow the spread of disease vectors, which could lead to the colonization of new geographical areas that were previously inaccessible (138).

In Brazil, high rainfall and a temperature increase of 2°C within the last decade were followed by an increased number of yellow fever cases in nonhuman primates, and mathematical models for YFV transmission forecasted that the number of cases will continue to rise due to climate change (136). A recent review suggested that rising temperatures would alter the vector competence of mosquitoes to increase the epidemic risk of CHIKV, DENV, and ZIKV in *Ae. aegypti* and *Ae. albopictus* mosquitoes (139). As an example of climate-driven infectious disease emergence, we can highlight dengue transmission for which sustainability is strictly related to climate. Correlations between increased temperature and dengue fever incidence have been recorded in Brazil (140).

The control and prevention of zoonotic rodent-borne viruses require understanding the complex interplay between the virus prevalence in the reservoir hosts, the environmental variables (such as climate and landscape), and the structure of the rodent population assemblies. The incidence of weather conditions, such as increases of temperature, rainfall, and humidity, on rodent abundances, population dynamics, and, as a cascading consequence, seroprevalence may be different according to the particular climatic environment (temperate-arid, tropical, or temperate-humid). For instance, some studies have found correlation (positive or negative) with precipitation and temperature on rodent abundance and HPS cases; however, others did not detect any significant influence of weather variables (141, 142). This emphasizes the relevance of local field studies for risk assessment and epidemiology, since the specific virus-host-environment ecology for a given virus is not easily generalizable.

6. PREPAREDNESS AND CHALLENGES

Strategies to identify and characterize emerging animal viruses that may represent a significant risk of spillover and spread to humans such as genomic surveillance systems, artificial intelligence, and machine learning that are associated with bolstered field programs to identify the natural host range of potential new pathogens have detected hundreds of new animal viruses with unknown zoonotic risk (143). Nevertheless, most animal viruses in nature remain unknown, and we hope most of them will not infect humans (11, 73, 144).

Among the actions undertaken during the COVID-19 pandemic, the implementation of viral genomic surveillance in a coordinated network, with standardized capabilities to allow worldwide comparative studies, had a preponderant effect in decision-making by global, and South American (145), health authorities. Considering the complex epidemiological panorama in South America, this expertise would be helpful for the genomic surveillance of other emergent viruses, such as

arboviruses or respiratory viruses. It is also worth mentioning that the highly diverse biomes of the Brazilian territorial area, comprising 8,510,000 km², and the profound inequality between regions (with the Human Development Index ranging from 0.842 to 0.418), are challenging implementation of long-term standardized genomic surveillance and other containment measures. These vulnerabilities emphasize the need for systematic permanent surveillance programs with governance, leadership, financial support, collaborative networks, community engagement, and workforce capacity. As an example of the need for constant surveillance, we can mention the Western equine encephalitis virus outbreak in horses that emerged in November 2023 in Argentina and Uruguay, after about 50 years without circulation in this region (146, 147), that was also detected recently in horses in southern Brazil.

Much of the information now used in epidemiological surveillance programs to forecast models of viral emergence and spillover has been derived from metagenomics. However, it is challenging to identify and translate these findings into evidence-informed indicators for public health emergency preparedness and target surveillance to the most crucial interfaces (148). Spillover events are almost always invisible and occur across biogeographical borders, where there is the opportunity for contact and cross-species transmission between animals and humans, leading to virus sharing and host shifting (20, 149, 150). Thus, in order to discover emerging pathogens quickly, genomic surveillance should be deployed to groups that better represent the human-animal interface, such as rural populations living near preserved areas, forest hikers, hunters, and individuals linked to illegal mining and animal trafficking.

In summary, detecting pathogenic emerging viruses relies on robust health surveillance systems and astute clinicians. Without well-resourced public health services, healthcare infrastructure, and trained staff in areas close to the human-animal interface, which should also be connected to regional genomic sequencing facilities, emerging pathogens can go unnoticed for long periods, resulting in delays in treatment and prevention measures.

7. CONCLUDING REMARKS

Viral emergence is multifactorial. From the molecular level, through the ability to engage with a different receptor or evade the immune system, to the ecological balance, where climate and habitat conditions influence the dynamics of hosts in a given environment, different pressures forge the path to virus emergence. In South America, the lack of native epidemic viruses is likely the consequence of human civilization's history and a subtle protective ecological balance. However, recent deforestation trends and worrying climate trajectories are bringing ecosystems closer to their tipping points, states marking abrupt shifts between contrasting ecosystem states when environmental conditions cross specific thresholds (151, 152), with irreparable consequences on biodiversity loss, water cycles, and global changes.

Health issues, and notably viral zoonotic diseases, are also getting closer to this tipping point. The preservation of Neotropical forest ecosystems offered, until recently, conditions that protect against large-scale emergence and spread of native viruses. But new or dramatically expanding factors are threatening this resilience and call for urgent prevention and mitigation actions and plans, relying on natural habitat preservation, sustainable development plans, and care of the most vulnerable populations. In this changing scenario, preparedness for new events of viral spillover is pivotal to detect an outbreak, isolate, identify and characterize the etiologic agent, and quickly apply this knowledge to interventions that promote public health.

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