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Epidemiology, Ecology, and Evolution of Human-Virus Interaction: An Overview of the Relevance to Human Health and Disease

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Abstract

Acquiring a systemic perspective on epidemic events is mandatory in an age in which such events are rapidly growing in both number and spatial distribution. In this work we describe the human/virus interaction through the 'deep time' of evolution. We show how ancient epidemics shaped animal and human biology influencing basic traits like multi-cellularity, immunity and cancer. Furthermore, on a much shorter time scale, we focus on the role played by globalization and anthropogenic environmental deterioration in the growing menace of recurring pandemics.

Keywords: retroviruses, cancer, biosphere, epidemics, prevention, SARS-CoV-2

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Introduction

Since the discovery of the tobacco mosaic virus in the last decade of the 19th century (Beijerinck 1898), viruses have been given an exclusively negative connotation for their tendency to cause dangerous diseases. Of course, no one can deny that viruses have caused and still cause suffering and death in human populations around the world. However, viruses do not exist to cause disease in humans and other organisms. They are biologically active molecular agents that lie on the border between the living and non-living world. Generally speaking, their major characteristics can be identified with *i)* their propensity for structural (genomic) change, *ii)* their ability to replicate and spread by infecting prokaryotic and eukaryotic host species, and *iii)* their need for a living host. Viruses elicit a remarkable interest in the biomedical field, However, a broader and more realistic view in recent decades emphasizes the essential role they play in ecological systems and biological evolution (Feschotte & Gilbert 2012). Epidemiologists gave a fundamental contribution to understanding viral diseases and their trends in human communities. However, the emergence and reappearance of many infectious diseases recorded in recent decades, with particular reference to viral epidemics, require innovative approaches for a better clarification of their origin (Levins & Lewontin 1985). In our opinion, what would be needed today to broaden the horizon of biomedical research is the recovery of a relationship with the natural sciences, in particular ecology.

As was unequivocally documented by the seminal work by Vitousek and colleagues (1997), we live in a 'human-dominated planet'. Over the past century, humanity has altered ecosystems more rapidly and extensively than in any other comparable time period in the past 12,000 years (UNEP 2005). The physical and chemical matrices of the planet have been modified, triggering deleterious alterations of the biosphere and accelerating a dangerous degradation of landscapes everywhere. The disturbance produced by our action on the natural environment has also significantly impacted on our health. Unfortunately, the effects of these processes over time are not easy to foresee, and they cast a shadow on our future (UNEP 2005).

Meanwhile, like any other component of the ecosystems, viruses have not remained insensitive to this transition and it is reasonable to assume that any newly emerging viral disease represents a new form of 'viral life' shaped by new environmental pressures (Modonesi 2020).

It should be noted that emerging viral diseases are mainly caused by RNA viruses whose transmission cycles involve interaction with ecological factors and evolutionary dynamics (Susser & Susser 1996). For a long time, epidemiological and biomedical sciences have neglected the eco-evolutionary nature of communicable diseases. All the epidemics of recent decades, as well as the pandemic triggered by the spread of SARS-CoV-2, remind us that our unequal relationship with the biosphere raises many troubling challenges that health systems around the world will face in the decades to come (Vitousek *et al.* 1997).

1. A Multifaceted Interaction

Within the natural world, associations between living beings can involve whole organisms or parts of them, such as cells, genes and genomes. For example, viruses usually exchange genes with their hosts: they receive foreign genes that integrate into their own genome and release their genes into the host's genome. This type of association, based on horizontal gene transfer (Burmeister 2015), is quite frequent and represents a widespread phenomenon both in aquatic and terrestrial biotopes. In light of this evidence, the coexistence and mutual interaction between humans and viruses can be described as an ancient and exemplary case of a symbiotic relationship among the many that can be found in nature.

As we will see below with regard to retroviruses, symbiotic phenomena are often characterized by horizontal gene transfer, highlighting that the so-called 'acquired genetic inheritance' provides an important contribution to non-Darwinian (Lamarckian) evolutionary processes.

Viruses interact with organisms from all the three domains of cellular life (*Bacteria*, *Archaea*, and *Eucarya*). However, the uncertain nature and origin of these infectious agents do not allow researchers to place them into an appropriate and definitive position within the tree of life (Moreira & Lopez-Garcia 2009). As a consequence, the scientific community raised many doubts about the legitimacy of considering viruses as 'living entities'. Furthermore, their complete inability to reproduce without exploiting a host cell (Lopez-Garcia 2012) explains why this topic still fuels a lively debate even among philosophers of science (Koonin & Starokadomskyy 2016).

Despite the conflicting conclusions expressed by researchers about the nature of viral particles, it is commonly accepted that viruses have influenced the evolution of a large number of unicellular and multicellular organisms, including our own species (Van Blerkom 2003). Phylogenetic analyses suggest that RNA viruses infecting vertebrates tend to broadly follow the evolutionary history of their animal hosts for hundreds of millions of years (Shi *et al.* 2015). In some ways, this is also consistent with the remarkable spread of retroviruses among modern vertebrates, which supports the hypothesis that their emergence dates back to around 450 million years ago. In other words, retroviruses could be contemporary infectious agents of the first vertebrates that appeared in the oceans of the Ordovician period (Paleozoic era) (Aiewsakun & Katzourakis 2017). Figure 1 gives very interesting hints on the evolutionary process and allows putting some fascinating hypotheses on the role of contingent events like epidemics in animal evolution. We can safely state that viruses are an integral part of natural history and not only a 'threat'. However, we must keep in mind that we are talking about 'deep history', i.e. extremely long periods of time.

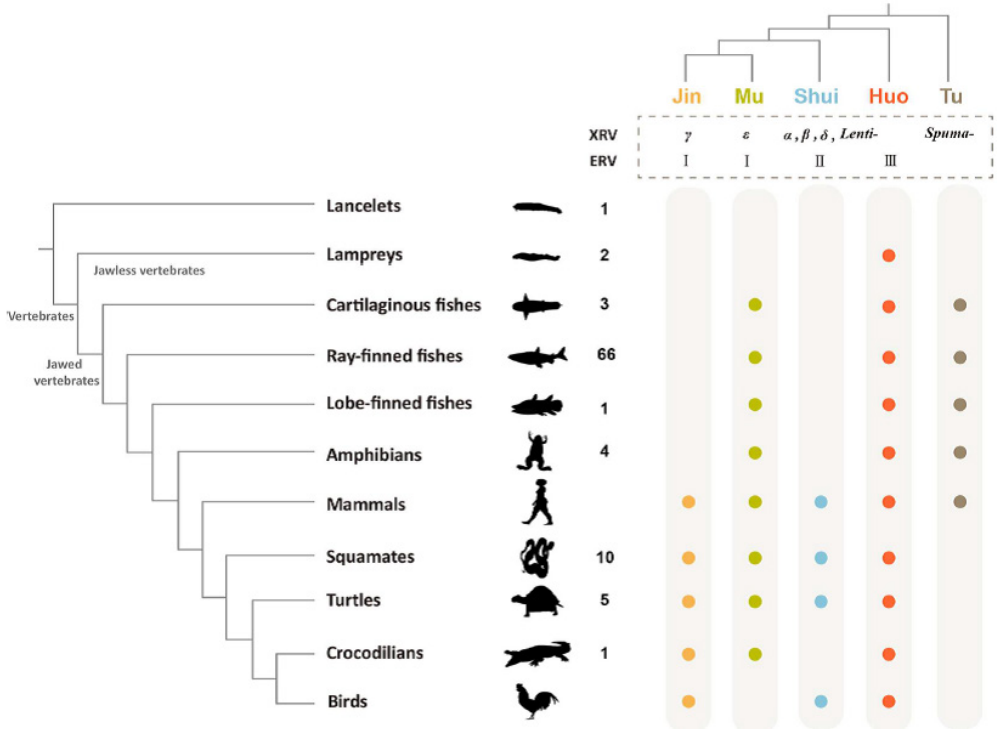

Figure 1: Distribution of the major retroviral clades along different vertebrates. Endogenous retroviruses of vertebrates illuminate diversity and deep history of retroviruses. (From Xu *et al.* 2018).

2. Symbiosis: Ecology of an Evolutionary Strategy

It has recently been estimated that a significant percentage of the DNA sequences detected in the human genome have a retroviral origin or derive from transposable elements (Gonzalez-Cao *et al.* 2016). Although hereditary symbiosis is still considered a rare phenomenon—'the quirk side of evolution', as Stephen Jay Gould put it (1977)—its frequency increases significantly when dealing with viruses and microorganisms. It is no coincidence that physicists interested in the cooperative dynamics of biological systems have coined the term 'collectivist revolution in evolution' to indicate the ecological processes that lead organisms to overcome genetic barriers between species (Buchanan 2009). In general, the symbiotic associations between different organisms are quite variable in the type of interaction and the biological effects on the partners involved. The association can be mutualistic (both partners benefit from the association), commensalistic (one partner benefits and the other remains unharmed) or parasitic (one partner benefits and the other is damaged) (Douglas 1994). A well-known example of mutualistic association is illustrated by lichens. With over 15,000 species, lichens are a successful partnership between a fungus and an algal or cyanobacterial species, or sometimes both. The fungus usually accounts for 90-95% of the lichen biomass and encloses the cells of the photosynthetic symbiont within a network of filaments. The fungus provides a robust structure, while algae and cyanobacteria contribute to the products of photosynthesis and to the fixation of atmospheric nitrogen (Douglas 1994).

However, the data picture of many ecological associations is still poor and unclear. Therefore, these associations do not fall into any of the aforementioned categories. Furthermore, the dynamic interaction established between two partners of a symbiotic relationship may change over time. Defining a continuum along a dynamic path that ranges between competition and cooperation (Dimijian 2000), as shown in Figure 2, could be a good solution to avoid wrong classifications.

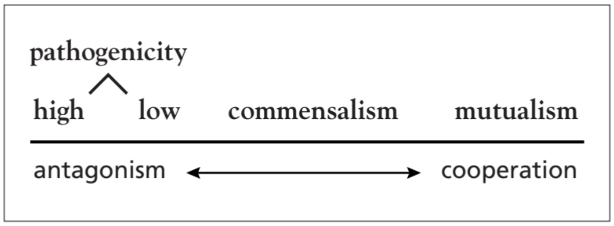

Figure 2: A continuum can be visualized between antagonistic and cooperative symbiotic relationships. Exact assignment of roles is usually difficult and reflects our incomplete understanding of most symbiotic relationships. (From Dimijian 2000).

It is worth noting that many viruses establish a positive or otherwise non-negative interaction with humans. The beneficial effects for the host range from a mutualistic relationship, in which its survival depends on the virus, to advantages that occur only in certain environmental conditions. However, the host/virus relationship can change gradually or abruptly, mainly due to external (environmental) interferences. Often the nature of these interactions, which are probably quite ancient, is clearly symbiogenic (Dimijian 2000). The adjective 'symbiogenic' comes from the neologism 'symbiogenesis' coined by the Russian biologist Konstantin Sergeevich Mereschkowski (1910) at the beginning of the 20th century. Symbiogenesis refers to a close association between different organisms due to ecological events, leading to molecular, morphological and functional changes. According to Mereschkowski, cell organelles such as mitochondria and chloroplasts are the descendants of bacteria that evolved in symbiosis within other cellular organisms. His ideas were updated by the modern 'theory of 'endosymbiotic origin of eukaryotic cell', developed by the American evolutionary biologist Lynn Margulis, which is widely accepted today (Margulis & Sagan 2002; Sapp *et al.* 2002).

It can be assumed that a significant variety of ecological relationships based on symbiogenic processes involved viruses, playing an important role in the origin and evolution of life (Roossinck, 2008). This opportunity that emerged during the natural history of living beings must have favored the emergence of new biological systems generated by the integration of creatures phylogenetically unrelated to each other, giving rise to a non-trivial and unconventional form of evolution referred to as 'reticulate evolution' (Carrapiço 2010; Gontier 2015). Reticulate evolution is a concept that accounts for the evolutionary change induced by mechanisms and processes of symbiogenesis, lateral gene transfer, hybridization and infectious inheritance (Carrapiço 2010; Gontier 2015). According to that interpretation, each emerging evolutionary entity possesses biological traits that go far beyond the sum of the individual properties of each original partner triggering the development of an integrated whole with innovative attributes. In this process, the new organism, or superorganism, develops functions and synergies that are not detectable in the individual species from which it was formed (Carrapiço 2010). The result can be viewed in Figure 3.

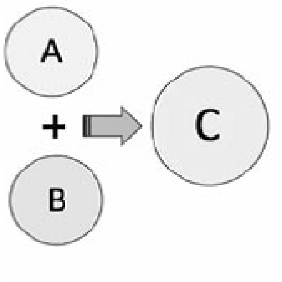

Figure 3: The new entities formed by the integration of two individual organisms (From Carrapiço 2010).

3. Very long and very short time scales

As mentioned before, the interaction between viruses and multi-cellular organisms has a very long and fascinating history and, like all the very long histories, is made of both light and dark. A paradigmatic case are the previously mentioned retroviruses which, by their peculiarity of having RNA as genetic material and their ability to integrate into host DNA by retro-transcription, allow us to keep track of ancient infections by the detection of retroviral sequences embedded in human and animal genome. Endogenous retrovirus sequences (ERVs) represent a genetic legacy due to ancestral integration of exogenous retroviral agents into the genetic makeup of mammals and other vertebrates (Feschotte & Gilbert 2012).

Once the genome of cells that give rise to gametes (eggs and sperms) has been colonized by viral sequences, copies of the pro-viral DNA can be further amplified due to germ-line re-infection events (Dewannieux *et al.* 2013). These sequences are ubiquitous in vertebrates, and in human genome account for around 8% of the genetic material (so largely outnumbering protein-coding genes) (Xu *et al.* 2018). These sequences, for the most part, belong to the group of long-terminal repeats (LTRs) which also include the mammalian apparent LTR retro-transposons. Just like structural genes, ERVs undergo epigenetic regulation by histone methylation/demethylation and have a tissue specific expression level. Moreover, they have a much greater tissue specificity than structural genes, so that we can obtain a more accurate discrimination of different cell populations by means of ERVs than with other genes (Tokuyama *et al.* 2018). This implies that they are now an integral part of our genetic makeup. Indeed, the lack of specific ERVs prevents the development of the embryo and also the maintenance of the organization of complex tissues depends on the ERVs (Fu *et al.* 2018; Liu *et al.* 2019).

	HERV-K	HERV-E	HERV-W	HERV-H	HEMO	HERV-FRD	HERV-R	HERV-P
Breast	X		X	X	X		X	X
Lymphoma	X		X	X				
Leukaemia	X						X	
Endometrial	X	X	X			X	X	
Prostate	X							
Seminoma	X		X					
TCC			X					
Ovarian	X	X			X		X	
Melanoma	X							
Lung	X			X	X		X	X
Colon	X		X	X				X
Pancreas	X							
Sarcoma	X							
Urothelial/Renal	X	X	X	X	X		X	
HNSCC	X						X	

Table 1: Overview of the human ERVs detected in several cancers. The lack of X only means that there is no record of the human expression of that ERV for that cancer, and not necessarily that it is not present. (From Bermejo *et al.* 2020).

This as for the 'sunny side': the above-sketched interactions describe the establishment of an unavoidable vital link between the expression of genes due to very ancient viral infections and human life. On the other hand, the 'dark side' concerns the involvement of ERVs in cancer and auto-immune diseases, that in turn are both 'tissue-based' pathologies and in a sense can be considered as the price we have to pay for being complex and very finely integrated organisms. Although the tumor mechanisms induced by ERVs have not yet been fully elucidated, the role of their sequences in the transformation of normal tissues into neoplastic tissues is widely recognized. Investigations of the past few decades suggest a broad association of different human ERVs with several cancers (Bermejo *et al.* 2020) (Table 1 above).

Let's now shift to a much shorter time scale and give a look at Figure 4. The exponential increase of epidemics episodes very clear starting from the Seventies, goes hand in hand with globalization processes to be intended as both destruction of former wild areas with a consequent increase of zoonotic infections passing by animals to humans and the unprecedented connectivity linking very far away areas. If and when these episodes, on the long run, will end up into mutualistic interactions is totally out of reach of our predictive ability. We can (and must) only focus on the rising menace of recurrent pandemics caused by a very recent ecological disaster.

Despite the substantial scientific attention that viruses rise due to their pathological outcomes in humans, animals and plants, a broader and more realistic vision has emerged in recent decades

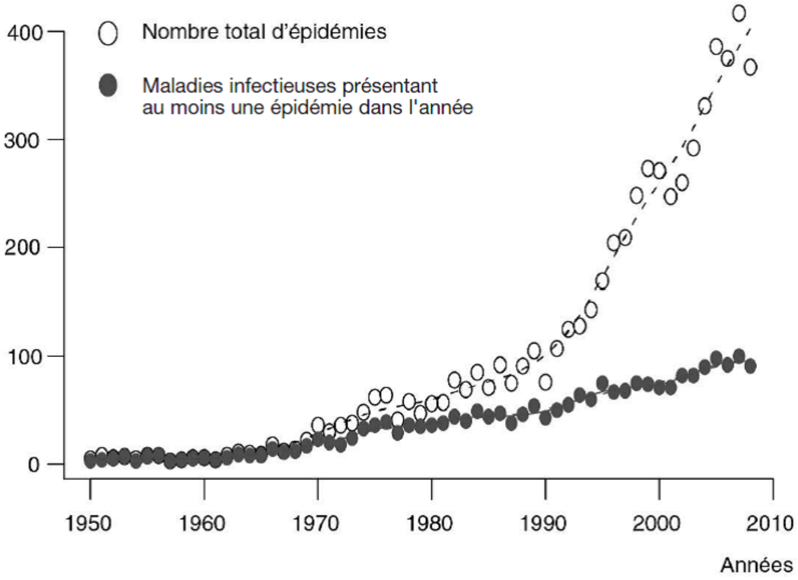

Figure 4: Evolution of the number of infectious disease epidemics in the world from 1950 to 2010 (from Morand & Figuié 2016).

that emphasizes the key role they play within the biosphere. This more comprehensive knowledge about viruses suggests that a different conceptual approach is needed in biomedical investigation of emerging viral pathologies. We should focus on the integration of epidemiological and ecological data in order to clarify what happens in the early stages of emerging viral epidemics. This would allow researchers to have a more complete range of information useful for studying the dynamics occurring at the host-pathogen interface. It is important to underline that in man-made environments such as urban, rural and industrial areas, the risk to public health due to the spread of an emerging pathogenic virus also depends on the population density, people's lifestyles and human mobility, as well as on social and economic factors together with the reactivity of political and health institutions. More succinctly, we call all these elements 'human ecology', giving this term a much more inclusive meaning than its common usage. Human ecology is the complex of biological, cultural, spiritual, social and political characteristics that allow us to define a profile of the relationship that each human population establishes with the environmental context. The intertwining of these elements designates the background affecting the behavior of a viral disease, showing its epidemiological, biological and clinical traits.

4. The relevance of time and space

Since the mid-20th century, ecological and evolutionary processes have been recognized as key factors in promoting the emergence of new viruses and the re-emergence of older ones. In the early 1950s, a 'systemic' look at infectious diseases was developed taking into account two important requirements for the health of human populations: their historical (evolution) and spatial (ecology) properties (Arrizabalaga 2018).

Starting from the concept of 'bio-cenosis', which refers to the complex of all living organisms that co-evolve and interact within a given territory, the term 'patho-cenosis' was coined to indicate a well defined set of pathological states of a population. According to such an approach, the frequency and distribution of each infectious disease depend not only on biological and environmental factors (i.e. pathogen, virulence, reservoir species, climate, degree of anthropization, and so on) but also on the frequency and distribution of all other diseases within the same population (Grmek 1997). A paradigmatic example is provided by the plague, which spread across Europe after the decline of leprosy between the 12th and 14th centuries and was followed by other infectious diseases in later times (Weiss & McMichael 2004). The so-called 'black death' influenced the pattern of transmission and distribution of other pathogens associated with human population density. The plague likely engaged a strong competition with other contemporary pathogens such as smallpox and measles. In turn, the smallpox and measles viruses were present in Europe well before the arrival of *Yersinia pestis*, which blocked their progression, and they only re-emerged around the 18th century when the plague had disappeared from Europe (Barquet and Domingo 1997; Hopkins 2002). The modern temporal and spatial reconstruction of the plague has had a significant weight in the history of biomedical sciences, because it has broadened the narrow mono-disciplinary perception of diseases as isolated entities. In the investigation of the events underlying the onset of infectious diseases, an integrated approach was proposed aimed at giving a more realistic weight to temporal and spatial factors and their mutual interaction. Since then, the health condition of a population has been conceived as a dynamic process influenced by a wide range of factors often neglected even by the most advanced epidemiological studies. It can be argued that in most cases both the appearance and the re-appearance of new and old viral epidemics depend on ecological, evolutionary and social processes and cannot be considered as mere accidental events. Revisiting the history of diseases from such an integrated perspective, namely taking into account the social and environmental contexts as well as the concomitance of other pathogens in the population, allows us to glimpse a logic in the sequences of events.

5. Are there any good viruses?

An important aspect of viruses concerns their ability to implement population dynamics very similar to the ecological behavior of unicellular and multicellular organisms. Nickbakhsh and colleagues (2019) have argued that positive and negative interactions between flu and non-flu viruses at the population level occur in the respiratory system of human hosts. In other words, when multiple pathogens have infected the same host organism, a competitive or cooperative interaction can arise. Interestingly, many cases of viral infections showing beneficial effects on human and animal hosts were investigated. Sometimes, the available data does not allow researchers to understand the mechanisms underlying these mutualistic interactions. For example, protective viruses often interfere with various biological functions of the pathogenic viruses, including their replication. In other circumstances protective viruses modulate the host's reaction by stimulating innate immunity (Barton *et al.* 2007). As can be guessed from the examples briefly reported below, this area of research has so far been poorly considered, but it deserves much more attention (Shen 2009).

Some long-term studies have shown that people infected with HIV-1 develop full-blown AIDS much more slowly if they are also infected with the *hepatitis G* virus, a virus that is fairly common in humans (Heringlake *et al.* 1998; Tillmann *et al.* 2001). Two other interesting cases concern human cytomegalovirus infection, which is involved in the suppression of HIV 1 superinfection, and *hepatitis A* virus, which can suppress infection with *hepatitis C* virus (Deterding *et al.* 2006; Shen 2009). Parato and colleagues (2005) showed that several oncolytic viruses can attack neoplastic tissues exerting a protective action on the host. In an experimental setting, rodents infected with murine gammaherpesvirus 68 (analogous to the human pathogenic Epstein-Barr virus), or with murine cytomegalovirus (related to human cytomegalovirus), have been shown to be protected from infection by both *Listeria monocytogenes* (responsible for foodborne infections in humans) and *Yersinia pestis* (the agent of the plague) (Barton *et al.* 2007). Another experimental study found that viruses can also protect against metabolic diseases. For example, mice prone to developing type 1 diabetes were found to be protected from the metabolic disorder when infected with lymphotropic viruses (Oldstone 1988).

Conclusions

An important issue mentioned above concerns the anthropization of a territory, the degree of which can be assessed by using different types of variables and indicators. In purely ecological terms, anthropization is the conversion of natural spaces and landscapes by human action. While in classical ecological thought anthropization has substantially to do with various forms of environmental degradation, a broader and more realistic conception of 'anthropized environment' also embraces less obvious aspects such as privatization, commodification and artificialization of environmental contexts and resources.

From a historical and anthropological point of view, it could be argued that whenever human societies encountered a survival problem or a limiting factor, they used their creativity to shape resources and territories and make them as consistent as possible with their own needs, such as in the case of the selection of plants, the domestication of animals, the regulation of waterways, the terracing of slopes, urban development and transport networks.

Today, however, in many cases anthropization is mostly indirect and conditioned by financial and economic speculation as well as by the use of invasive technologies.

The impressive deforestation of huge territories of the world represents perhaps the most dramatic and emblematic case of anthropization, even beyond the beneficial effects that these natural environments have on climate regulation.

A sort of 'Promethean' vision of the nature/society relationship has now been strengthened, starting from the assumption that, with the help of science, humanity will free itself from the constraints of nature in achieving the true human freedom.

Even in terms of public health, such an ideology can be very dangerous. Globally, natural forests cover around 4,000 million hectares (ha), corresponding to 30% of the Earth's surface. The world is losing its forests at an alarming rate of over 3 million hectares per year. Over a quarter of the reduction in forest habitats is due to the deforestation of large areas to make way for permanent crops for the production of commodities (IPBES 2019).

Deforesting means losing biodiversity, that is to say the key factors in the emergence of zoonotic diseases. According to recent data, about 75% of the Earth's terrestrial environment has been severely altered by aggressive economic activities. When natural habitats are transformed and replaced with artificial environments, the risk of infectious disease outbreaks increases.

Deforestation exposes humans and livestock to the spread of zoonotic pathogens. These interactions increase the likelihood that animal viruses can jump from reservoir species to our species (IPBES 2019).

The interstitial pneumonia (COVID-19) outbreak caused by Sars-CoV-2, first detected in Wuhan, China during the second half of 2019 must be seen as a loud and clear alarm coming from the global ecosystem.

To conclude, it is difficult to assess the impact of SARS-CoV-2 pandemic in promoting the integrated approach outlined above. Again, we see both a light and a dark side. The positive side depends on a marked interest in zoonotic viral infections and their mode of transmission through intermediate species. Attention to environmental problems could highlight a growing tendency to enhance prevention strategies based on our relationship with ecosystems. The dark side is very evident in terms of both a deep cultural crisis of science made clear by the extreme fragmentation of competences exhibited by scientific community and a predominant economic interest aimed exclusively at cure (in the form of vaccination) of specific epidemic events. Such an approach is undoubtedly more consistent with the prevailing economic order, but it is also far less effective than serious preventive strategies.

The struggle for a broader perspective that translates into interdisciplinary research and concrete policy acts (we are full of environmental chatter with no practical consequences) suggests that the systemic approach we are advocating here, is at this time, mandatory.

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