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Emerging and re-emerging human infectious diseases: A systematic review of the role of wild animals with a focus on public health impact

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ABSTRACT

Infectious diseases continue to impose unpredictable burdens on global health and economies, a subject that requires constant research and updates. In this sense, the objective of the present article was to review studies on the role of wild animals as reservoirs and/or dispersers of etiological agents of human infectious diseases in order to compile data on the main wild animals and etiological agents involved in zoonotic outbreaks. A systematic review was carried out using PRISMA guidelines, using the PubMed, Scopus and SciELO platforms as data banks. The descriptors used were “zoonosis”, “human infectious diseases” and “wild animals”. The results show that wild animals (mainly bats, birds and primates) play an important role in the dissemination of etiological agents (mainly viruses, as a new coronavirus called 2019 Novel Coronavirus) in extensive geographic regions. Moreover, these wild animal organisms can act as the site for essential biotic synergy among several pathogenic microorganisms, promoting a higher rate of adaptation, mutation and even genetic recombination, with consequent stimulation of new strains and subtypes, inducing new infectious agents with unknown virulent potential. In conclusion, the monitoring of these diseases and adequate preparation for possible epidemics and pandemics are fundamental conditions for the mitigation of their future impact. The zoonotic threat of these etiological agents and the impact on public health can be enormous as shown by the ongoing epidemic of 2019 novel coronavirus (2019-nCoV) infections.

KEYWORDS: Zoonosis; Epidemics; 2019-nCoV; Virology; Epidemiology

1. Introduction

Globally, there exists several ecosystems with rich biodiversity, which are gradually deteriorating due to an increase in anthropogenic activities[1]. The economic and technological advancement in agriculture & industrialization (directly and/or indirectly lead to an increase air and soil pollution), and population growth (incites unbridled urbanization of previously uninhabited natural areas), are a few determinant factors linked to the degradation of such environments. Correspondingly, these conditions encourage increased human-wildlife interactions, facilitating the dissemination of infectious & parasitic agents to new hosts & habitats, which consequently establishes new potentially harmful relationships, revamping the existent ecological niches in disease transmission cycles[1,2].

The emerging infectious diseases (EIDs) are those with an increased incidence in the past 20 years that could amplify in the near future. They can be caused by known etiological agents or newly identified strains of such; accounting for at least 12% of all

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human pathogens. Some examples are West Nile fever, influenza, Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and the current outbreak of viral pneumonia linked to a new coronavirus called 2019 Novel Coronavirus (2019-nCoV). There are reemerging infections as well, like tuberculosis, which can be drug resistant[1–3].

Wild animal EIDs, can be classified in three groups, based on these fundamental epizootiological criteria: EIDs associated with “overflow” of domestic animals to wildlife populations living in their proximity; EIDs directly related to human intervention, through translocation of either host or parasite; and EIDs without evident involvement of domestic animals or humans. This situation has two important biological implications. Firstly, many wild species are reservoirs of several pathogens that threaten the domestic animal and/or public health. Secondly, EIDs of wildlife represent a considerable menace to the preservation of global biodiversity[3].

Ebola, SARS, Nipah Virus Encephalitis (NiVE), and 2019-nCoV are some of the more prominent EIDs, originating from wildlife, presenting global epidemic risks, and generating, today, vast economic and social burdens to humanity[4]. Moreover, the transmission of these diseases to humans casts a significant burden on global health systems[5,6]. It is estimated that over a billion cases of zoonotic diseases occur annually. New emerging zoonoses are responsible for progressively encumbering health systems and global economies, particularly where populations are densely agglomerated, and hindering environmental resources[2].

Despite the insistence on controlling these pests, focus must primarily be on disease prevention, and health & environmental education interventions. There is also the need for thorough investigation of the zoonotic epidemiology in high-risk animal-human interfaces, in order to evaluate the prospective emergence of viral diseases and appropriate suitable prophylactic measures worldwide. The threat of a new human pandemic is probably more likely in high-risk interfaces, promoting the reemergence of former diseases. As for viral diseases, reliable data on the circumstances at the point of their dissemination does not exist for several viral species. Comprehensively, animal disease data is generally incomplete due to inaccurate surveillance of wild animals worldwide[5].

Characterizing the animals that act as reservoirs and, in general, surveying the antigenic variants of wild life origins, are extremely important. Furthermore, the environmental and anthropogenic risk factors that may influence the transmission of infectious diseases related to these animals must be determined, thereby increasing the efficacy of the designated prophylactic measures[7].

These infectious diseases continue to impose huge and unforeseeable burdens to the global health and economy. Thus, adequate surveillance of these diseases and preparation for potential epidemics and pandemics is fundamental to mitigate the impact of future outbreaks[8]. One of the challenges of controlling

the dissemination of etiological agents is precisely the copious diversity of the animal reservoirs, making it easier for these agents to perpetuate in several habitats[2]. Because of both the lack of data around this theme and its importance to public health, the present study aims to review studies on the role of wild animals as reservoirs or dispersers of etiological agents of human infectious diseases in order to compile data on the main wild animals and etiological agents involved in zoonotic outbreaks.

2. Materials and methods

2.1. Strategy to find and select the articles

To perform this study was used PRISMA guidelines. The PubMed, Scopus and SciELO databases were used to search articles, published up to April 2019, and premised on the wild animals acting as reservoirs of etiological agents of importance to public health. The search strategy was based on three components: (1) wild animals participating in the transmission or dispersion of etiological agents of human diseases; (2) zoonosis; (3) human infectious diseases which might have the participation of wild animals in their transmission cycle. The search filters were developed according to synonym dictionary of the MeSH terms (Medical Subject Headings) platform of the digital library PubMed/Medline (US National Library of Medicine National Institute of Health). After that, these descriptors were adapted to the Scopus and the SciELO (Scientific Electronic Library Online) platforms. The following descriptors and Boolean operators were used: “wild animals AND human infectious diseases”, “zoonosis AND human infectious diseases”, “zoonosis AND wild animals” and “animal reservoirs AND human infectious diseases”. Having then obtained an ample amount of data from these filters, there was a consensus reached as to which articles would meet the inclusion criteria. Neither language nor chronologic restrictions were applied when searching for the articles. The initial screening was carried out considering the title and abstract of all articles found. Duplicated studies were eliminated by contrasting authors, title, year and journal of publication. After this first selection, all potentially relevant studies were downloaded in their entirety to have their eligibility assessed.

2.2. Data extraction, exclusion, and inclusion criteria

The exclusion of the articles was based on well-defined criteria, as follows: (1) studies that discussed infectious diseases, but had no relation to wild animals, (2) zoonosis with no relation to wild life, and (3) studies with incomplete texts or secondary studies (such as editorials, editors’ letters, Master or Doctoral theses, book chapters, and articles whose complete text was unavailable). Reference lists of the selected articles were also examined to find potentially relevant

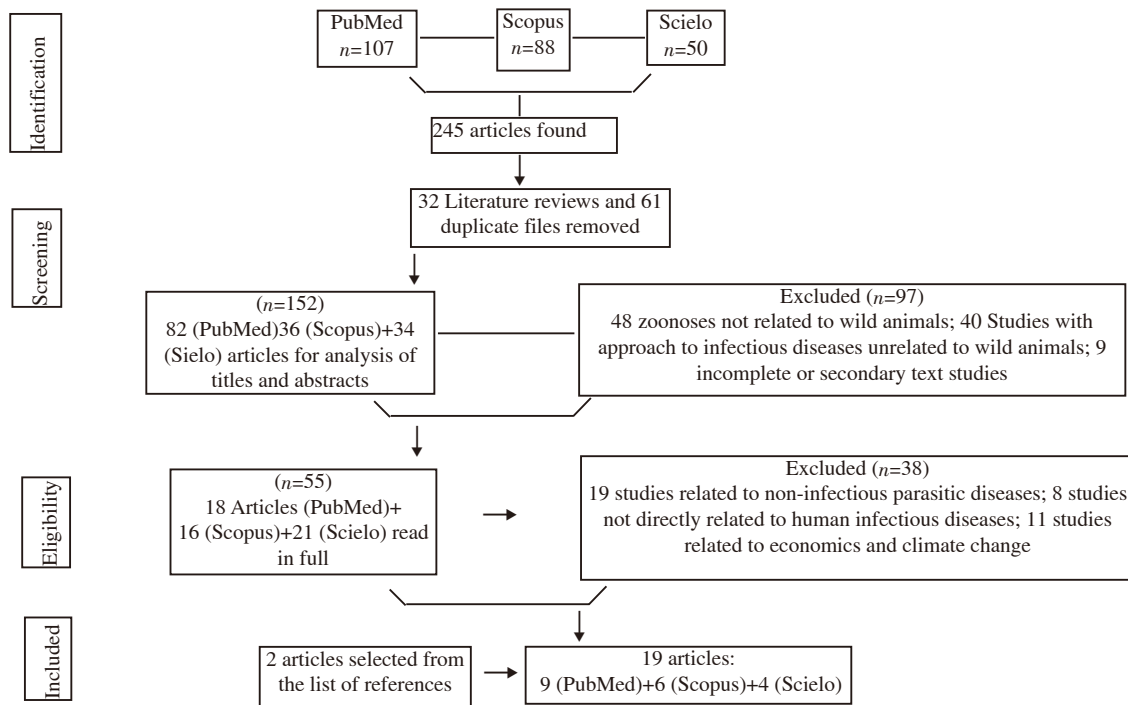


Figure 1. Flow diagram of review survey results, based on items from preferred reports for Systematic Reviews and Meta-Analyses: The PRISMA Statement.

documents. The criteria for including the articles were: (1) must be data analysis about zoonosis, and (2) must encompass in its study some relation between an infectious disease and wild animals in the transmission cycle of the etiological agent. Such criteria were defined with the goal of fulfilling the proposed objective: considering with greater depth the role of wild animals in the transmission cycle of human infectious diseases.

Qualitative data was extracted from all the selected articles. The data extraction was classified as follows: (1) characteristics of the publication: author, year, journal and country; (2) characteristics of the animal: species; (3) characteristics of the disease: viral, bacterial, parasitic, cases in humans; and (4) main results of the study.

3. Results

In total, 245 articles were found. After applying the inclusion and exclusion criteria of the present study, 19 articles were selected for the review[3,5,7–23], as shown by Figure 1. The description of the qualitative data extracted from the studies included in this review-characteristics of the publication: author, year, country, and main conclusion; kind of the wild animal; characteristics of the disease: species, and cases in humans - are shown in the Table 1.

The majority of zoonoses cited in the studies, with the aforementioned specific descriptors, had links to mammals ($n=16$). The types of mammals, more expressively, were bats and primates (Non-Human Primates[3,5,16,23], *Cercocebus atys*[12,15], *Pan troglodytes*[12,14,15], and *Gorilla gorilla*[14]), and, less expressively,

wild rodents[5], *Dromedary camels*[8], African buffalos[15], wild boars[18,22]. The second largest group of animals identified as reservoirs or dispersers of etiological agents of human infectious diseases were wild birds ($n=7$). There was one report of disease related to arthropods (ticks)[22] and another to amphibians (salamanders)[3].

Furthermore, research affirmed that the main etiological agents were viral ($n=16$), with the minority being bacteria ($n=2$)[17,22] and parasites ($n=1$)[23]. Among the etiological agents found included: Influenza Virus, Coronavirus, Nipah Virus, Ebola Virus, Paramyxovirus, Rhabdovirus, Hendra Virus, Menangle Virus, West Nile Virus, Bird Influenza, Filovirus, Human Immunodeficiency Virus (HIV), *Orthohantavirus/Hantavirus*, Human Type-4 Cells Lymphotropic Virus, Hepatitis E Virus, Leptospirosis, *Borrelia burgdorferi*, Marburg Virus, Rift Valley Fever Virus, Parvovirus, Arbovirus, and gastrointestinal parasites in general.

The data shows the epidemiological circumstances involved in the zoonotic overflow, amplification and dissemination of several etiologic agents (Figure 2), that can be transmitted directly to humans, without the need for wild animal reservoirs (Figure 2A). Nevertheless, in some cases, these wild animals function as reservoirs and dispersers of etiological agents (Figure 2B). As the microorganisms do not trigger symptomology in the wild animals, they remain long periods in nature, being dispersed expansively across geographical regions. This along with epidemiological surveillance failures can substantiate the reemergence of particular disease outbreaks in these areas[3,8,16,18] (Figure 2C). Another factor that promotes the emergence of new infectious diseases is

Table 1. Description of the qualitative data extracted from the studies included in this review: characteristics of the publication: author, year, and country; main conclusion; kind of the wild animal; characteristics of the disease: species, and cases in humans (all studies shows human cases).

Source/Year	Studies regions	Etiological agent	Wild animal	Further informations
[3]2018	World	Virus: Ebola and Marburg; HIV; Nipah; Hendra; Menangle; West Nile; Avian Influenza; Filovirus; Paramipovirus; Coronavirus type SARS and MERS type; <i>Hantavirus</i> ; <i>Borrelia burgdorferi</i>	Bats; Wild Birds; Amphibians; Salamanders; Chimpanzees	Emerging diseases are closely linked to wildlife, where animals are the major drivers.
[5]2015	World	Virus: Nipah; Ebola; Paramyxovirus; Rabdovirus	Bats; Wild Birds; Wild Rodents; Primates	The evolutionary selection of viruses capable of infecting a wide range of hosts has been a key hypothesis underlying the theory of the emergence of diseases.
[7]2015	Colombian	Anger virus	Bats	The rabies virus in wild-type hematophagous bats were facilitated by deforestation of the natural habitats of these species. Urban architecture style provides an artificial habitat that allows physical contact between species and the transmission of anger between them.
[8]2016	World	Virus : Ebola; Low and highly pathogenic avian influenza H7N9/HPAIVs of subtype H5Coronavirus MERS	Wild Birds; camel; Bats; Dromedaries.	Wild bird populations may represent a direct source of infection for domestic birds of the Avian Influenza virus. Vaccination of camels and dromedaries helps to prevent MERS.
[9]2017	World	Virus: Influenza A; Corona; Nipah; Ebola	Bats	While understanding the role of biodiversity is important in understanding disease risk, further research is needed on how to manage ecosystems to mitigate the emergence of diseases and outbreaks while ensuring other ecosystem functions and services.
[10]2017	African continent	Ebola Virus	Bats	Of vital importance are policy interventions on wildlife trade regulation and the need to conduct investment assessments and development projects in relation to the impacts of the disease environment.
[11]2013	World	Coronavirus; SARS	Bats	Bats infected by different viruses rarely present clinical symptoms of the disease. The pathogenesis and potential threat of bats transmitted viruses to humans and the impact on public health remain unknown.
[12]2012	World	Virus: HIV; Virus, Coronavirus SARS; Anger Avian influenza; Nipah; Hendra; <i>Hantavirus</i>	Chimpanzees; Bats	The dynamics that occur between the reservoir of the fauna and hosts generate new hypotheses about the viral evolution. This fact will help to address some unanswered questions in the study of viral zoonosis in wild animals and stimulate new research in this area.
[13]2012	South African	Ebola and Marburg viruses	Chimpanzees; Bats	The adoption of mobile technologies and appropriate surveillance approaches will improve the timely and complete capture of events that would otherwise have been lost using routine surveillance systems in the animal and human health sectors.
[14]2014	World	Human T-cell lymphotropic virus type 4 (HTLV-4)	Gorillas	The results confirm the importance of gorillas in the emergence and evolution of retroviruses and other human infections. In addition, it is believed that contact with gorillas is associated with the origin of human infections by the HIV-1.
[15]2014	World	Virus : Ebola; Rabies; Rift Valley Fever; H5N1, H5N2 Influenza	African buffalo; Monkeys; Wild ducks	Evidence suggests that wildlife should not be seen as a direct source of threat of pathogens, but as an indirect source of candidate pathogens. It is necessary to address human behavior and actions, which are the underlying cause of most emerging diseases.
[16]2001	African	Virus : Nipah; West Nile	Chimpanzees; Bats; Wild Dogs and Birds	As human environmental changes are largely responsible for their emergence, the threat posed to biodiversity and human health by zoonotic diseases reflects yet another consequence of anthropogenic influence on ecosystems.
[17]2013	Brazil	Rabies virus; Leptospirosis; Cinomose; Parvovirus	Wild and domestic Dogs	Dogs are potential predators and agents that disseminate fatal wildlife diseases to humans due to lack of adequate containment in rural properties coupled with inadequate vaccination.
[18]2016	Colombian	Influenza; Hepatitis E; Parvovirus; <i>Hantavirus</i>	Wild Birds and Pigs	The use of semiquantitative methods for the analysis of zoonosis in developing countries is rare due to the lack of epidemiological surveillance data. The control of diseases that affect human health by wild animals requires strategies that reduce the transmission of these pathogens.
[19]2012	Brazil	Anger virus	Bats	The presence of rabies virus in synanthropic populations of non-hematophagous bats poses a serious risk to human health and requires attention and control measures.
[20]2008	Colombian	Anger virus	Bats	The outbreak originated from wild bats and the human transmitter was a cat confirming this domestic species as a link between rabies from wild origin and the urban ecosystem.
[21]2001	Brazil	Arbovirus	Wild Birds	The migratory behavior of wild birds determines the introduction of the virus in other regions, considering the pathogenicity to the man and the confirmation of the circulation of this viral agent in urban area.
[22]2019	Italy	Hepatitis E virus	Wild boars	It was detected Hepatitis E virus in wild boars. Phylogenetic analysis suggesting the identification of a novel genotype 3 subtype. Further investigations at the wild/domestic species and human interface are therefore necessary to gain a deeper understanding of HEV dynamics.
[23]2019	Malaysia	<i>Ascaris</i> spp. and other 44 species of gastrointestinal parasites	Non-human primates	There were no great differences in parasite species among the wild, urban, and captive primate's populations. At least 33 species discovered in this study are of known public health importance and there is a potential to contaminate human.

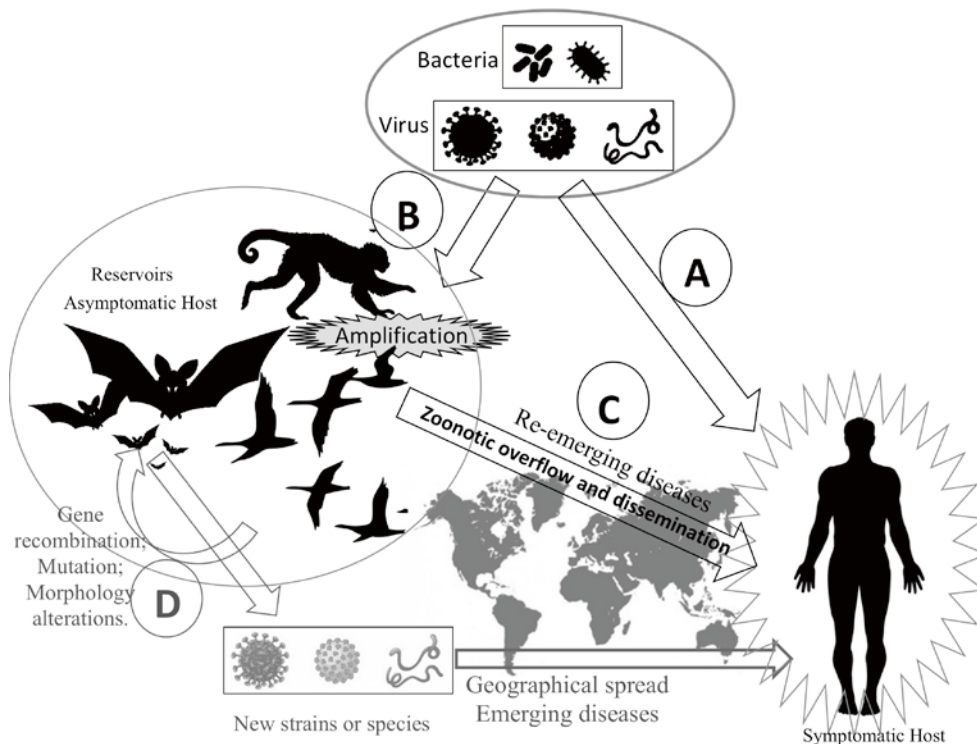


Figure 2. Role of wild animals on amplification and dissemination of etiological agents that cause human infectious diseases, and epidemiological circumstances involved in the zoonotic overflow, and biotic interactions that trigger the emergence of new etiological agents with potential impact to public health.

the perpetuation of the virus in accidental hosts. The maintenance of viruses inside the body of an unusual host may increase the possibility of error in the process of RNA duplication and emergence of mutation in a relative short period. This fact can trigger changes in virus morphology, creating new infectious agents with unknown virulent potential, using new adaptive strategies and resistance to vaccines, consequently increasing the transmission rate of the virus in vulnerable populations (Figure 2D).

4. Discussion

There is discontinuity in scientific knowledge about the real role of wild animals in times of outbreaks of human infectious diseases. All selected studies treated wild animals as reservoirs or geographic dispersers of etiological agents that caused cases of infectious diseases in humans. However, some etiological agents even today have unknown sources of contamination; as with the case of human infection by the MERS-CoV or 2019-nCoV. About MERS-CoV molecular investigation indicated that bats may contribute to its transmission amongst anthropoids. Nonetheless, the data on this association is still mitigated and rudimentary[25–27]. 2019-nCoV is one of the cases where there may have been gene recombination, a mutation triggering to morphological changes in the coronavirus that naturally infects wild animals, possibly snakes or bats, according to

recent research[6,28,30]. This shows that despite the ample literature on the role wildlife plays in the dissemination and transmission of human infectious disease, there's still no direct link correlating it with serious human diseases.

Recognizing the epidemiological circumstances involved in the zoonotic overflow, amplification and dissemination, is pertinent in prioritizing adequate surveillance and predictive techniques for the emergence of new pathologies with potential impact to public health[3,5,6]. Since most etiological agents of human infectious diseases do not develop symptoms in the disperser animals, how they act as reservoirs is not often researched and/or diagnosed appropriately[5,6]. Therefore, this knowledge gap should induce the convergence of research in this field for the purpose of training knowledgeable professionals, to aid in the orientation of appropriate preventive health practices, according to each etiological agent's distinct characteristic.

According to the analyzed data, the viruses present greater risk of becoming more perilous, considering they can coexist with several viral species within the same organism[28–33]. This increases the probability of these viruses undergoing recombination, culminating in wild-type strains with potential risk to the general public health[34,35]. For example, bats are described as hosts of arenaviruses, herpesviruses, lyssaviruses, paramyxoviruses and filoviruses[3,36–38]. As a single animal can be a reservoir of several types of virus, genetic material

exchange (by gene recombination) between them is plausible. Recombination is defined as the process of intermolecular exchange of genetic elements. From this can derive new strains, subtypes and even new virus species, generating diseases with unknown pathogenicity[34,35]. Prime examples are the Ebola, H1N1 Influenza and a new subtype of Hepatitis E virus described in wild boars[22].

Several viral agents, discussed in this review, were involved in important outbreaks emphasizing the importance of the etiological agents of emerging and re-emerging diseases, on public health, in the global sanitary context. For example, 2014 Ebola virus outbreak was conspicuous. It circulated through many African nations, provoking 21 759 cases with over 8 600 deaths[29]. In China, the current 2020 outbreak of viral pneumonia linked to a new coronavirus 2019-nCoV, that originated there in December 2019[6]. Its persistence can be associated with gene recombination, the mutation triggering distinct morphological changes in the coronavirus that naturally infects wild animals, even snake or bats, according to recent researches[28,30]. Areas where there are agglomerations of animal species coexisting, under high stress conditions, as in the Chinese wet markets, have already been responsible for infectious diseases epidemics in China and Southeast Asia, including the virus responsible for SARS, which killed almost 800 people worldwide in 2003[1,36]. This environment can be a catalyst for immune systems disorders within these animals, being a favorable circumstance for inconspicuous viral recombination and mutations, which then generates etiologic agents with unknown pathogenicity, triggering catastrophes to global public health. The sanitary authorities might have implemented researching the origins of the outbreak and its relation to wild animal reservoirs, had there been more supporting studies on the dissemination of such diseases[39–41].

In regards to Brazil, one should allude to the reported cases of the *Hantavirus* infections in the frontier regions, which revealed the probable existence and distribution of the disease reservoir in that region. Population growth, unbridled and unplanned urbanization with social exclusion and invasion of previously uninhabited natural areas, are anthropogenic activities that result in destabilization of varying ecosystems, and facilitate the approximation/exposure of humans to exotic pathologic agents[31,42–44].

The infectious diseases whose microbial transmission benefits from diverse environmental factors, through adapting & building resistance, usually attack humans after they have established themselves in these ecosystems[32,45,46]. The origins of this kind of transmission are influenced by ecological components, such as climatic variations, fauna and flora[31,47–52]. Thus, one has to confront the capricious efficacy of prophylactic strategies, since they are required to complement the dynamic pace of the mechanisms involved in the human-health-environment equilibrium[48]. When considering the prevention of epidemics and pandemics, keeping blockades in ports, airports and roads are of little to no effect without the constant surveillance of viral, bacterial, fungal and parasitic

loads from migrant birds and wild animals that might traverse from affected to unaffected areas[49–52].

There are considerable difficulties in controlling the dissemination of etiological agents, because they become increasingly diversified as anthropogenic biomes develop; in such context, many species of birds and mammals notably emerge to the forefront[2,47,50]. The fragmented context of knowledge has been challenged, and the integration of varying expertise has become fundamental to maintaining the balance among vital processes in changing environments[48,50–53]. Understanding that human health and animal health is a single entity (“One Health”)[8,10,37,46,48,53], promotes incentives for research on animals that will fill gaps in the science that directly affects global sectors, as described in this review.

There is a huge gap in the scientific knowledge on the actual role of wild animals in human infectious diseases outbreaks. There are many challenges to identifying which wild animals are reservoirs to specific etiological agents. Another challenge is determining the possible biotic interactions that trigger the emergence of new efficient subtypes and/or strains.

It was identified that viruses are the main etiological agents involved in this process and the principal wild animals are birds and mammals, due to their genetic proximity to humans, although these agents do not trigger symptomatology in these animals, nonetheless, there is insignificant research and diagnostic data.

Surveys need to be constant and perennial. Only then, will the predictability of complex biotic relationships between these distinct pathogens and their wild animal reservoirs be more analogous. This lack of adequate research leads to failure in Eco-epidemiological control strategies of the diseases, allowing for greater occurrence throughout major geographical zones, and the development of new diseases with a detrimental impact to public health.

Conflict of interest statement

We declare that we have no conflict of interest.

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Authors' contributions

MCC and RSB conceived of the presented idea and supervised the findings of this work. MCC, MDR, NAJM and LMC developed the

theory, performed the data collection, and wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

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