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ECO-EPIDEMIOLOGY AND NEW GENERAL PRINCIPLES OF BIOSAFETY: ENVIRONMENTAL ASPECTS OF THE COVID-19 PATHOGENESIS

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ABSTRACT

The COVID-19 pandemic has repositioned, in the focus of epidemiology, zoonosis and environmental issues that favor the onset and contagion of infectious diseases. Thus, through bibliographic research, using a theoretical-qualitative method, we sought to analyze the influence of environmental aspects on the pathogenesis of some infectious diseases, especially COVID-19, and what response can be formulated if the incidence of these environmental factors occurs. We concluded the environmental factor and human behavior have been essential in the appearance of several infectious diseases. Thus, only complex thinking can lead epidemiology to the understanding of the causes, measures to mitigate the spread and treatment. For this reason, eco-epidemiology and bioethics approaches were brought up, which consider problems comprehensively, integrating new areas of knowledge. Finally, new general principles of biosafety were proposed to deal with zoonotic diseases.

Keywords: bioethics; biosafety; epidemiology; principles; zoonosis.

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ECOEPIDEMIOLOGIA E NOVOS PRINCÍPIOS GERAIS DA BIOSSEGURANÇA: ASPECTOS AMBIENTAIS DA PATOGÊNESE DA COVID-19

RESUMO

A pandemia da COVID-19 reposicionou, no foco da epidemiologia, a zoonose e as questões ambientais que favorecem o aparecimento e contágio de doenças infecciosas. Assim, por meio de pesquisa bibliográfica, com método teórico-qualitativo, procurou-se analisar a influência de aspectos ambientais na patogênese de algumas doenças infecciosas, em especial da COVID-19, e qual resposta pode ser formulada caso a incidência desses fatores ambientais se verifique. Concluiu-se que o fator ambiental e o comportamento humano têm sido essenciais no aparecimento de várias doenças infecciosas. Assim, somente o pensamento complexo pode conduzir a epidemiologia à compreensão das causas, às medidas para mitigar a propagação e ao tratamento. Por isso, se trouxe as abordagens da ecoepidemiologia e da bioética, que pensam os problemas de maneira abrangente, integrando novas áreas do saber. Por fim, propôs-se novos princípios gerais da biossegurança para lidar com doenças zoonóticas.

Palavras-chave: *bioética; biossegurança; epidemiologia; princípios; zoonose.*

INTRODUCTION

It was not only due to technological and medical advances that epidemiology has undergone major changes in the last 100 years. The most significant transformation was methodological. Diseases cannot be analyzed by fragmentary theories, which segment scientific knowledge.

This has been quite evident in the COVID-19 pandemic. Its implications on planet Earth have yet to be studied. The social, economic, philosophical, political and public health effects are far from being fully understood, due to the fact that, at this moment, people are still trying to control the infectious disease and because we are in the middle of the pandemic.

However, diseases like COVID-19 are a constant in human history. Only in this century, diseases such as the Severe Acute Respiratory Syndrome (SARS), in 2004, the Avian Influenza, in 2005, and the Swine Influenza, in 2009, occurred, which had a certain repercussion in the press due to its reach, even if not compared to the effects of COVID-19.

One aspect that has stood out in the analysis of these infectious diseases, and especially of COVID-19, is that in most cases they occur due to zoonosis, that is, they are transmitted in the relationship between other animals and human beings.

Finally, the purpose is to analyze the influence of environmental aspects on the pathogenesis of some infectious diseases, especially COVID-19, and what response can be formulated for the incidence of these environmental factors.

This is a bibliographic research, with a theoretical-qualitative method, undertaken through sources of epidemiology, bioethics and biosafety.

In this sense, the article dealt with four main points: (a) zoonosis; (b) how intervention and human relationships in the environment are means of enabling the spread of diseases, such as COVID-19, in humans; (c) what is the methodological response of current epidemiology; and (d) how bioethics and biosafety can assist in responding to these problems.

1 ZOONOSIS, INFECTIOUS DISEASES AND ENVIRONMENTAL ISSUES

The relationship between humans and nature is inevitable, being a question of the species' survival. However, at the same time, this relationship puts the species in danger. An area of knowledge called spatial (or landscape) epidemiology studies the spatial variation of disease risk and incidence. It is possible to verify, through the relationships between human beings, the interference in the natural environment and, consequently, in the ecology of beings that may cause infections. The creator of the term *landscape epidemiology*, the Russian physician Eugene Pavlovsky, declared that, among other causes, an infectious disease depends on agents that can spread the transmission of the infection from one organism to another, causing the pathogen circulation (LAMBIN *et al.*, 2010).

In this sense, human interference in the environment and biodiversity has accentuated the spread of diseases originating from bacteria, viruses or other beings, which can trigger the return of a disease or the appearance of a new one, as, possibly, it was the case of COVID-19.

Lambin et al. (2010), for example, reviewed the conclusions of eight case studies, in different locations, regarding the impact of environmental changes on diseases transmitted by vectors and/or animals. They were: (a) West Nile virus (WNV) transmission in the Senegal River basin; (b) Tick-borne encephalitis (TBE) incidence in rural parishes of Latvia; (c) Sandfly abundance in the French Pyrenees, (d) Rift Valley Fever (RVF) in the semiarid region of the Ferlo, Senegal; (e) Animal hosts of West Nile Fever (WNF) in the Camargue region, France; (f) Rodent-borne Puumala hantavirus (PUUV) in Belgium; (g) Geographic distribution of human cases of Lyme borreliosis (LB) in Belgium; (h) Risk of malaria re-emergence in the Camargue.

Based on such case studies, Lambin et al. (2010) used different methods, such as soil mapping, spatial statistical models, and knowledge about diseases, to verify the relationship between changes in the environment, vectors, animal hosts and humans. Thus, they synthesized the study into ten propositions related to landscape epidemiology. These propositions, followed by comments, are presented below.

1. **Landscape attributes may influence the level of transmission of an infection**: the behavior and characteristics of arthropod vectors and non-human hosts depend on the landscape characteristics. Thus, the distribution of vectors and the level of transmission depend on the environment.
2. **Spatial variations in disease risk depend not only on the presence and area of critical habitats but also on their spatial configuration**: fragmented landscapes, ecotone (transition areas between different ecosystems), increase the likelihood of contact between different species,

which can cause the spread of infectious diseases.

3. **Disease risk depends on the connectivity of habitats for vectors and hosts:** the proximity of vector and host habitats does not necessarily mean the transmission of diseases, as it may be that the natural landscape itself limits their reach.
4. **The landscape is a proxy for specific associations of reservoir hosts and vectors linked with the emergence of multi-host diseases:** certain diseases can affect humans through different hosts, based on a previous and complex relationship between different hosts and vectors, caused by changes in the landscape.
5. **To understand ecological factors influencing spatial variations of disease risk, one needs to take into account the pathways of pathogen transmission between vectors, hosts, and the physical environment**: the transmission of diseases to humans, in addition to occurring directly, from contact with the host, can also occur indirectly, without contact with the host, through the permanence of the virus in the environment, due to climatic conditions and soil characteristics. Thus, a disease can begin to spread due to characteristics changes that previously existed in a given region, which naturally controlled transmission.
6. **The emergence and distribution of infection through time and space is controlled by different factors acting at multiple scales**: diseases can arise as a result of political and economic changes in a given region, by altering behavior for human survival, such as urbanization, for example, causing humans to enter a region, previously uninhabited, potentially infectious for them.
7. **Landscape and meteorological factors control not just the emergence but also the spatial concentration and spatial diffusion of infection risk**: climate change can create factors that spread infectious diseases, previously controlled by natural climatic factors, for example, a higher incidence of rain in a given region.
8. **Spatial variation in disease risk depends not only on land cover but also on land use, via the probability of contact between, on one hand, human hosts and, on the other hand, infectious vectors, animal hosts or their infected habitats**: the type of activity carried out by human groups in a region influences the risk of having infectious diseases.
9. **The relationship between land use and the probability of contact between vectors and animal hosts and human hosts is influenced by**

land ownership: public places have more access from individuals in general than private places, which makes it possible to verify that there is a higher incidence of infectious diseases in the former.

10. **Human behavior is a crucial controlling factor of vector-human contacts, and of infection:** preventive measures must be adopted in order to minimize the risks of infection, which makes human behavior fundamental in the fight against infectious diseases.

Despite being hypotheses that depend on more studies to be consolidated, the above propositions give an indication of how there is a direct relationship between human actions and the transmission of infectious diseases. There is a combination of social factors (such as migration, land use, politics and economics) and ecological factors (such as the pathogenic cycle and the characteristics of vectors, hosts and pathogens, and knowledge of ecosystems) that influence transmission. The emphasis, however, is on the fundamental human role for the spread of infectious diseases.

Kilpatrick and Randolph (2012), in turn, draw attention to the fact that, in the last two or three decades, the incidence of endemic pathogens has intensified, which is not associated with natural cycles, but, rather, with human participation. On the one hand, pathogens have appeared in places different from their origin, which is related to human migration, taking the pathogen to new places, on the other hand, the increase in pathogens in their original habitats also depends on a certain human participation, that influences local change. In this sense, displacement, urbanization and deforestation are actions that increase the possibility of transmitting pathogens.

The authors infer that the best way to deal with endemic pathogens includes urban planning and control of ecological communities. And, quite emphatically, they state: “History suggests that successful control needs prompt identification, swift action, and occasionally draconian social measures” (KILPATRCK; RANDOLPH, 2012, p. 1953).

Since the 1940s, 400 infectious diseases have been identified. Relatively recent pandemics, such as HIV, SARS and H1N1 influenza, arose from animals and were caused by ecological and social aspects. Despite repeated pandemics in recent decades, it remains difficult to predict them before they are among human beings. The result is damage to health, economy and life in general.

Morse et al. (2012) ascertain that: (a) the number of new pathogens has risen considerably in recent years, even with all scientific care; (b) the appearance of diseases is related to anthropogenic aspects; and (c) the appearance of zoonotic pathogens of wild origin is related to the population density close to environments of high biodiversity of wildlife. The researchers suggest that, based on models, global resources should be used in the most susceptible regions, in an attempt to prevent infectious diseases or to deal quickly with possible outbreaks. For this, data on the characteristics of infectious diseases, the diversity of wildlife, population density and possible changes in that density should be used, in order to propose probabilistic models of a given location to generate a new infectious disease, indicating critical points on the globe.

Researchers work with the notion that there are different stages of transmission of infectious diseases. Morse et al. (2012) divide it into three, as follows:

a) **Stage 1:** called pre-emergence state, it is identified by the transmission of microbes (viruses, bacteria, protozoa, etc.) to non-human animals, with dissemination in other wild animals. It is generated by ecological, social and socioeconomic changes, causing an increase in the pathogen in its hosts.
b) **Stage 2:** localized emergence, in which there is transmission, at first, from non-human animals to people and, later, between humans, by some generations of the pathogens.
c) **Stage 3:** full pandemic emergence, which is the moment when there is a large-scale global spread, propagated in air travel. The greater the information on the process involved, the greater the chance of preventing pandemics, which are rare, due to the fact that most pathogens are not capable of perpetuating large transmissions.

Regarding the arrival at stage 3, the following example from SARS is quite enlightening about the transmission process:

> For example, SARS, which originated from the SARS-like coronaviruses of bats, emerged in China in 2003 and was due to hunting and trading of bats for food. In the wildlife markets of southern China these bat viruses seemed to become stage 1 pathogens, which spilled over to civets before being transmitted to people and achieving stage 2. SARS coronavirus then underwent repeated cycles of transmission in people, and spread nationally and then globally (i.e., reached stage 3), including 251 cases as far away as Toronto (MORSE *et al.*, 2012, p. 1958).

It can be seen that human interference in the environment, through the significant modification of natural areas, such as urbanization or agricultural activities, allows greater contact between humans and animals that are affected by infectious diseases.

A recent study (GIBB et al., 2020) corroborates this hypothesis, bringing more elements that emphasize this notion. The authors gathered information from 6,801 ecological assemblages, fauna, through a set of biodiversity data called Projecting Responses of Ecological Diversity in Changing Terrestrial Systems – PREDICTS, with data from host-pathogen and host-parasite associations, creating a global data set regarding the zoonotic diversity of hosts (bacteria, viruses, protozoa, helminths and some fungi). This data compiles 3.2 million registers. The study compared the host community of wildlife in primary vegetation (locations with a minimum of human alteration), with the host community in nearby locations, which suffered some degree of human alteration, divided into: secondary vegetation (vegetation that recovered from previous alterations); managed ecosystems (crops, pastures and plantations); and urban locations of varying impacts. In these locations, 376 host species were registered, which were compared between land types.

The research (GIBB et al., 2020) considered innumerable host species, but took special care in relation to mammals and birds, since such groups are known to be the main reservoirs of zoonoses, with mammals being remarkably close phylogenetically to human beings. Thus, of the 546 mammals studied, 190 species had at least one pathogen shared with humans and 96 species had at least one pathogen not shared. This illustrates how humans are susceptible to mammalian diseases. The authors drew attention to bats, rodents and certain birds as highly disease-transmitting species. They found that land use has effects on host communities, since the number of species (18 to 72%) and individuals (21 to 144%) capable of transmitting diseases is greater in environments where there is human intervention than in nearby environments without interference.

The study of environmental causes of diseases has long been linked to climate change. However, in recent years, among researchers, it has been realized that the changes produced by humans in land use are potentially harmful, as they increase the risk of infection and disease. Such changes include loss of biodiversity, alteration of landscapes and greater contact between humans and other animals, making humans more susceptible to endemic pathogens, which can generate pandemics.

> Overall, our results indicate that the homogenizing effects of land use on biodiversity globally have produced systematic changes to local zoonotic host communities, which may be one factor underpinning links between human-disturbed ecosystems and the emergence of disease. […] The global expansion of agricultural and urban land that

> is forecast for the coming decades – much of which is expected to occur in low-and middle-income countries with existing vulnerabilities to natural hazards – thus has the potential to create growing hazardous interfaces for zoonotic pathogen exposure. In particular, the large effect sizes but sparser data availability for urban ecosystems (especially for mammals; Extended Data Fig. 4) highlight a key knowledge gap for anticipating the effects of urbanization on public health and biodiversity. Our findings support calls to enhance proactive human and animal surveillance within agricultural, pastoral and urbanizing ecosystems and highlight the need to consider disease-related health costs in land use and conservation planning (GIBB *et al.*, 2020, p. 4).

Even a precautionary perspective limited to the economic aspect, the increase in cultivation areas and the growth of cities must consider the health cost produced by the new risks and epidemics.

1.1 The COVID-19 pandemic

COVID-19 first appeared in the Wuhan region, Hubei province, China, in December 2019. The first patients had a relationship with the region's market, which sold live animals.

> Since Dec 8, 2019, several cases of pneumonia of unknown aetiology have been reported in Wuhan, Hubei province, China. Most patients worked at or lived around the local Huanan seafood wholesale market, where live animals were also on sale. […] On Jan 7, a novel coronavirus was identified by the Chinese Center for Disease Control and Prevention (CDC) from the throat swab sample of a patient […] (CHEN, 2020, p. 507).

Although recent studies suggest that the virus was already present in countries before the outbreak in China (BASAVAJARU et al., 2020; CHAVARRIA-MIRÓ et al., 2020), there is strong evidence that the virus started in bats, even though other wild animals are not discarded as potential transmitters. Bats are seen as animals with a high chance of infecting humans with diseases. After the SARS (Severe Acute Respiratory Syndrome) outbreak, numerous coronaviruses potentially harmful to humans were discovered. Also in January 2020, Chinese researchers (ZHOU et al., 2020) sequenced the genome of five patients at an early stage of the disease and found that 96% of the virus genome in patients was identical to the bat coronavirus genome, moreover, they noticed that the virus belongs to the SARS-CoV species.

There is a possibility that the virus was transmitted to another host before it reached humans, but further research is yet to be done.

> Phylogenetic analysis showed that bat-derived coronaviruses fell within all five subgenera of the genus Betacoronavirus. […] However, despite the importance of bats, several facts suggest that another animal is acting as an intermediate host between bats and humans. First, the outbreak was first reported in late December, 2019, when most bat species in Wuhan are hibernating. Second, no bats were sold or found at the Huanan seafood market, whereas various non-aquatic animals (including mammals) were available for purchase. […] Therefore, on the basis of current data, it seems likely that the 2019-nCoV causing the Wuhan outbreak might also be initially hosted by bats, and might have been transmitted to humans via currently unknown wild animal(s) sold at the Huanan seafood market (LU *et al.*, 2020).

Zhou et al. (2020), calling attention to the fact that COVID-19 has its origin in natural reservoirs, highlight the need to: (a) increase surveillance in large geographic regions potentially transmitters of diseases; (b) advance preparation of vaccines that fight infectious diseases caused by this group of viruses; and, what they consider most important; and (c) creating regulations capable of dealing with domestication and consumption of wild animals.

Clearly, the way humanity has dealt with the environment and biodiversity has caused diseases to spread constantly. COVID-19 is no different. However great the evidence that human interference significantly increases the spread of disease, human beings, globally, still do not have, among other things, a development plan.

In this sense, more than just dealing with the pandemic itself, it is necessary to be concerned with human behavior in relation to land use, demographic factors, urban planning and legislation.

Such concern is not unreasonable, as recent discoveries (JOHNSON et al., 2015) call attention to the fact that pandemics caused by zoonoses are becoming diseases with greater pandemic potential, causing a greater transmission between humans in a global way, as is the case of COVID-19. The pandemic potential is associated with the host's plasticity, which consists of the host's ability to adapt to the environment, the ability to transmit between humans and the geographic reach.

In addition to the fact that borders are not an obstacle for infectious diseases to remain within a national territory, given the level of globalization achieved, specifically, in the Brazil's case, with an immense territory and different types of natural habitats, there must be a concern with the modification of such habitats, including deforestation, illegal animal trade, and, mainly, forest degradation, since it is an ecosystem with different wild species, including microbial life.

2 ECO-EPIDEMIOLOGY

It is clear, therefore, that contemporary epidemiology is aware of the importance of environmental aspects for the emergence, spread and prophylaxis of diseases.

Didactically, Susser and Susser presented, in 1996, two important articles that narrate the four eras of epidemiology. It is provocative to highlight the environmental variable.

he first moment of epidemiology was called by them the Era of Sanitary Statistics and was based on the miasma paradigm (SUSSER; SUSSER, 1996a).

The Miasma Theory explained the origin of diseases due to the unhealthiness of the environment, that is, its genesis was in the set of odors derived from matter putrefied in the soil, in water tables and in the air and thus contaminated the human being.

There are reports of miasmatic theory in ancient Greece, and Hippocrates himself was based on it. It is certain that until the 19th century the belief in harmful emanations from the environment prevailed, which justified sanitary movements, with wide use of statistics that intended to analyze the levels of morbidity and mortality and with measures of soil drainage and sanitation. Health statistics sought to relate pathologies to the unhealthy environment.

The second era, described by Susser and Susser (1996a), was the infectious diseases epidemiology, founded on the Germ Theory, which argued that the primary cause of diseases is infection by microorganisms. With that, the explanation of the spontaneous generation of invading organisms was abandoned and started to defend that the microorganisms were transmitted from individual to individual, which imposed measures of isolation, vaccination and use of antibiotics.

It was in this second era that the Spanish flu pandemic took place at the beginning of the 20th century. Although the Germ Theory was simplistic about some pathologies,

> Whatever the causes, the great scourges of communicable disease did come under control in the developed countries. Once the major infectious agents seemed all to have been identified and communicable disease no longer overwhelmed all other mortal disorders, the force of the germ theory paradigma faded. With notable exceptions such as Rene Dubos, few anticipated the recrudescence of communicable disease or new global epidemics (SUSSER; SUSSER, 1996a, p. 670).

This relative control over infectious agents took epidemiology to the third era, the era of chronic diseases[3], whose paradigm is called by Susser and Susser (1996a) "black box", which intends to address the risk factors that influence the onset of diseases. As a result, the environment has returned to the focus of an intervening or pathogenic factor. The control of diseases required the control of social factors (sedentarism, quality of food, etc.) and environmental factors (pollution, exposure to chemical agents, passive smoking, etc.).

The current epidemiological era, described as emergent by Susser and Susser as early as 1990, is the era of eco-epidemiology, which has the "Chinese box" as a paradigm, as it would involve various levels of organization (molecular, social and individual) to sustain the orientation of the epidemiology for public health.

Chinese boxes are boxes of different sizes that nestle, each embedding in the next larger box. Thus, figuratively, they provide an illustration for situations, where resources and concepts are arranged in levels.

Epidemiological guidelines cover different levels of organization, which consider not only physical factors, but also relational factors, especially when interacting with the environment. Even because, "[a] fully adequate causal model for public health must explain the disease at the ecological level as well as at lesser and more refined levels of organization" (SUSSER; SUSSER, 1996b, p. 675).

Another important difference between the era of eco-epidemiology in relation to the previous ones comes in the wake of the philosophy of contemporary science: the critique of universalism. However, the central idea will be to combine it with ecologism, since it cares about the spatial location and the interactions between the levels of organization, with emphasis on the social and molecular levels.

In the words of Susser and Susser (1996b, p. 674):

> The practical implication of a localizing ecological paradigm for the design of epidemiological research is that an exclusive focus on risk factors at the individual level within populations – even given the largest numbers – will not serve. We need to be equally concerned with causal pathways at the societal level and with pathogenesis and causality at the molecular level.

3 In Brazil, the public health system entered the third era of epidemiology only in 1992, with new guidelines from the National Center of Epidemiology – Cenepi. In 2002, at Funasa (National Health Foundation), Sidant – National System for the Surveillance of Noncommunicable Diseases and Grievances was created. Brazilian epidemiology, as a public policy, started to combine two systems, one of infectious diseases and the other of chronic diseases (TEIXEIRA; COSTA, 2012).

Epidemiology, like other Biological Sciences, in its causal searches, observes specific facts to extract generalizing concepts from them. However, human reality is not limited to Biology and this is where the failure is most evident, because the influence of other factors is neglected. For this reason, Susser and Susser (1996b) affirm that universalization will be safer the smaller the observed phenomenon.

Once again, we turn to the Chinese boxes. At a first level, as at the molecular level, the repetition of the observable pattern most certainly leads to a universalizing result. However, the authors point out:

> But above the level of molecules, no biological entity can conform entirely to universal laws because of the overarching contexts and the interactions between levels within a biological structure. And the banal fact is that each society is influenced by its economic, political, and cultural circumstances as well as by its mix of peoples, climate, and topography. What is most universal is least biological and, most of all, least human (SUSSER; SUSSER, 1996b, p. 674).

For this reason, the proposed new paradigm would address the relationships within and between levels of organization, combining determinants and results in an ecological procedure.

Thus, the pathogenesis cannot be explained by a single factor, but by a set of factors. Likewise, contamination, diffusion, evolution and prophylaxis also permeate these various organizational levels, with the imposition of broad contextualization, without the segmentation common to the sciences.

Therefore, the new biomedical techniques behave in an interdisciplinary way, using molecular, genetic and behavioral studies.

Applying the knowledge of Susser and Susser (1996b) to the COVID-19 pandemic, it can be seen that the examination of causes, diagnosis, prophylaxis and prognosis must go through several levels of analysis. At the molecular level, the means and transmission window of the coronavirus are determined in order to minimize its continuity. At the genetic level, the existing strains of SARS-CoV-2 and their proximity to other syndromes are determined, which is important in the treatment and vaccine development process. At the social level, biosafety behaviors are encouraged in commercial establishments, workplaces and transportations. At the population level, the population risk factors that lead to the most severe conditions are analyzed, as is the case of the age group. At the global level, the connections between different societies are assessed in order to understand the likely contamination trail, the virus's propagation mechanisms, as well as its variability in strains.

Finally, the pathogenesis of COVID-19 cannot be limited to the factor of genetic variation of a coronavirus strain, as such a mutation would not find a place without human intervention, which created new environmental conditions for that. Similarly, the spread of the disease is not explained simply by the pathogenicity of SARS-CoV-2, but by human behavioral aspects.

Hence the need to return the methodology of complex thinking to epidemiology, as Edgar Morin (2003) would say. Complex thinking requires that the diverse knowledge collaborate in a common knowledge project, but also that the way of organizing thought permeates all disciplines in order to give unity to them.

> It is necessary to replace a thought that isolates and separates with a thought that distinguishes and unites. It is necessary to replace a disjunctive and reducing thought with a complex thought, in the original sense of the term complexus: what is woven together.
>
> In fact, the reform of thought would not start from scratch. It has its antecedents in the culture of humanities, literature and philosophy, and is prepared in the sciences (MORIN, 2003, p. 89).

Therefore, the complex encompasses several dimensions and realities, but not as a sum, but as a functional unit that is born from the interactions between all these dimensions and realities. Specifically in the theme of infectious diseases, it is essential to consider the principle of self-eco-organization, which "is specifically valid, obviously, for humans – who develop their autonomy depending on their culture – and for societies – who develop depending on its geological environment" (MORIN, 2003, p. 95).

3 BIOETHICS AND NEW GENERAL PRINCIPLES OF BIOSAFETY

On one hand, it can be said that the complex thinking of Morin (2003) is closely related to the ecologism of Susser and Susser (1996b), because this presupposes the interrelation methodology between the different levels of organization. On another hand, bioethics intrinsically presents complex thinking[4] and, therefore, it becomes fundamental for epidemiology.

4 Such a statement is in line with the need to extend the problems of reflection on life beyond scientists. Along these lines, Morin also states, "The problem of science goes beyond scientists. Clemenceau said that 'war is too serious to be left in the hands of the military'. Science is too serious to be left to scientists alone. We also know that science has become too dangerous to be left in the hands of statesmen. In other words, science has also become a civic problem, a citizen's problem" (MORIN, 2007, p. 78).

Furthermore, the dual function of bioethics – reflective and pragmatic – has a lot to contribute to equalizing the problem.

As an instance of reflection, bioethics behaves philosophically, that is, in a critical and dialogical way. For this reason, it can be said that it is "a democratic field of dialogue, in which a shared transdisciplinary knowledge is reflexively built on the issues that involve life in all its manifestations, both in a singular and systemic perspective". (NAVES; REIS, 2019, p. 16).

And as a pragmatic instance, bioethics assumes a deontological role, to guide behavior and decision making. Therefore, it will be from its reflective-pragmatic perspective, that contemporary epidemiology must be analyzed, so that the various organizational levels, within Chinese boxes, are explored.

In the case of the COVID-19 pandemic, multilevel analysis, as it turned out, goes through several important issues, and they commonly come up against bioethical dilemmas, such as patient selection, the social impact of isolation measures, the conflict between privacy and collective health etc.

However, in view of this article's purpose to analyze the influence of environmental aspects on the pathogenesis of some infectious diseases, especially COVID-19, the bioethical focus will be on the interaction of humans with other animals. What precautionary measures should be applied? Act in advance to prevent such contact between different species? Or allow contact under special measures?

It is reiterated that, currently, the main thesis to explain the emergence of SARS-CoV-2 at the Wuhan market, in China, is its mutation and the passage to new hosts.

The main characteristic of viruses is to replicate, inserting the genetic material into the host cell. In this process of replication, genetic mutations are common and are made randomly. Individuals of strains that are more prone to new invasions multiply and those of less favorable strains tend to disappear.

At the Wuhan market, animals that, in the wild, did not live together, were brought together. And there, animals lived in a stressful situation, with blood and fluids falling from cage to cage. Undoubtedly, there was a favorable environment for virus mutations. It is speculated that, replicating numerous times, the coronavirus of a specific wild host, went through several mutations, until one of them was able to infect a new host species, and so on, until reaching the human being (WHO, 2021).

In this specific case of COVID-19, the contact between animals took place through deliberate human intervention. However, the emergence of the new pandemic agent and interspecies contact will not always come directly from this voluntary action.

Interspecies contact may result from the suppression of a native forest for agriculture or livestock, causing the geographical displacement of a certain animal and leading to the necessary leap for a new genetic mutation in a pathogen to give rise to a new pandemic. Or, still, it can result from the melting caused by the global warming, which releases in the rivers and seas microorganisms dormant for centuries capable of migrating from host to host to the human being.

It is for this reason that, for years, scientists have already predicted a major pandemic and are now predicting the arrival of infectious waves. The warning had been launched, but the need to apply the bioethical precautionary principle had been ignored.

The precautionary principle was born out of bioethical concerns about the risk not yet measured and uncertain according to the current state of knowledge. Van Rensselaer Potter, considered one of the fathers of bioethics, in the work *Bioethics: Bridge to the Future*, published in 1971, reserves a chapter called "dangerous knowledge". By dangerous knowledge Potter was referring to the one who accumulated faster than the wisdom to manage it.

In Potter, you can already see the ideas of risk and unpredictability of the consequences, which is why he proposes that bioethics be a "bridge", capable of mediating the relations between Sciences and Humanities, and focused on environmental problems and health issues.

Still in the work *Bioethics: Bridge to the Future*, in chapter 5, entitled *Dangerous Knowledge: The Dilemma of Modern Science*, Potter (1971, p. 69) states:

> It will be argued that knowledge can become dangerous in the hands of specialists who lack a sufficiently broad background to envisage all of the implications of their work and that educated leaders should be trained in both sciences and humanities. All the implications cannot be foreseen in any case, and all plans must provide for revision.

Precaution went from a bioethical principle to a legal principle, imposing caution when dealing with conduct that brings uncertain and serious risks in the face of a situation.

Carlos María Romeo Casabona explains this appropriation of Law and reports the transformation that this implies:

> The precautionary principle involves changing the forecasting model (knowledge of risk and causal links) to that of risk uncertainty, incalculable damage and the possible causal link between one and the other, as regards the existence, in some of them, of an assumption generally supported by statistical calculations and probabilities. However, both models converge in the prevention of a feared damage, which is the common goal (ROMEO CASABONA, 2007, p. 34).

The incidence of the precautionary principle requires: (a) a context of scientific uncertainty, which prevents the identification and/or measurement of risks; and (b) the possibility that these uncertain risks cause serious damage, in the sense of their repercussion, control and reversibility.

It is at this point that new questions about biosafety should be raised, seeking to determine procedures that act in the prevention, elimination or reduction of risks to human health and the environment, as well as the maintenance of ecosystems' balance. Biosafety, with its pragmatism, is legitimized in bioethics.

Schramm (2010) stated that biosafety would be a new field of biotechnology, concerned with the safety of scientific procedures: "[…] bioethics analyzes the morality of biotechnologies and biosafety calculates and weighs the risks inherent in biotechnologies from the point of view of its safety" (SCHRAMM, 2010, p. 105).

Historically, biosafety originated from more localized concerns, especially in genetic research, but it has expanded its scope of work over time and now it faces a new challenge: the management of living beings, in view of interspecies contact and their "original" diseases.

That is why, at its origin, in 1975, at the Asilomar meetings in California, biosafety established guidelines for the safety of experiments with recombinant DNA. Although the term "biosafety" was not used at the time, it was Asilomar's document that launched the basic guidelines of biosafety in relation to genetic engineering, such as: (a) work with fastidious microorganisms, that is, "demanding" microorganisms in terms of survival and multiplication conditions, which would not survive outside the laboratory; (b) classify the experiments according to the required level of containment; (c) abort any experimentation with known carcinogens; and (d) not conducting experiments with genes that produce toxins or that determine antibiotic resistance (BERG et al., 1975).

Such guidelines, called by many as principles, were proposed for risk assessment in DNA research. It can be seen that they were directed to a specific segmentation of research, that is, they did not focus on all research involving living organisms, much less dealt with environmental interventions by humans or the monitoring of interspecies relationships.

In fact, the Asilomar meetings did not outline principles of biosafety, at least not as synthetic rules of action, which guide or impose conduct, in the same way as the principles of bioethics or the principles of Environmental Law. At most, it can be said that all these meetings stemmed, naturally and explicitly, from the principles of prevention and precaution. However, specific normative principles of biosafety have not been established.

The common use of the expression “principles of biosafety” was much more towards the affirmation of what it is *its starting point* than to express a *must-be* of the sciences towards biological risks. In fact, it is in this sense that Cardoso et al. (2005, p. 161) express themselves: “The basic principle of biosafety is risk control and risk management”.

The phrase demonstrates this frequent use of the term as a premise or objective of biosafety, but without the directive character that can guide decision-making and assist in the solution of concrete problems.

Although it looks at other international documents or state standards, there has not been a broader normative concern with biosafety until then. Few normative principles have been put forward by the specialized literature, as is the case of the containment principle, aimed at the management of infectious agents in the laboratory environment, and the principle of sealing to genetic engineering in human germ cells and human embryos.

The containment principle establishes the obligation to reduce the exposure of personnel and the immediate laboratory environment (primary containment) and the protection of the environment external to the laboratory (secondary containment).

The principle of sealing to genetic engineering in human germ cells and human embryos is a prohibitive norm, which aims to prevent genetic editing that can be passed directly to descendants.

Although these two principles effectively represent normative precepts, even if they are aimed at specific scientific experiments (infectious agents and use of genetic engineering), there were not many principles of biosafety established.

Thus, as a specification of the precautionary principle, widely accepted worldwide, it is proposed both the elaboration of new general principles and the re-reading of some existing precepts, but sparse and specific for facing certain biological risks, in order to raise them to guiding principles of biosafety, especially regarding the purpose of this article. They are:

a) **Step-by-step introduction principle**: this principle already exists as a guide for the introduction of genetically modified organisms. It is understood, however, that this precept must be elevated to a general principle of biosafety, including for organisms that have not undergone any genetic engineering procedure. Thus, even domesticated animals – such as goats, cattle, buffalo, horses – should be gradually introduced into new environments, considering the risks of the interspecies relationship. The Directive 2001/18/EC of the European Parliament and of the Council of the European Union, of March 12th, 2001, on the deliberate release into the environment of genetically modified organisms (GMOs), brought in its declaration 24:

> The introduction of GMOs into the environment should be carried out according to the 'step by step' principle. This means that the containment of GMOs is reduced and the scale of release increased gradually, step by step, but only if evaluation of the earlier steps in terms of protection of human health and the environment indicates that the next step can be taken (EUROPEAN UNION, 2001).

As a general principle of biosafety, "step-by-step introduction" must be understood not only as the gradual insertion of the organism, but also the realization of previous studies on the other living beings with which the new organism will have contact, as well as monitoring the genetic variability of its pathogens.

b) **Principle of sealing superfluous contacts between organisms**: the gathering of species from different habitats should be avoided, especially when referring to live specimens.

The Wuhan Market, as well as so many others scattered around the world, with live species trades is not expected to remain. The absolute containment of its pathogens is practically impossible, therefore, the confinement of different species of animals in the same place, especially those that do not usually live together, carries a great biological risk.

c) **Principle of ecotones' preservation**: legislation must provide special environmental protection to ecotones, which, as they are transitional ecosystems, are natural barriers of contact between species from different biomes.

This special protection can be done in several ways, such as by establishing permanent protection areas for ecotones, for the imposition of licenses and studies for enterprises that intend to establish themselves there and for the fiscal incentive for their maintenance and correct handling.

There is a real and urgent need to think, bioethically and globally, about biosafety applied to the eco-epidemiology of infectious agents.

FINAL CONSIDERATIONS

It is no longer possible to think of epidemiology unrelated to social and environmental factors. The urgency of complex thinking forced an approach through Chinese boxes, which demonstrate the integration of the organizational multilevel to think about a disease.

The search for the genesis of a pathology goes beyond molecular and genetic considerations. COVID-19 is a paradigmatic example of this approach, as it evokes approaches that integrate the environment, interspecies contact and human behavior.

Thus, the response to the pandemic is not only echoed in Medicine, but in bioethics, as a transdisciplinary reflection on human action on life, and on biosafety, not only to reduce the transmissibility of the disease, but mainly to act in a precautionary way. For this purpose, it is proposed to impose new general principles of biosafety, capable of dealing with new zoonotic pathogens.

The proposed principles act to avoid interspecies contact, which can stimulate the selection of new strains capable of migrating from a host species to humans.

The step-by-step introduction principle, which was already known in the application to GMOs, must be elevated to the general principle of biosafety, to achieve the introduction of organisms that have not undergone any genetic engineering procedure and to impose the lesson of previous studies on the other species with which the new organism will have contact, as well as monitoring the genetic variability of its pathogens.

The principle of sealing superfluous contacts between organisms prescribes that the gathering of species, especially those from different habitats, must be avoided.

Finally, regarding the principle of ecotones' preservation, which are transition areas of ecosystems, they must receive special environmental protection, as they act as natural barriers for contact between species of different biomes.

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