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Live animal markets: Identifying the origins of emerging infectious diseases
Jorge Galindo-González

Abstract
Emerging infectious diseases (EIDs) of zoonotic origin appear, affect a population and can spread rapidly. At the beginning of 2020, the World Health Organization pronounced an emergency public health advisory because of the SARS-CoV-2 coronavirus outbreak, and declared that COVID-19 had reached the level of a pandemic, rapidly spreading around the world. In order to identify one of the origins of EIDs, and propose some control alternatives, an extensive review was conducted of the available literature. The problem can originate in live animal markets, where animal species of all kinds, from different origins, ecosystems, and taxonomic groups are caged and crowded together, sharing the same unsanitary and unnatural space, food, water, and also the ecto- and endoparasitic vectors of disease. They defecate on each other, leading to the exchange of pathogenic and parasitic microorganisms, forcing interactions among species that should never happen. This is the ideal scenario for causing zoonoses and outbreaks of EIDs. We must start by stopping the illegal collection and sale of wild animals in markets. The destruction of ecosystems and forests also promote zoonoses and outbreaks of EIDs. Science and knowledge should be the basis of the decisions and policies for the development of management strategies. Wildlife belongs in its natural habitat, which must be defended, conserved, and restored at all costs.

Introduction
An emerging infectious disease (EID) is one that appears and affects a population for the first time or that has existed previously, but that is spreading rapidly, whether in the number of people infected or new geographic areas affected. Many EIDs are zoonotic in origin, meaning that the disease arose in an animal and crossed the species barrier to infect humans [1]. In January 2020, the World Health Organization declared a Public Health Emergency of International Concern [2] because of the outbreak of what would be known as the SARS-CoV-2 coronavirus that causes COVID-19 disease, which would quickly reach pandemic proportions. By the end of March 2021, worldwide more than 126 million people had been infected and more than 2.77 million had died [3], putting the world’s economy at risk.

Viruses, bacteria, fungi, protozoa, and other microorganisms have been present throughout the history of the planet, and life on Earth is so dependent on them that without them, life would collapse [4]. There are still so many species of microorganisms to discover; by looking for them, more will be found. Estimating the number of species that inhabit Earth is a complex task. In spite of 250 years of research and taxonomic classification, and with more than 1.24 million species catalogued and classified, approximately 86% of extant terrestrial species and 91% of the marine species have yet to be described. There are an estimated 8.75 million (±1.3 million SE) species worldwide, of which only 1.24 million are described [5].

If viruses are added to this list, the number becomes incomprehensibly large. By way of example, on an average there are around 10 million viruses and a million bacteria in a single liter of sea- or freshwater [6,7], so, if they are looked for, they will be found. This has been the purpose of some researchers who have dedicated themselves to searching for viruses in wild species of animals with the aim of raising alarm about the risk of possible epidemiological outbreaks [8–11]. Only 6590 different viruses have been described (International Committee on Taxonomy of Viruses ICTV [12]), yet there are an estimated 10^{31} virus particles on the planet [6,13]. These data give us an idea of the immense diversity and abundance of microorganisms that exist in nature. Wherever viruses and bacteria are sought, new species will be found. Viruses have always been present...
Table 1

Most important historic pandemic events occurred worldwide in the history of humanity including SARS and MERS coronavirus. Showing infectious diseases caused by different microorganisms that have caused great human losses.

| Date       | Disease           | Infectious disease | Microorganism                          | Deaths         | Location                                                                 |
|------------|-------------------|--------------------|-----------------------------------------|----------------|--------------------------------------------------------------------------|
| 165–180    | Plague of Athens  | Smallpox or Measles| Variola major, V. minor Morvillivirus sp.| 5–10 million   | Roman Empire                                                             |
| 541–750    | Plague of Justinian| Bubonic plague     | Yersinia pestis                         | 25–100 million | Egypt, Constantinople, Europe, West Asia                                  |
| 1346–1353  | Black Death       | Bubonic plague     | Yersinia pestis                         | 75–200 million | Worldwide                                                                |
| 19th century| Black Death       | Bubonic plague     | Yersinia pestis                         | 10–20 million  | China, India                                                              |
| 1518–1520  | Smallpox          | Smallpox           | Variola major, V. minor                 | 5–8 million    | Dominican Republic, Haiti, Mexico                                       |
| 1545–1548  | Cocoliztli        | Cocoliztli         | Possibly Salmonella enterica            | 5–15 million   | Mexico                                                                   |
| 17–18th century| Smallpox       | Smallpox           | Variola major, V. minor                 | 90% Native Americans | North America                                      |
| 1816–1993  | Several phases    | Cholera            | Vibrio cholera                          | ±2–3 million   | India, China, Asia, Europe, Russia, America, Worldwide                  |
| 1889–1890  | Russia flu        | Influenza A        | Virus H3N8                              | 1 million      | Uzbekistan, North America                                                |
| 1918–1920  | Spanish flu       | Influenza A        | Virus H1N1                              | 20–100 million | Worldwide                                                                |
| 1918–1922  | Russia typhus     | Typhus             | Bacteria Rickettsia prowazekii          | 2–3 million    | Russia                                                                   |
| 1957–1958  | Asian flu         | Influenza A        | Virus H2N2                              | 2–4 million    | China, Worldwide                                                          |
| 1968–1970  | Hong Kong flu     | Influenza A        | Virus H3N2                              | 1–4 million    | Hong Kong, Worldwide                                                      |
| 2009       | H1N1              | Influenza A        | Virus H1N1                              | 575 thousand   | Asia, Africa, Worldwide                                                   |
| 1976–present| HIV/AIDS          | HIV/AIDS           | Virus                                   | 37.9 million + | Worldwide                                                                |
| 2002–2004  | SARS              | SARS-CoV           | Coronavirus                             | 774            | Southeast Asia, Egypt                                                    |
| 2012–present| MERS              | MERS-CoV           | Coronavirus                             | 941+           | Worldwide                                                                |
| 2019–present| COVID-19          | SARS-CoV-2         | Coronavirus                             | 4.5 million +  | Worldwide                                                                |
alongside all of the species of plants, animals, fungi, and bacteria. Humans are all full of viruses and bacteria, most of them beneficial, with which they interact continuously without realizing it. There are 219 species of viruses recognized by the ICTV that infect humans, and new species of human viruses continue to be identified at a rate of three or four per year [14]. Diseases caused by different microorganisms have been present in the history of humanity causing great losses (Table 1). Predicting future outbreaks of zoonotic diseases continues to be a significant scientific task, but the true challenge is prevention. In addition, what is crucial is identifying what is being done to promote the outbreak of new diseases.

The live animal markets, also known as wet markets, provide a source of vertebrate and invertebrate animals (aquatic and terrestrial) for clientele in the tropical and subtropical regions of the world, which are widespread in Asian and African countries and in countries where they have migrated. Mammals of all kinds, live poultry, reptiles, and fish are sold, and they are usually close to markets that sell fish, red meat, or prepared food. Live animal markets have been identified as a source of zoonoses [15–23].

The aim of this review is to point out that live animal markets are an important source of origin and transmission of EID due to forced interactions among species that should never happen, and to propose some alternatives for its control. To find out, an extensive review was carried out of the available literature through Clarivate and Google Scholar since it includes studies that are not indexed by ISI or Scopus. Search was performed from August to December 2020; search terms were as follows: “SARS-CoV-2,” “COVID-19,” “bats,” “coronavirus,” “wet markets,” “zoonosis.” Search was limited to these terms to appear only in the title of the article, but without limiting the year of publication, author or region, paying special attention to the most recent publications. Purely medical and health articles were left out. In addition, a secondary search was made by reviewing the reference section of each article, looking for new references.

The ecology of zoonotic jumps
From their origin, all of the species on Earth—plants, animals including humans, fungi, bacteria, etc.—are exposed to an exuberance of micro-organisms and pathogens, with which they have interacted and evolved for hundreds of millions of years. Just like other species, microorganisms (the causes of diseases and infections) are subject to the same ecological and evolutionary pressures and interactions with other organisms; they are in constant change, adapting to their environment and most definitely, to their hosts [24–27]. The conceptual framework of epidemiological theory is well developed for evaluating the introduction and contagion of an EID in a host population. To understand the jump of a pathogen between species, the following conditions must be met: a) the new host species must be exposed to the pathogen; b) the pathogen needs the ability to infect the new host, that is, the pathogen and the host have to be compatible; and for the jump to be successful; c) The pathogen should be sufficiently transmittable among the individuals of the new host population in order to successfully invade the new host population [24,28,29], understanding that the pathogen must have a low degree of lethality or cause a slow death, otherwise infected individuals in the new host population will die before the pathogen has had the opportunity to reproduce and spread. Pathogens that prevail are those characterized by low lethality.

Pathogens are generally well adapted to their hosts. They are quite specific. For example, the viral diseases myxomatosis in rabbits or the canine parvovirus cannot be transmitted to humans. The jumps or outbreaks of zoonotic diseases from wild animals to humans only rarely occur naturally; they are strongly affected by anthropogenic changes in the environment [25,29,30] and in most cases there is an intermediate species, such as domesticated animals, prior to the infection of humans [31–33].

More than 77% of EID exhibit the dilution effect, which holds that increased species diversity could reduce disease risk by regulating the abundance of an important host species [25,34]; in other words, any disturbance that reduces the diversity of species in an ecosystem will have important effects by increasing the chances of disease outbreaks. In a natural, pristine ecosystem with its great abundance and diversity, there are pathogens present in their hosts but at low densities and there are no epidemic outbreaks. An ecosystem with a high degree of species richness: a) reduces the rate of encounter between susceptible and infectious individuals; b) reduces the probability of transmission given an encounter; c) decreases the density of susceptible individuals; d) increases recovery rate; and e) increases the death rate of infected individuals [25]. Large-scale human actions such as deforestation, changes in land use for agriculture and animal husbandry, illegal hunting and trade in wild species all simplify ecosystems, leading to a drastic decrease in the number of species and shrinking interaction networks among species. Survivors tend to be generalist and opportunistic species, whose abundance increases significantly along with that of their pathogens. They take advantage of the lack of competition and predators, and the abundance of resources, thus altering the host—pathogen equilibrium [35–37].
induced scenario, the rate of encounter between humans (or their domesticated species) and the pathogens of opportunistic species increases the probability of pathogen transmission [11,25,33–36]. With this, comes the appearance of unknown diseases. Moreover, changes in natural conditions often drive genetic evolution, such as genetic reassortment and recombination, possibly resulting in the transition of microbes from nonpathogenic to pathogenic, from low virulence to high virulence, thus causing emergence of zoonotic diseases [23,27].

**Coronavirus**

Coronaviruses (CoVs) have been identified in species of birds and in several mammals, including bats, rodents, camels, cows, pigs, dogs, palm civets (*Paguma larvata*), raccoon dogs (*Nyctereutes procyonoides*), and pangolins among others [11,15,38–40]. Previously, CoVs were considered pathogens that only caused mild illnesses such as seasonal flu, until the appearance of Severe Acute Respiratory Syndrome (SARS-CoV) at the end of 2002. So far, more than three hundred types of coronavirus have been described, but only seven species are known to cause illness in humans (HCoV), four of which (HCoV 229E, OC43, NL63, and HKU1) are the viruses that cause the mild symptoms of the common cold. However, the other three coronaviruses can cause serious diseases: the aforementioned SARS-CoV; MERS-CoV, the coronavirus responsible for Middle East Respiratory Syndrome that broke out in 2012, and SARS-CoV-2, which is responsible for the current pandemic [10,38,41]. The majority (60.3%) of EID outbreaks are caused by zoonotic pathogens and of these 71.8% were caused by pathogens from wildlife. We must be aware that viruses such as influenza and coronaviruses are RNA viruses, recognized for their great propensity to vary because of frequent replication errors due to mutation, deletion, rearrangement, and recombination [16,24,26,27,41], providing them with enormous possibilities for adaptation and evolution. Examples are the appearance of the Nipah virus in Perak, Malaysia; SARS-CoV in the province of Guangdong, China; and the emergence of many influenza viruses [11,16,32,33]. So, the manipulation and management of wildlife species must be severely regulated through international legislations, with strong sanctions for those who do not comply with them, in order to prevent potential public health threats.

**So, what about bats?**

Bats are very abundant, with a worldwide distribution. They are found in just about every terrestrial ecosystem, with the exception of the Arctic and Antarctic and some remote islands. Each species has its geographic niche and bats are the most diverse and abundant group of mammals in the tropics. Globally, they are the mammals with the second highest number of species after rodents [42–44]. More than 1400 species of bats have been identified worldwide [45]. Bats have developed an incredible diversity of behavioral, refuge, and feeding habits. They eat insects, scorpions and millipedes, fruit, nectar and pollen from flowers, and leaves; carnivorous bats eat mice, birds, lizards, small bats, frogs, and fish. The hematophagous bats feed on the blood of mammals and birds. It is precisely because of their abundance and diversity of habitats that they are essential for maintaining the dynamic equilibrium of ecosystems. In addition, by providing multiple services, they benefit humans by improving food supply, their well-being, the economy, and ecosystems [42–44,46].

With the recent emergence of SARS-CoV-2, bats have been erroneously mentioned and without evidence as possible carriers of these coronaviruses (SARS and MERS) and other similar viruses (swine acute diarrhea syndrome (SADS), transmissible gastroenteritis virus (TGEV) in pigs, and swine epidemic diarrhea (PED) [11]. Bats are reservoir hosts of several zoonotic viruses [17,47–51], including the Hendra and Nipah viruses, which have emerged in Australia and East Asia, respectively [52]. In spite of the natural viral load that bats carry, the viral zoonotic risk between taxonomic groups of birds and mammals was found to be homogeneous [39], meaning that bats do not represent a particularly greater risk than other groups of wild animals. The observed number of zoonosis per animal order increases as a function of its species richness [39]. To date, not a single bat has been found to be a carrier of SARS-CoV-2, nor for that matter has any other wild species; experimental data suggest that not all bat species may support SARS-CoV-2 replication [53].

Today, we can assert that an ancestral coronavirus (approximately between 40 and 70 years ago; [11,38]), was dispersed in different species, possibly in a bat, pangolin, or palm civet, and SARS-CoV-2 probably in some another mammal, hitherto unknown [10,33,40,52], only sharing a common ancestor. The lineage that gave rise to SARS-CoV-2 is not a recent recombinant; it has been circulating undetected for decades in bats, being transmitted to other hosts such as pangolins. This lineage at least not involving any of the bat or pangolin viruses sampled to date. Pangolins could be acting as intermediate hosts for bat viruses to get into humans [38,40,52].

In 2013, a coronavirus (sarbecovirus RtTG13) sampled from a horseshoe bat (*Rhinolophus affinis*) was reported in Yunnan province [38,51]. The virus, that so far, is the closest (at molecular level 96.2%) available bat virus to SARS-CoV-2; however, the sarbecovirus RtTG13 cannot enter human cells, as the virus membrane spike (S) protein’s receptor-binding are not compatible with human cell membrane receptors (ACE2) [11,17,53–55]. Bats in the genus *Rhinolophus* are natural reservoirs of SARS-like viruses, providing strong evidence that SARS-CoV is indeed a new zoonotic virus with a wildlife
origin [52]. To date, there is no evidence to show that SARS-CoV-2 has passed from a bat to a human, and even more so, although the RaTG13 coronavirus in bats shares 96.2% of its genetic material with SARS-CoV-2, does not come from the latter, nor does it come from the former. The existing diversity and dynamic process of recombination amongst lineages in the bat reservoir demonstrate how difficult it will be to identify viruses with potential to cause significant human outbreaks before they emerge [38]. Bats or any other species should not be blamed for the current pandemic [56].

However, preliminary data from experimental infection from different countries suggest that pigs can be infected with SARS-CoV-2 in its current form [57], as can ferrets [58], mink [59], catarrhine primates [60], cats, dogs, tigers, and lions [61]. At present, there is no evidence if these animals are capable of transmitting it to humans [62]. If at some point we find a wild species carrying SARS-CoV-2, we will hardly know if this is a natural reservoir host of the virus or just one more victim of the current pandemic, considering the hundreds of millions of people who have currently been infected with CoVid-19 in the world.

The problem
Humanity is currently concerned with the prediction of zoonotic disease events, and it has become a major scientific challenge. In response to the increasing frequency of EID events caused by animal-borne (zoonotic) pathogens, recent approaches evaluate biogeographic patterns and foci of infectious human diseases [11,15,40,50,63–65], there are also searches for new viruses to raise the alarm about potentially dangerous diseases [8,9,11], and searches among wild species to find the culprit of pandemics [10,33]. However, the most important and truly relevant thing is to find the origin of these breakouts, and not referring to identifying a certain species or group of animals, but rather what type of human activities or actions are favoring zoonotic jumps and infectious outbreaks in human populations. The propagation of EIDs has been attributed in large measure to the anthropogenic changes to the environment [25,29,35–37], although also to the appearance of live animal markets.

Live animal markets: The great mistake
Different species of wild animals interact freely in their natural environment, whether during prey—predator interactions, when competing for food, space or during intraspecific competition, as ectoparasite cleaners or simply interacting when using their environment’s resources. These species have interacted naturally for millennia, since they belong to the same ecosystem and biogeographic region. However, there are factors that are unique and are contributing to the origin of EIDs and the zoonoses that humans are so concerned about. The live animal markets [16,18–23,32]—in these type of markets, there is a dense concentration of a large number of species that under natural conditions would never encounter each other, and that have never in their evolutionary history interacted, simply because they do not share the same ecosystem. In the wholesale markets of Asia and other parts of the world, one can purchase the entire gamut of wild species, frozen, dead, or alive from all over the world: sea urchins, snakes, turtles, sea cucumbers, insects, bats, groundhogs, field rats, hedgehogs, civets, and a whole host of others that, in most cases, are poached and sold illegally [10,17,22,23,33,41]. Moreover, these animals are found alongside domesticated species such as ducks, chickens, dogs, cats, pigs, rabbits, etc., interacting with humans. Hundreds of mammals, birds, reptiles, amphibians, etc., come from a broad range of very diverse ecosystems and biogeographic regions: forests, deserts, wetlands, rivers, oceans, etc (Figure 1). These animals suddenly find themselves in unhealthy circumstances with overcrowding, in open cages piled one on top of the other, many of them injured and with open wounds, weak and under highly stressful conditions, eating together and defecating on each other, day after day. The worst part is that while sharing food, coming into contact with each other’s excreta and exchanging all kinds of fluids, as well as a diversity of ecto- and endoparasites, these animals all become vectors for hundreds of microorganisms, bacteria, and viruses now in close contact with humans. This creates the possibility of the latter invading a whole new range of hosts, that have different ecological dynamics, and across distinct functional groups that do not ever come into contact in nature.

These conditions are a prime breeding ground with enormous potential for giving rise to new interactions among all kinds of bacteria, viruses, fungi, and protozoa. These interactions develop and grow, promoting new relationships that should never occur, and under totally unnatural conditions that constantly test and refine the survival capacity and adaptability of all these microorganisms. In this scenario, the pathogens encounter numerous hosts with different traits that offer a plethora of possibilities for new colonization and transmission [41,66,67]. These markets are a time bomb, and have in the past exploded [15–23,68]. The result is zoonoses, diseases that are transmitted from one species to another: a microorganism from one species that is now able to infect another, including humans; an infectious agent, previously unknown to science but now identified that has the ability to cause public health problems at the local, regional, or global level [15,16,22,33,41,57,67,69,70]. Thus, pathogens can now move to an intermediate species, quite possibly caged, where they can mutate, recombine, and evolve, achieving the ability to infect domesticated species and humans (Figure 1). It is also important to consider unwanted peridomestic wildlife in markets, such as rodents, bats, dogs, cats, and birds, which are generally
neglected, and represent a source of potential infectious microorganisms [23]. This is the short story of what very possibly caused coronaviruses such as SARS, MERS, and possibly SARS-CoV-2 as well. It is also possible that a SARS-related coronaviruses evolved into SARS-CoV-2 in humans after spilling over from an animal source, followed by rapid transmission of this human-adapted strain [41,71]. Recently, SARS-CoV-2 has been detected in palm civets (P. larvata) and raccoon dogs (N. procyonoides) caged in Chinese markets [15,52], and farmed minks [59], probably by human-to-animal transmission of a disease or pathogen (Zooanthroponosis). HCoV and SARS-CoV-2 have also been found in human fecal samples [33]. Animal-to-animal transmission has also been demonstrated, ferrets (Mustela furo) and domestic cats (Felis domesticus) are susceptible to infection by SARS-CoV and that they can efficiently transmit the virus to previously uninfected animals that are housed with them [52]. Just one market breaking the rules, is enough to unleash a pandemic on the entire planet.

To the situation of these wet markets we can add another anthropogenic disasters that we have brought upon the environment that drastically reduce the biodiversity of ecosystems: human overpopulation; multiple, enormous cities with an endless generation of garbage and pollution; the formidable capacity of humans to travel and for global transport; deforestation and the fragmentation of forests; changes in land use; extensive animal husbandry and agriculture; hunting and removing wild animals from their habitats, and finally, climate change [72]. Human actions have brought about the current environmental and health crises.

Concluding remarks
It has been shown that live animals in markets are the potential intermediate host(s) of various viruses that increase the opportunity for transmission of infection to humans [8,10,15,18,20,23]. The existing diversity and dynamic process of recombination amongst virus lineages in the bat reservoir and other wild animals demonstrate how difficult it will be to identify viruses with potential to cause significant human outbreaks before they emerge [38]. Hence, the best we can do is leave wildlife where it belongs, in its natural habitat, and should be defend and conserved at all costs [35,36]. As
we have seen, it makes no sense to look for pathogens in wild species with zoonotic potential, as we will find them. What is clearly demonstrated is the great risk of new outbreaks of EIDs with the manipulation of wildlife and their overcrowding in markets.

We must strive to improve legislations related to live animal markets and the wildlife trade, and establish high sanitary standards. Laws should be used to prohibit the trade in wild animals, in order to prevent the outbreak of new viruses in the future [10,37]. While much attention is given to wildlife as being exotic species deliberately brought to markets, assessing the unwanted peri-domestic wildlife in markets, including rodents, bats, cats, dogs, and birds, is highly recommended [23].

Ecosystems and natural environments left must be preserved. Humanity need to try to recover as much of the area of disturbed ecosystems as possible and convert them into conserved ecosystems using massive programs for the restoration of ecosystems and forests reforestation. Society should pursue science that is based on objective and verifiable knowledge, to create a solid foundation for the decisions and policies that guide management strategies. We must considerably slow down the growth of the human population. People must ban all forms of local, national, and international illegal trade in wildlife [37], and elaborate massive programs of environmental education and information on not to manipulate wild fauna, and public awareness of the risk of wildlife overcrowding in markets, to prevent future zoonosis. Here, the efforts of international organizations like CITES (https://cites.org/eng/disc/what.php), WWF, and other organizations dedicated to the protection of wildlife in its native habitat are indispensable. The laws and regulations implemented to protect wildlife should be firm and clear [37], with international regulations and sanctions for countries that do not comply with international standards. In the words of Sir David Attenborough, “This is not about saving our planet, it’s about saving ourselves. If we take care of Nature, Nature will take care of us.”

Declaration of competing interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.coesh.2021.100310.
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