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COVID-19, from an emerging infectious disease to a global pandemic: How ecological, biological and epidemiological factors can influence the emergence of zoonotic pathogens

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Abstract

The emergence of an infectious disease in the human population and its ability to reach epidemic or pandemic proportions is the result of a complex interplay between globally distributed ecosystems, pathogens and their human or animal hosts. In this review, we present an overview of our current understanding of the different factors that can influence zoonotic transmission of animal pathogens to humans, with particular emphasis on those behind the current COVID-19 pandemic, as well as previous infectious disease outbreaks in humans. Understanding the interactions between these factors will be vital in predicting future pandemics. Increased awareness of our vulnerability to new infectious diseases at the ecological, biological and societal levels will allow us to question our relationship with the world that surrounds us, to prioritise changes in behaviour, infrastructure, and our environmental impact, and to improve our ability to control and prevent such outbreaks in the future.

Discipline : BIOLOGY

Keywords : ZONOSIS, EMERGING INFECTIOUS DISEASE, COVID-19, VULNERABILITY, ECOLOGY, ONE HEALTH

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the coronavirus disease 2019 (COVID-19) pandemic

Starting in late 2019 in Wuhan, in the Hubei Province of China, the world witnessed the emergence of a novel virus able to cause respiratory disease in humans (Zhou *et al.*, 2020; Zhu *et al.*, 2020). Following the investigation of initial clusters of patients presenting with pneumonia of unknown cause linked to a wholesale seafood market in the city, characterisation of patient samples through molecular biology techniques and subsequent isolation of the virus revealed the etiological agent to be an emergent coronavirus in the *Betacoronavirus* genus. This new virus was initially named “2019 novel coronavirus” or “2019-nCoV” and later changed to “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)”, by the Coronavirus Research Group of the International Committee for the Taxonomy of viruses, after analysis of the genetic makeup of the virus and its similarity to a previously known SARS coronavirus (SARS-CoV-1) that emerged in China in 2003 (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020).

It became rapidly apparent that the novel pathogen was capable of person-to-person transmission, with many cases subsequently reported in Wuhan in patients who had had no contact with the wholesale markets or animals. Indeed, epidemiologists from the Chinese Center for Disease Control and Prevention found that only around 1% of the patients had had direct contact with the live-animal market, whilst more than 75% were residents of Wuhan or had been in contact with people from there (Guan *et al.*, 2020). The situation rapidly escalated, with 79,394 laboratory-confirmed cases and 2,838 declared deaths in China by the end of February 2020, and the spread of the virus to more than 50 countries. With the continuing spread of the disease to more than 100 countries and an ever-increasing number of cases, a global

pandemic was declared by the WHO on the 11th of March 2020 (World Health Organization, 2020). As of 18th January 2022, the ongoing pandemic situation has seen more than 323 million confirmed cases worldwide and more than 5.5 million deaths, although globally the true number of deaths linked to the pandemic might be even double or quadruple this figure (Adam, 2022).

Infection with the virus causes a respiratory disease ranging from mild (low fever and mild fatigue, without pneumonia) to severe (severe pneumonia, severe respiratory failure, and multiple organ failure). Even from an early stage of the outbreak it was apparent that elderly patients, or those presenting with pre-existing chronic diseases including diabetes, hypertension, cardiovascular disease or obesity, were most vulnerable to severe disease and poor prognoses for clinical outcome. The symptoms associated with infection are consistent with isolation of the virus from airway epithelial cells from infected patients and the ability of the virus to replicate in cells of the upper or lower respiratory tract (Guan *et al.*, 2020). The ability of viruses to infect specific types of host cells or tissues is linked to their surface glycoproteins and the capacity of these proteins to interact with specific receptor proteins on the surface of target cells. For coronaviruses such as SARS-CoV-1 and -2, this cellular tropism is determined by the viral surface or spike protein that can bind to the angiotensin-converting enzyme 2 (ACE2) receptor found on the surface of many cell types in humans, particularly the bronchus and lung parenchyma as well as in the heart, kidneys and gastrointestinal tract. This tissue distribution is generally thought to be consistent with the pathology of COVID-19. For SARS-CoV-1, viral replication has also been observed in the kidneys and the small and large intestine of infected patients (Li *et al.*, 2003). The intrinsic ability of many animal coronaviruses to use such ubiquitous receptors for their entry essentially means that they already have a certain pre-adaption for zoonotic transmission from their natural hosts (Cui *et al.*, 2019).

SARS-CoV-2 and the origins of the human coronaviruses

SARS-CoV-2 is in fact one of seven coronaviruses known to cause disease in humans. Coronaviruses are single-stranded, unsegmented RNA viruses belonging to the subfamily *Coronavirinae* of the *Coronaviridae* family. The *Coronavirinae* subfamily can be further divided into four major genera according to antigenic (serotype) and genomic characteristics: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*, with the two former genera primarily infecting mammals. Indeed, of the identified coronaviruses causing respiratory and gastrointestinal tract infections in humans, HCoV-NL63 and HCoV-229E belong to the *Alphacoronavirus* genus, whilst HCoV-OC43, HCoVHKU1, the Middle East respiratory syndrome coronavirus (MERS-CoV), as well as the aforementioned SARS-CoV-1 and -2, belong to the *Betacoronavirus* genus. Four of these viruses are endemic in humans (HCoV-229E, -NL63, -OC43 and -HKU1) and considered as members of the “common cold” viruses that constitute a large share of all upper and lower respiratory tract infections in adults and children. All four of these viruses are of zoonotic origin, at some point jumping species to emerge in the human population. Genetic analyses suggest an origin for these viruses in major livestock species while earlier versions of these four viruses may have existed in bats and rodents. Indeed, HCoV-NL63 and -229E are thought to have originated from bat reservoirs, whilst HCoV-OC43 and -HKU1 are thought to have once been rodent-associated pathogens (reviewed in (Corman *et al.*, 2018)). Interestingly, for HCoV-OC43, a bovine coronavirus has been suggested to be a possible ancestor, from which this virus may have emerged in the context of the “Russian flu” pandemic at the end of the 19th century (Vijgen *et al.*, 2005). Two group 2 coronaviruses, human coronavirus OC43 (HCoVOC43). In the context of the current pandemic it is interesting to draw comparisons with this earlier outbreak, potentially also caused by a novel zoonotic coronavirus, and considered to be the first pandemic to occur in a highly connected world (Valleron *et al.*, 2010). The 1889

pandemic also spread rapidly, taking only 4 months to travel the planet, peaking in the United States only 70 days after the original peak in St. Petersburg, with a mortality rate differing between geographic regions, higher in southern than in northern Europe for example, and ranging from 0.1% to 0.28% (Valleron *et al.*, 2010). To clarify, an epidemic refers to an often sudden increase in the number of cases of a given disease above what is normally expected in a given population in a given area; a pandemic is an epidemic that has spread over several countries or continents, usually affecting a larger number of people (Akin and Gözel, 2020). In comparison, endemic refers to the constant presence and/or usual prevalence of a disease or infectious agent in a population within a geographic area. The 1889 pandemic killed an estimated 1 million people worldwide out of a global population of about 1.5 billion, and is thought to have persisted until 1895, at which point it is probable that enough people had immunity to the virus to reduce the number of susceptible hosts and therefore its spread.

Such examples remind us that emerging viruses are nothing new. Viruses such as influenza, measles and HIV have all previously “emerged” in the human population. Molecular studies suggest an expansion of human viruses with the arrival of agriculture around 12,000 years ago, a societal change that brought with it increased contact between humans and domesticated animal species including sheep and cattle, as well as an increase in the size of human settlements and contact and trade between such settlements, all factors facilitating the transmission of infectious diseases from animals to humans and thereafter within human populations. The measles virus for example, is estimated to have “jumped species” from cattle to humans sometime between the 6th and 12th centuries (Furuse *et al.*, 2010). The “full” emergence of this virus in humans and the supposed resulting epidemic was likely preceded by limited outbreaks involving a virus that had not yet fully acclimated to humans. Indeed, measles requires a susceptible population of more than 500,000 individuals to support an outbreak, a situation that occurred at the time of the growth of major settlements

in medieval Europe (Furuse *et al.*, 2010). In populations not previously exposed to the virus, the disease can be devastating - in 1529, a measles epidemic in Cuba killed two-thirds of the native population. Two years later, the same virus was responsible for the death of half of the population of Honduras, having already ravaged Mexico and Central America (McNeill, 1989). Other striking examples of viral emergence include the 1918 “Spanish” flu outbreak or the global HIV pandemic and the estimated 37 million people who have died since recognition of the disease in 1981, not to mention the more recent epidemics caused by the re-emerging Ebola virus in West and Central Africa (the 2014 outbreak caused over 11,000 deaths and a public health crisis in the region) (Morens and Fauci, 2020).

In this article we present an overview of the different ecological, biological and epidemiological factors or drivers that are thought to influence the emergence of zoonotic pathogens at each level, with particular emphasis on the factors behind the current COVID-19 pandemic, but also with examples from other viral disease outbreaks in humans. Indeed, many of these factors are far from being unique to the current situation and will likely continue to play roles in future cross-species outbreaks. A better understanding of the parameters that allow viruses to cross these species barriers to infect other animal species or humans will be essential in meeting the challenges of future emerging pathogens. Given the high prevalence, wide ranging distribution and large genetic diversity of pathogens with zoonotic potential and their host species and our ever-increasing encroachments into the habitats of potential animal host species, cross-species infections are likely to continue to occur periodically, if not more frequently. The ongoing pandemic has also made it acutely obvious that we are currently unable to predict if such “spillover” events will lead to sustained transmission in humans, and therefore the scale of such outbreaks.

The zoonotic potential of viruses

Phylogenetic analysis of the complete SARS-CoV-2 viral genome revealed that the virus was most closely related to a group of SARS-like coronaviruses that had previously been found in bats in China in 2018 (Hu *et al.*, 2018). Importantly, these viruses were seen to share around 90% of their genetic sequence with a related human/civet SARS-CoV virus responsible for the outbreak that occurred in 2003, resulting in nearly 8,000 cases of infection and 800 deaths worldwide (Feng *et al.*, 2009; Sallard *et al.*, 2021). Indeed, many bat CoV sequences have been identified in studies looking to understand the evolutionary relationship between bat viruses of this family and their natural host reservoirs in an effort not only to catalogue and understand the range of viruses circulating in wild-animal species such as bats, but also with the aim of better understanding if, how, and even when, such viruses might pose a risk for disease and spread in humans.

Even if the exact origins of SARS-CoV-2 are currently unknown (Guo *et al.*, 2020; Latinne *et al.*, 2020; Liu *et al.*, 2020; Sharun *et al.*, 2021; Xiao *et al.*, 2020) and even controversial (Burki, 2020; Maxmen and Mallapaty, 2021; Nie, 2020), studies of this nature, which should not be considered as “gain-of-function” research, are vital if we wish to be able to anticipate future zoonotic outbreaks. Such studies are being undertaken not only in China, but also notably in Europe with such previous research programs as “Preparedness, Prediction, and Prevention of Emerging Zoonotic Viruses with Pandemic Potential using Multidisciplinary Approaches” (PREDEMICS, 2011-2017)¹ and “ANTICIPating the Global Onset of Novel Epidemics” (ANTIGONE, 2011-2016)², not to mention ongoing international surveillance programs such as the Global Influenza Surveillance and Response System

1 - The PREDEMICS project (2011-2017) from European Commission is available at: *Preparedness, Prediction and Prevention of Emerging Zoonotic Viruses with Pandemic Potential using Multidisciplinary Approaches* [online]. [Accessed 25 March 2022]. Available at : <https://cordis.europa.eu/project/id/278433>

2 - The ANTIGONE project (2011-2016) from European Commission is available at: *ANTICIPating the Global Onset of Novel Epidemics* [online]. [Accessed 25 March 2022]. Available at : <https://cordis.europa.eu/project/id/278976>

(GISRS, 2014-2018)³ that rely on communication and data sharing between agencies worldwide. Such studies involve understanding the zoonotic potential of animal viruses, that is to say, the ability of a virus circulating in a non-human animal host species to effectively infect and multiply in a new host species such as humans, to sufficient levels to be able to cause symptoms, disease and the possibility of ongoing transmission within the new host species. At the ecological and biological levels, the zoonotic potential of a virus, or indeed any non-human infectious pathogen, is governed by the ability of the pathogen to overcome a series of barriers to transmission and infection, known as the species barriers. These barriers are commonly divided into interspecies, intrahuman and interhuman barriers (Figure 1). The interspecies barrier determines the nature and level of human exposure to zoonotic pathogens, whilst the intrinsic, intrahuman barrier determines the ability of a zoonotic pathogen to productively infect a human host and to survive a host immune response. Lastly, the interhuman or human-to-human barrier concerns the ability of a pathogen to be transmitted efficiently between humans and to establish the transmission chains that may then cause outbreaks, epidemics, or even pandemics (Gortazar *et al.*, 2014). A zoonotic virus that is able to cause disease in humans is thus already able to more or less effectively overcome one or more of these barriers (Figure 1). For a pathogen to be able to establish itself sustainably in humans through ongoing transmission chains, all three barriers must be effectively surpassed.

3 - The GISRS project (2014-2018) from European Centre for Disease Prevention and Control is available at: *Global influenza surveillance and virus sharing* [online]. [Accessed 25 March 2022]. Available at: <https://www.who.int/initiatives/global-influenza-surveillance-and-response-system>

Factors linked to the emergence of zoonotic viruses in humans and their spread

The interspecies barrier

The interspecies barrier, by its very nature, involves ecological processes that determine the dynamics of animal and human populations and the connections between them (Figure 1). The emergence of zoonotic pathogens in humans depends on the interactions between humans and the reservoirs of infected animals and/or vector hosts or their environment. In general terms, the probability of triggering a larger chain of transmission, or even an epidemic, depends on the extent to which human populations are exposed to a potentially pathogenic zoonotic agent. However, the simple act of sharing a geographical area with infected animals is clearly insufficient, because the number of cases of transmission triggering an epidemic is relatively rare, despite the fact that many people are in contact with wild animal species and despite the vast viral diversity found within these animal species.

This first category therefore encompasses the direct factors that favour or cause the emergence and/or increase in the frequency of zoonotic transmission. At one level, this is essentially the increase in the frequency of contacts between humans and wild animals, such as in connection with cultural practices, as in Wuhan, and more widely in China and in Asia, in wildlife and wet markets (Everard *et al.*, 2020; Haider *et al.*, 2020; Sabin *et al.*, 2020; Zhu and Zhu, 2020). One of the main factors favouring the transmission of viruses from animals to humans is through contact with wild animals for food but also with wild animals bred in captivity, such as for example, mink in China, The Netherlands, or Belgium, etc., or captured for trade (pangolins, etc.). It has been estimated that repeated contact is responsible for 70% of zoonoses (Jones *et al.*, 2008). Likewise, transmission of zoonotic viruses from bats or rodents to other intermediate animal species, such as primates, cattle, pigs or horses, before further transmission to humans is a common occurrence in outbreaks (Ebola viruses in

Africa, Nipah virus in Malaysia, numerous cases with swine flu, etc.). The emergence of COVID-19 is likely linked to the presence of such animals in markets, despite difficulties in obtaining sufficient and reliable information from the Chinese government (Mizumoto *et al.*, 2020). Even if the hypothesis of the pangolin as an intermediate host between bats and humans (Zhang *et al.*, 2020) is no longer privileged in the case of COVID-19 (Frutos *et al.*, 2020), the hunting of this wild animal, legally or illegally, is emblematic of human activity at this level favouring the appearance of zoonoses and epidemics. The idea that human activity, in the form of interaction with wildlife species and their pathogens in the interests of scientific research (potentially even including research into biological weapons) (Balali-Mood *et al.*, 2013; Nie, 2020) can also potentially produce and influence opportunities for zoonotic transmission events should probably also be mentioned here, especially given the context and discussions surrounding the current pandemic, as mentioned above.

Increased human exposure to animal pathogens may result from changes in the dynamics of any of these populations; either from, for example, increased contact between humans and the animal reservoir, or through population growth, increased human activity and/or by changes in the geographic area where this expansion includes overlapping habitats (Gortazar *et al.*, 2014). This may occur through the expansion and densification of human activities leading to poor ecosystem health, in particular intensive breeding and cultivation or deep-forest hunting. The increasingly extensive anthropisation of vast areas on the planet in the last half of the 20th century, particularly linked to intensive cultivation of land for human food or farm animals, is largely responsible for the intensification of encounters with wildlife. These activities cause the destruction or reduction of wild habitats and also their fragmentation, through deforestation, urbanisation or the occupation of ever larger areas around cities (Everard *et al.*, 2020). Road construction contributes to the fragmentation of wild habitats. Massive deforestation is linked to cultivation and intensive farming,

a large part of whose production is exported elsewhere (Karesh *et al.*, 2012). The continuing encroachment of humans into previously uninhabited areas continues to bring not only humans but potentially also domesticated animals, also vulnerable to infection with a zoonotic pathogen, into contact with potential reservoir species. Deforestation and climate change may also push some wild animal species to modify their geographical and ecological distribution, potentially placing them in greater proximity to inhabited or agricultural areas.

To this encroachment of natural habitats for agriculture or the use of land by humans for tourism or livestock, can be added the drying up of water resources. For example, the overexploitation of water tables outside of cities forces wild animals in rural areas into closer proximity to urban dwellings. One can also list the loss or depletion of the buffer zones that formerly existed between the territories regularly and intensively used by humans (habitat, agriculture, industry) and the wild world. These buffer zones reduced direct encounters with wild animals (Everard *et al.*, 2020).

Today, the poor health of ecosystems is widely blamed for the repeated appearance of zoonoses. It is not only linked to the demographic changes and expansion of the human population (7.8 billion people), but also to overconsumption, the globalization of trade and the decline in biodiversity. One of the causes of the latter is the change in diet since World War II which has resulted, in particular, in an increase in meat consumption and has favoured intensive breeding and also intensive agriculture for the feeding of slaughter animals. The decline or erosion in both agricultural or wild biodiversity is due to the disappearance of wild species following the destruction of natural habitats, climate change and the depletion of the genetic diversity of cultivated species. This erosion of biodiversity is involved in the emergence of zoonotic disease, firstly at the level of what can be termed the “dilution effect” of a pathogen. Indeed, in a balanced ecosystem, the pathogen is distributed in many species, which reduces the risk of its transfer to the human species. In addition, the presence of predators naturally regulates the

host population. This has been particularly demonstrated in the case of Lyme disease, where deer and rodent populations have increased following the disappearance of their predators (Karesh *et al.*, 2012). At the genetic level, the decline in biodiversity is mainly due to intensive agriculture, which concentrates one selected species of an animal or plant population in one place (monoculture). Indeed, breeding a single variety of animals is also thought to reduce resistance to pathogens and thus accelerate contagion (Everard *et al.*, 2020).

If further examples were needed, in the area affected by the 2014 Ebolavirus epidemic, human-made environmental changes have been significant (Alexander *et al.*, 2015). The Guinean forest surrounding the epidemic areas contains about a quarter of all African mammalian fauna. Human activity in these areas has been spectacular, with cumulative forest loss estimated to be at around 85% and the landscape is now dominated by forest and agricultural mosaics. Indeed, it is suspected that the increase in the number of outbreaks of Ebola virus disease in Africa since 2000 is the result of increased contact between wildlife and humans.

Beyond the proximity and frequency of contacts between the wild species carrying viruses and humans or domesticated animals, ecological factors that can influence the rates of viral transmission also include those that affect the prevalence rates and viral diversity in the animal host (Thibault *et al.*, 2017). The prevalence of zoonotic pathogens in the animal reservoir or vector populations can in turn be influenced by the health and immune status of these populations. Such influences can come from the loss or change of a habitat or a host species, or even from their stress, as the result of the ecological impact of human activity for example (Martina *et al.*, 2017; Vourc'h *et al.*, 2021). For instance, a study focusing on the potential effects of deforestation in the Côte d'Ivoire and the transmission of certain viral species by mosquitoes, showed a link between habitat degradation and abundance of mosquitoes present, as well as in the virus populations that they harbour (Junglen *et al.*, 2009). In this study, differences

were observed in the prevalence of mosquitoes and their viruses in disturbed and undisturbed (primary forest) habitats. Specifically, it was found that disturbed habitats, including human habitats, appear to support the proliferation of endemic viruses more efficiently than virgin primary forest. Thus, changes in habitat have an impact not only on the distribution of genera and species of mosquitoes, but also in influencing the distribution of the viruses that they carry and the risk of human disease. Such factors can also include the forced evolution of pathogens and transmission under pressure, e.g., through intensive use of pesticides, fertilizers, antibiotics and antiparasitic treatments, which can increase the resistance of pathogens and/or increase the abundance of the insect vectors of these same pathogens (Dafale *et al.*, 2020; Everard *et al.*, 2020; Karesh *et al.*, 2012).

The unequal distribution of resources on Earth among human populations, as well as their exhaustion by the population explosion, are indirect causes of the emergence of zoonoses. Hunting or scavenging for bushmeat is cultural, but use of the practice in increasingly deep tropical forests can also be linked to the poverty of local populations and unmet food needs (Friant *et al.*, 2015). Since the first epidemics of the Ebolavirus in Zaire (now the Democratic Republic of the Congo) and Sudan in 1976, Ebolavirus epidemics have struck sporadically in Central and West Africa (Lawrence *et al.*, 2017). Although the precise natural reservoir species that harbour Ebolaviruses remain elusive, several species of fruit bats are suspected of carrying the virus and some human epidemics have been directly linked to exposure to bats, including the outbreak of 2014 (World Health Organization, 2015). For many other outbreaks, it has been difficult to pinpoint the source of human cases, but activities that bring humans closer to mammalian species through activities such as hunting and the bushmeat trade are often involved. In Gabon in 1996, the origin of thirty-seven cases of infection was most likely a chimpanzee that was found dead in the forest and eaten by people foraging for food. Eighteen people who participated in the preparation of the animal fell ill and ten other

cases occurred among members of their families. During epidemics, communication campaigns encourage people not to touch or eat wild animals (especially fruit bats or primates found sick or dead) in rural areas. Indeed, it should be noted that, as with humans, gorillas and chimpanzees are also victims of epidemics of this virus. In the mid-1990s, in Minkébé National Park in northern Gabon, more than 90% of the anthropoid monkey population died during an Ebola epidemic. From 2003 to 2005, a large number of animals died in Odzala National Park in the north of the Republic of Congo. Other smaller parks have also been affected and it is estimated that a third of the world's population of gorillas protected in national parks have died in the past fifteen years (Bermejo *et al.*, 2006; Rouquet *et al.*, 2005).

The intrahuman barrier

The intrahuman barrier refers primarily to the ability of an invading pathogen to replicate within a new host organism (Figure 1). During this amplification step, the ability of the pathogen to successfully replicate to high loads in the presence of innate and/or adaptive immunity is thought to be one of the most important parameters that would then favour efficient transmission of the pathogen from the infected individual to the next host (Herfst *et al.*, 2017; Richard *et al.*, 2017). At the cellular or tissue level, factors driving amplification of the pathogen involve the molecular interplay between a pathogen's immune antagonistic proteins and host cell factors and/or the ability of a pathogen to "hide" from the host immune system. To a greater or lesser extent, any pathogen that is able to infect and to cause disease in humans has already evolved or acquired a range of mechanisms to overcome a host innate immune response. These interactions are influenced in turn at the individual or host level by other factors governing the immune response, including the host genetic background, pre-existing immunity or the presence of any infection or disruption to the normal functioning of the immune system including co-morbidity. The vulnerability of individuals to viral infection is in some respects influenced on a larger scale at the

community or even country level by more distal factors including public health strategies for treatment, vaccination or access to medical care, which are likewise, governed by many of the socio-economic factors that can also influence the interhuman interface for an emerging pathogen. Following zoonotic transmission to a new host species, fidelity-associated mutations and selection in the novel host environment may gradually optimise interactions between the virus and its new host (Taubenberger and Kash, 2010; van Dorp *et al.*, 2020). These changes often affect interactions between viral surface proteins and their cellular receptors, or between viral replication enzymes and their required cellular cofactors or partners (Diehl *et al.*, 2016; Dietzel *et al.*, 2017; Urbanowicz *et al.*, 2016). Most pathogens have an affinity for specific tissues determined by selective susceptibility of cells and host defence mechanisms as well as local environmental factors including tissue barriers, temperature and pH. If receptor distribution and expression is similar between the reservoir and the recipient host, these gradual changes do not generally cause changes in disease patterns, but this optimisation of the virus to its new host can and does give rise to the appearance of new viral variants within a population, particularly in the context of a larger scale epidemic or pandemic in which the virus is given ample opportunity to adapt and to evolve under the selective pressure of host immune responses and transmission events. This can occur at many levels; variants may show increased or prolonged shedding owing to higher replication, increasing the chances of spread to susceptible individuals. Likewise, such variants might show better survival in the environment, require a lower dose of virus to initiate productive infection in a newly infected host, show increased affinity for human cell receptors or be better at evading innate or acquired immunity. Many of these changes have been implicated in the emergence of new SARS-CoV-2 mutants during the current pandemic and have likely given rise to highly transmissible “variants of concern” such as “delta” or more recently, “omicron” (Araf *et al.*, 2022). Another factor potentially influencing onward transmissibility is the virulence characteristics of the infecting pathogen. For efficient onward

transmission, the infecting pathogen must be able to overcome the inhibitory effects of host defence mechanisms and cellular susceptibilities to infection. Virulence characteristics allow the virus to initiate infection, spread in the body and replicate to large enough numbers to then favour transmission. These factors include the ability of the pathogen to replicate under specific conditions including inflammation and a host febrile response, in the presence of host inhibitory factors including interferon. For example, some strains of bacteria have developed genotypes that have highly effective virulence including more efficient transmission (Nuermberger *et al.*, 2004; Toungousova, 2004) but the same does not always hold for viruses, as many highly virulent virus families or strains are not associated with higher transmissibility.

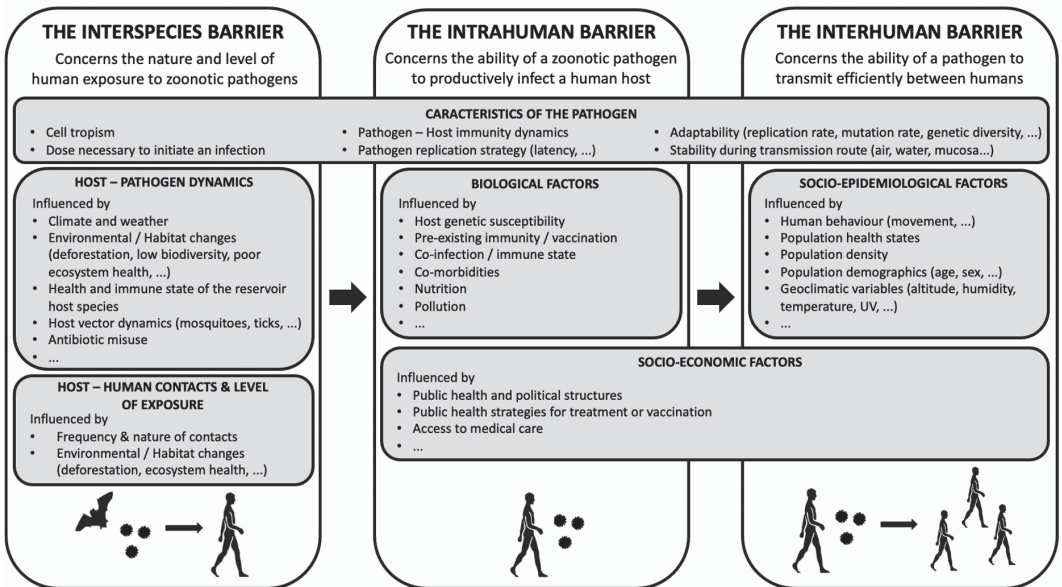
In addition, the ability of a virus to adapt can be affected by changes in pathogen population genetics at the consensus level, but also by genetic variability of the pathogen population as a whole. This is certainly true for RNA viruses in particular, which exist as a population of closely related genetic variants within the host setting known as a quasispecies. Indeed, the ability of a pathogen to quickly adapt and to generate a genetically diverse population is considered critical for the survival of a pathogen faced with a range of selective pressures.

The interhuman barrier and the diffusion of an epidemic

All viruses currently circulating in humans and that are able to cause latent infection and/or disease have been able to cross the species barriers to become human viruses at some point. Species jumps resulting in viruses that are fully “adapted” for human transmission are likely the result of multiple contacts and attempts to overcome these barriers. In general terms we can identify several stages for zoonotic transmission/exposure to the virus, occasionally resulting in productive infection that can then occasionally lead to ongoing transmission events and the spread of the virus within a population. While some adaptation is often necessary for efficient and prolonged transmission of an emerging virus within the human population, some animal viruses, including Ebola-

viruses or Nipah virus (Clayton, 2017), appear to be already able not only to easily cross the species barriers between their host species and humans, but also to be transmitted efficiently between humans. In real terms, whether the outcome of an initial zoonotic transmission of a pathogenic virus to a human is an isolated event, the onset of a localized outbreak or the onset of an epidemic/pandemic is determined by the human-to-human transmission capacity of the virus as well as the socio-epidemiological factors that affect human behaviour and health states, including population density, age demographics and geoclimatic variables (Demongeot *et al.*, 2020; Seligmann *et al.*, 2020) (Figure 1).

Figure 1. The three barriers to zoonotic transmission and the major factors that influence the ability of an emerging or re-emerging zoonotic pathogen to cause epidemics/pandemics in humans. For a pathogen to be able to establish itself sustainably in humans through ongoing transmission chains, all three barriers must be effectively surpassed. Further elements and details are given in the text.



In the case of COVID-19, the rate of spread has been astounding, commensurate with the presence of 28 million people of Chinese origin currently living outside of China in almost every country on Earth (Étienne, 2010) and also with considerable business and tourism travel between China and the rest of the world. Transmission of infectious disease between humans is obviously favoured by certain ways of living and by the densification of populations in certain parts of the world, which increases the rate of contamination within a given population. The capacity for human-to-human transmission can be represented by a term called the basic reproductive number or R_0 of a virus in the human population, where R_0 is the average number of new infections that will occur from a single infected individual. Thus, emerging pathogens for which interhuman transmission is currently a limiting factor, but which have an R_0 close to 1 should be monitored, because their emergence or re-emergence in populations with even subtle differences or changes in demographical, ecological or behavioural factors can favour epidemic spread. Indeed, for a novel pathogen, the R_0 can vary during the course of an outbreak as it is also influenced by epidemiological factors including susceptible population characteristics, disease transmissibility rate and any control measures adopted. This point was unfortunately illustrated by the Ebola virus outbreak in 2014 in West Africa with the largest epidemic ever known of this virus (Alexander *et al.*, 2015; Althaus, 2014; Lawrence *et al.*, 2017) and again in many instances during the current COVID-19 pandemic in countries trying to maintain an R_0 of under 1 (Hellewell *et al.*, 2020; Petersen *et al.*, 2020; S. Zhang *et al.*, 2020). For SARS-CoV-2, R_0 estimates have ranged between 1.5 and 6.68 between studies, with an average value of around 2.5 (Petersen *et al.*, 2020; Shetty *et al.*, 2020).

Throughout history, human movement, be it through exploration, trade or conquest, has always played a big role in spreading infectious disease between vulnerable populations. This has been shown many times throughout history for viruses that affect human health and

society, notably by the spread of the measles and yellow fever viruses to the Americas by Europeans or the epidemic of “Spanish” flu that killed between 20 and 40 million people worldwide in 1918 and 1919. The transmission of viruses (and other infectious diseases) is also now believed to have played a crucial role in the “success” of European colonialism in the New World. From 1492, Europeans brought with them diphtheria, influenza, measles, mumps, scarlet fever, smallpox, typhoid fever, typhus and yellow fever, causing a 50 to 90% reduction in the native population (McNeill, 1989; Morens and Fauci, 2020). Human movement is also believed to have been a factor in the unprecedented scale of the Ebola virus outbreak in West Africa in 2014. Indeed, if war, a growing population, poverty and an insufficient health infrastructure (among other social conditions in the regions affected) are factors explaining the scope and duration of the epidemic, another factor often mentioned is that of human mobility across the region (Alexander *et al.*, 2015). Indeed, a complex set of sociological and economic factors influence human movement across the landscape and can have crucial impacts on the dynamics and spatial spread of infectious diseases. In West Africa, human movement is considered a specific feature of the region, with migration rates more than 7 times higher than movements in the rest of the world. For example, it is estimated that 11% of West Africans live outside their country of birth, including between 30% and 40% of people residing outside their district or village of birth. Large-scale population movements in the region, both within countries and between countries, are in part caused by decades of conflict and the search for better socio-economic opportunities, as well as interactions between historical ethnic communities that often do not follow current geopolitical boundaries. The location and nature of the index case may also play an important role in the rapid spread of an epidemic. In the case of the Ebola virus outbreak of 2014, a cluster of linked infections occurred in Guéckédou, Guinea, a small village bordering Sierra Leone and Liberia near major road networks (Baize *et al.*, 2014). Infected individuals quickly moved

from the initially infected village to other locations, eventually leading to the introduction of the virus into large urban centres, such as Liberia's capital, Monrovia. The regional expansion of the epidemic in Senegal, Nigeria, or Mali has been associated with travel from affected regions. Funeral attendance was also another important human factor related to the transmission of this virus and the movement of populations in the region. Indeed, traditional funeral practices and rituals in the region, which involve the washing of the deceased by relatives and thus a close physical contact, were estimated to be the source of 60% of cases of transmission in Guinea (Alexander *et al.*, 2015). In addition, many people are known to have travelled between regions and even between countries to attend funeral ceremonies, and as symptoms develop between two and twenty-one days after contact, many returned to their homes carrying the disease.

Tourism and globalised trade contribute in another way to the spread of the virus - an epidemic becomes a pandemic when it spreads to another continent (Correa-Martínez *et al.*, 2020; Shi *et al.*, 2020). Likewise, travel increases the spread of viral variants (which themselves often show increased transmissibility between humans), as seen with the so-called "English" or "alpha" variant, which arrived in Europe through travel linked to the end-of-year celebrations in 2020, and which largely displaced the previous viral strain to circulate throughout France, Europe (Kupferschmidt, 2021), and beyond. The same pattern has since been repeated for both the "delta" and "omicron" variants. This fact has gradually forced countries to, at least temporarily, close their borders in an effort to reduce the spread of such variants (Linka *et al.*, 2020)⁴.

4 - *Le Monde* avec AFP. 2020. Aéroports fermés, mesures de confinement... le monde s'organise face à la pandémie. *Le Monde* [online]. 12 March 2020. [Accessed 28 April 2021]. Available at: https://www.lemonde.fr/planete/article/2020/03/12/aeroports-fermes-mesures-de-confinement-le-monde-s-organise-face-a-la-pandemie_6032784_3244.html ;
Le Monde avec AFP et Reuters. 2021. COVID-19 : la France durcit les conditions d'entrée pour les voyages à destination et en provenance du Royaume-Uni. *Le Monde* [online]. 16 December 2021. [Accessed 24 January 2021]. Available at: https://www.lemonde.fr/planete/article/2021/12/16/COVID-19-la-france-durcit-les-conditions-d-entree-pour-les-voyageurs-en-provenance-du-royaume-uni_6106265_3244.html

Poverty is another major factor in transmission, and poorer populations, because of their deficient or insufficiently varied diet, often have weakened immune systems making them more susceptible to disease or have decreased access to affordable healthcare (Rodriguez-Leyva and Pierce, 2021). Even in Europe, the COVID-19 mortality of poorer populations in the United Kingdom has been shown to be double that of people from wealthy backgrounds (Mikolai *et al.*, 2020). In this context, mention should be made of the perverse effect of the emergency measures taken recently, which have used underpaid people to perform so-called essential tasks for the population, and among them, the medical personal who have been particularly affected by the epidemic (Basso *et al.*, 2020; Qi *et al.*, 2020). Likewise, as mentioned above, poverty linked to geopolitical problems can lead to the displacement of entire populations. In addition, restrictions in access to drinking water favours the lack of hygiene. It is known that in the case of COVID-19, for example, washing one's hands for more than 20 seconds is crucial to stem the spread of the virus (Everard *et al.*, 2020).

Factors aggravating mortality and co-morbidity linked to COVID-19

Underlying health problems can also contribute to viral virulence, spread and mortality rates. For more than a year research has focused on understanding the factors linked to increased mortality or to long forms of the disease linked to COVID-19. The most "at risk" profiles are firstly those over 65, particularly males. People with cancer, people who are immunocompromised and women who are pregnant in the third trimester of pregnancy are particularly susceptible to developing a severe form of the disease. To this list of "very high risk" profiles can be added people who have received an organ transplant or people with Down's syndrome over 40 years of age (INSERM, 2020). "At risk" profiles include people with high blood pressure, a history of cardiovascular disease, obesity, chronic respiratory disease, diabetes, renal failure, cirrhosis of the liver, splenectomy and even schizophrenia (Pollard *et al.*, 2020). Analysis of this list also shows the existence of behavioural

factors related to diet and sedentarisation, which promotes obesity and cardiovascular problems, as well as alcoholism, etc. (Methnani *et al.*, 2020).

In addition to these socio-cultural factors, there are specific environmental factors that are known to affect the transmission and pathology of pathogens including COVID-19. Air pollution, particularly microparticles and NO₂, through inflammation of the respiratory tract and mucous membranes, directly promote the entry of the virus into the body (Copat *et al.*, 2020; Pozzer *et al.*, 2020; Sharma and Balyan, 2020). People living in cities, truck drivers, people working in polluted atmospheres or heating themselves with wood fires, are thus particularly exposed. If the regular consumption of tobacco has been suggested to slow down the entry of the virus into the cells, smoking, on the other hand, once the disease is contracted, promotes serious and long forms of the disease (Engin *et al.*, 2020). Indirectly, air pollution is thought to favour contraction of the disease and the development of serious forms, because the microparticles reduce the amount of ultraviolet light and therefore the production of vitamin D, and consequently can lead to a depletion of the immune system (Bourdrel *et al.*, 2021).

Conclusions

The expansion of human populations and the consumption of resources will ensure that we will continue to see the emergence of zoonotic viruses from their reservoir hosts, including rodents, bats or wildfowl, in humans and domestic animals. We do not yet fully understand the interactions between the various factors that influence the ability of zoonotic viruses to cross the ecological, biological or epidemiological boundaries that prevent such transmission. If we are to prevent or even to anticipate future outbreaks, we will need to better understand the range of viruses hosted by wild animal species, as well as the factors that lead to increased interspecies virus transmission. As in the past, the modes of transmission of infectious diseases continue to change and human activities (climate change, movement, the development of agriculture and changes in land-use) play a role in changing risk levels. The emergence of new pathogens exceeds our ability to predict or prevent their occurrence. In this context it is important to emphasize the need for education and prevention efforts against the spread of emerging infectious diseases, including the development and availability of vaccines against, for example, coronaviruses, ebolaviruses or henipaviruses, and the launch of global initiatives for the future in order to be better prepared to deal with future epidemics/pandemics (Plotkin, 2017).

The COVID-19 pandemic has highlighted the vulnerability of our current systems and indeed of humanity itself to infectious disease outbreaks and their spread at a global level. It shows the need for solidarity of humans with other living species on Earth and questions the foundations of modern society and its relationship with nature. To better combat infectious diseases, it is obvious that we need to better understand the weaknesses in the barriers that separate us from animal pathogens as well as the multiple points of convergence between human, animal and environmental health and the pathogens that surround us. Understanding the interactions between these factors will be vital in terms of our ability to predict future pandemics. The notion of “One Health” needs to be more central than ever in strategies to combat

epidemics of existing or emerging/re-emerging pathogens (Mackenzie and Jeggo, 2011; Schneider *et al.*, 2021). It can be hoped that the current situation may stimulate a general movement to reassess human activities both globally and ethically, according to the orientations of sustainable development (Vourc'h *et al.*, 2021). Indeed, an increased awareness of our vulnerability to new or re-emerging infectious diseases at the ecological, biological and societal levels will hopefully allow us to begin to question our relationship with the world that not only surrounds us but of which we are an integral part. It is clear that a certain acceptance of our vulnerability will be required if we are to prioritise changes in our behaviour, in our infrastructures, in our environmental impact and in addressing global poverty, changes that will be essential in terms of our ability to control or even to prevent such outbreaks in the future.

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