The Link Between Covid-19 and Biodiversity: A Report Commissioned by the French Public Authorities

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The coordinators of this report would like to thank all the contributors who, in this busy period, have worked hard to respond quickly to the requests of the FRB and provided precise information that is rigorously supported by the most recent national and international scientific literature for each question raised.

English revision, H. Citerne

1. PURPOSE OF THIS APPROACH

1.1. Government expectations

The major public health, economic and social crisis resulting from the Covid-19 pandemic raises many questions as to its origin, its dynamics and the mechanisms that explain it. This pandemic also raises questions about the future: on the implication of environmental issues in this type of phenomenon, and on the conditions that would have allowed to, if not prevent, then at least better anticipate this crisis and reduce its impact, in order to be better prepared in the future. Decision-making structures, governments and ministries confronted with widely divergent views and opinions, particularly on the link between Covid-19 and the biodiversity crisis, have turned to research organizations for answers to the following questions:

- How is the current health crisis related to wildlife? What role did wild species play in the emergence of this pandemic?
- What is the link between this type of crisis, biodiversity loss and the destruction of natural habitats? Can we draw a parallel between the damage done to biodiversity and the increase in zoonotic diseases, which are a source of epidemics and even pandemics?
- What is the link between this type of crisis, food production and transportation systems (for humans, livestock, agricultural products)? Can certain agricultural and food production systems, or the increasing rate of international transport, directly or indirectly facilitate the evolution of an emerging infectious disease into an epidemic and ultimately into a pandemic?

The relevant ministries and research institutions of the AllEnvi alliance (The National Alliance for Environmental Research) have entrusted the FRB (The French Foundation for Biodiversity Research) and its Scientific Council with the task of giving the biodiversity science community's perspective on the current crisis, and on the relationship between zoonotic diseases, biodiversity and ecosystem services.

This report had three objectives:

- identify the issues for which there is consensus in the scientific community (including regarding the questions raised by the different departments);
- outline the issues that remain open to question, because of dissensus within the research community or gaps in the scientific knowledge;
- deliver messages to decision makers; make science-based recommendations for actions or options of measures that could be taken, in order to assist public decision-making.

1.2. Mobilization of the FRB

In addition to its president, director and core staff members, the FRB has mobilized its Scientific Council and a panel of external experts that were selected by associated research institutions or members of the Scientific Council (nearly 40 people in total). A support group was established to oversee the preparation and production of the report. Biodiversity research often involves field data collection and multifactorial analyses that require a publication timeframe that is often longer than that of other branches of experimental biology. Moreover, understanding a particular situation within a complex system requires making comparisons with other similar situations. Given that this pandemic is very recent, it is normal at this stage that very little scientific work has been published on the link between Covid-19 and biodiversity. The Committee has therefore decided to include in this report data on zoonotic diseases from the last 20/30 years (SARS, Ebola, Zika, Dengue fever, Lyme's disease, etc.) and to clearly identify what is known, or not known, about outbreaks of infectious diseases, with emphasis on the evidence available for Covid-19.

The committee has come up with a list of questions (and sub-questions when necessary), which have been divided into two categories:

- The factors underlying the emergence of zoonoses;
- Possible measures that could be taken to reduce the risk of zoonoses.

Each question, or sub-question, is the subject of a dedicated fact sheet (22 in total) containing the following sections:

- Elements of scientific consensus;
- Elements of scientific dissensus;
- Lack of knowledge or analytical bias;
- Research needs;
- Special case of Covid-19.

The content of these sheets is based on articles published in international peer-reviewed journals. Articles cited in the text can be accessed through their link. Each sheet is written by a single author, and is reviewed by the entire group of scientists involved. Clearly showing dissensus should allow the expression of the diversity of opinions on a given topic.

1.3. Delivery of the report

In addition to these fact sheets, the report also contains this introduction, a glossary and a summary of the general trends associated with zoonotic diseases.

In view of the scope this project, the extremely tight schedule set by the ministries and the lack of knowledge on Covid-19, the timeline for the delivery of this report was as follows:

- 5th May 2020: release of a draft version, comprising all sections, with for each an indication of the stage of validation by the group of experts on that date.
- 6th May 2020: oral presentation to stakeholders, at their request.
- Mid-May 2020: publication on the FRB website of the French version of this report. The fact sheets and summary will be updated regularly as new information becomes available.

The report was handed over to the public authorities in its current form. Unlike procedures used notably by the IPBES, there is no review process by the public authorities that commissioned this work.

1.4. Dissemination and disclaimer

As indicated above, the report is freely accessible on the FRB website.

The views and recommendations expressed in this report are based on the review of scientific knowledge by a small group of specialists in the field of biodiversity sciences; consequently, these findings may not have the full support of other scientific communities, but may open up the debate between the scientific and decision-making arenas.
Although a wide range of experts from different research institutions have contributed to this report, the latter does not necessarily reflect the views of the research institutions and does not engage their responsibility in any way.

2. GLOSSARY

Co-evolution: Co-evolution is defined by Jantzen (1980, Evolution) as the evolutionary change of a life trait in individuals of one species in response to a trait in individuals of a second species, followed by an evolutionary response of the second species to the change in the first.

- Here: The reciprocal and adaptive genetic changes in interacting host and pathogen species (Woolhouse *et al.* 2002, Nat Genet).

EcoHealth: The EcoHealth concept is defined as an ecosystem approach to health, which focuses on environmental and socio-economic issues and was initially developed by epidemiologists working in the field of biodiversity conservation. The EcoHealth paradigm applies an integrative approach to health issues and links public health to the management of natural resources and, more broadly, to the environment. EcoHealth can be viewed as a One Health approach that emphasizes interdisciplinary approaches and active citizen participation (Roger *et al.* 2016, Inf. Ecol. & Epidemio.).

Emerging: Emerging diseases can be defined as infections that have newly emerged in a population or already exist but are rapidly increasing in incidence, global distribution or have a new clinical expression (Morse 1990). They are sometimes distinguished from epidemics on the basis of their geographical spread; the term may also be less alarming to the public.

Endemic: In the context of disease, the concept of endemic refers to the constant presence and/or usual prevalence of a disease or infectious agent in a given population or geographic area (CDC 2012). As endemics spread across populations and areas, they can evolve into epidemics/pandemics.

Epidemic: An epidemic is the occurrence of more cases of disease, injury, or other health condition than expected in a given area or among a specific group of persons during a particular period. Usually, cases are presumed to have a common cause or be related to one another in some way (CDC 2012).

Epidemiology: The discipline of epidemiology addresses the influence of various factors (individual health, environment, lifestyle, social environment) on diseases, particularly on their frequency, distribution and etiology, but also on any other specific biological or social phenomenon (*Med. Biol.* T. 201971).

Exposure: In relation to health, exposure is having come into contact with a cause of, or possessing a characteristic that is a determinant of a particular health problem (CDC 2012).

Global Health: Global Heath can be defined as the area of study, research and practice that gives priority to improving human health and achieving health equity for people across the world, drawing on the contributions of medicine, public health, epidemiology, demography, economics and sociology. Global Health can be measured from various global diseases, their prevalence worldwide and the risk of a reduction in life expectancy (Beaglehole and Bonita 2010, Glob Health Action Wikipedia page).

One Health: The One Health concept defines a collaborative and integrated approach to human, animal, plant and environmental health, to reinforce prevention systems and enable the early and systemic management of diseases with multifactorial causes. Antimicrobial resistance, which threatens human, animal and environmental health, is an emblematic example that uses surveillance and reporting tools to improve global health security and achieve developmental gains. Infectious diseases and antimicrobial resistance are just a part of the One Health approach, which can be applied to a wide range of issues (e.g. water and soil pollution affecting animals and the environment) (World bank group 2018).

Pandemic: An epidemic occurring over a widespread area (multiple countries or continents) and usually affecting a substantial proportion of the population (CDC 2012).

Pathocenosis: This is a synthetic approach for the historical study of diseases, which models the interactions between the different diseases in a population and whose distribution curve has a mathematical expression (Coste *et al.* 2016).

Pathosystem: The subset of an ecosystem that involves parasitism, and can potentially include all hosts and parasites in the ecosystem (Kempken 2013, Technology & Engineering).

Planetary health: The concept of planetary health is defined as the achievement of the highest possible level of human health, well-being and equity in the world through judicious choices for human systems - political, economic and social - that shape the future of humanity and the Earth's natural systems and define the environmental limits within which humanity can flourish. In more simple terms, planetary health refers to the health of human civilization and the state of the natural systems on which it depends (Whitmee *et al.* 2015).

Risk: Risk is defined as the potential for consequences where something of value is at stake and where the outcome is uncertain, recognizing the diversity of values. Risk is often represented as the probability of occurrence of hazardous events or trends multiplied by the impacts if those events or trends occur. Risk results from the interaction of vulnerability, exposure and hazard (IPCC).

Spillover: The initial invasion of a pathogen into a new host (Keesing *et al.* 2010).

Vulnerability: The propensity or predisposition to be adversely affected. Vulnerability encompasses a variety of concepts and elements including sensitivity or susceptibility to harm and lack of capacity to cope and adapt (IPCC).

Zoonosis: Diseases and infections where pathogens are naturally transmitted from vertebrate animals to humans (Haddad *et al.* 2019).

3. LIST OF ISSUES ADDRESSED

3.1. Understanding zoonotic diseases

- Is the frequency of zoonotic diseases increasing, if so, since when? **(SHEET 1)**
- Are there more contacts between humans and wildlife, and if so, why? **(SHEET 2)**
- What is the geography of emerging zoonotic diseases? How can it be explained? **(SHEET 3)**
- Are certain human populations more at risk? (**SHEET 4)**
- What roles can co-evolutionary processes between humans and pathogens play? **(SHEET 5)**
- Are certain taxonomic groups more likely to cause zoonotic diseases? If so, why? **(SHEET 6)**
- What do we know about the processes that enable different types of human pathogens to cross the species barrier? **(SHEET 7)**
- Are intermediate hosts always critical for the emergence of zoonotic diseases? **(SHEET 8)**
- What are the evidence-based links between zoonotic diseases and biodiversity loss? **(SHEET 9)**
- What are the evidence-based links between zoonotic diseases and deforestation (and the development of agriculture and monospecific plantations)? **(SHEET 1)**
- What are the evidence-based links between zoonotic diseases and the development of human infrastructure (roads, etc.)? **(SHEET 1)**
- What are the evidence-based links between zoonotic diseases and urbanization? **(SHEET 1)**
- Is there a link between the increase in the number of zoonoses, climate change and exceptional climatic events? **(SHEET 1)**
- What are the evidence-based links between zoonotic diseases and the development of bushmeat consumption wildlife trafficking associated with traditional pharmacopoeia? **(SHEET 1)**
- Is it possible to generalise the mechanisms of interaction between livestock, the environment and health be generalized? **(SHEET 1)**
- What is the link between zoonotic diseases and the development of large-scale livestock farming, the reduction in the number of farmed species and the genetic homogenization of these species? **(SHEET 1)**
- What is the risk posed by human epidemics to wild species (e.g. primates) and pets? **(SHEET 1)**

3.2. Recommendations for addressing the risk of zoonoses

- Should we develop zoonotic disease prediction methods (and models), and on what basis, or should we prioritise the monitoring of weak signals of potential zoonoses? **(SHEET)**
- Is it possible to identify sentinel species? **(SHEET)**
- Could the management or eradication of wild species and populations that are likely to cause zoonoses be an alternative? How can we avoid the negative reactions in certain sections of the population to species seen as as potential sources of zoonotic diseases and epidemics? **(**Error! Reference source not found.**)**
- Can the development of protected areas help reduce the risk of zoonotic diseases? What are the processes involved and what would be the required level of protection? **(**Error! Reference source not found.**)**
- Does maintaining high species/genetic biodiversity prevent or limit the emergence of zoonotic diseases? What generalizable is the dilution effect? **(**Error! Reference source not found.**)**

4. SYNTHESIS AND MAIN MESSAGES

Synthesis of the contributions of biodiversity sciences to the understanding of zoonoses

The links between humans and other species imply a wide variety of interactions and feedbacks resulting from the multiplicity of utilitarian, relational and ethical approaches that motivate them and that fall within the dimensions of human well-being. Health issues are one of the dimensions of human well-being. Biodiversity and its components have many positive and sometimes negative effects on human health. The epidemiological risks associated with some zoonoses are one of the dimensions of the risks linked to some elements of biodiversity; they are modulated by the modalities of interactions between humans and these elements of biodiversity.

There has been an increase in the number of epidemics in humans over the past 50 years, with mortality varying greatly from case to case **(SHEET 1)**. The increase in the number of epidemics of zoonotic origin can, in part, be explained by the multiplication of contacts between humans and wildlife **(SHEETSHEET 2)**. On a global scale, the different geographical areas do not present equivalent risks in terms of infectious or parasitic emergence, and emerging zoonoses mainly originate in the intertropical zone **(SHEETSHEET 3)**. However, it is difficult to determine whether or not certain human populations have differences in susceptibility to zoonotic diseases **(SHEETSHEET 4)**. Host-pathogen interactions are accompanied by co-evolution processes that depend on the time scales considered, but also on the respective generation times of humans and pathogens **(SHEETSHEET 5)**.

Some groups of animals are more frequently the cause of zoonoses than others **(SHEET 6)**. Crossing the "species barrier" to humans appears to be easier within primates, which are phylogenetically closer to humans, and between humans, and some species that have long been commensal to them **(SHEETSHEET 7)**. The presence of an intermediate host, allowing the infectious agent to become pathogenic to humans, is possible but not mandatory **(SHEETSHEET 8)**.

There is increasing evidence that global environmental change, the loss of biodiversity **(SHEET 9)** and its associated regulatory services, and the emergence, or increase in the prevalence of zoonotic diseases are linked. Biodiversity loss weakens the functionality of existing communities and their associated services, and is particularly critical to issues related to land use change and wild-domestic animal interactions in agricultural systems **(SHEET 11)**. Zoonotic risk can be increased by the erosion of biodiversity through ecological, epidemiological, adaptive and evolutionary and anthropogenic factors. There is thus a strong consensus in favor of a link between deforestation, in its various dimensions, and the multiplication of zoonoses in Asia, Africa and South America. Many factors directly or indirectly associated with deforestation explain this situation **(SHEET 1)**. The development of human infrastructures, and especially communication channels, acts as a facilitator of zoonoses and contributes to transforming them into epidemics and pandemics **(SHEETSHEET 1)**. Urban development **(SHEETSHEET 1)** increases health risks by promoting contact with certain elements of wildlife, particularly in sub-urban areas. Urban centers can be both sites of disease emergence and be the location of epidemy outbreaks. Recent trends, such as the trend towards eco-tourism and closer contact with nature, could in some situations favor contact with forest infectious agents, transmitted in particular, in some countries, by non-human primates. This in no way diminishes the benefits to human well-being of reconnecting with nature.

Climate change is one of the factors affecting the distribution and activity of species and therefore certain zoonoses, particularly when they involve arthropod vectors which modify their distribution area. Climate-sensitive pathogens can thus be identified, particularly in northern countries **(SHEET 1)**.

The link between bush meat consumption and trade and emerging infectious diseases has been established in several cases. The risks of infection are amplified by a lack of public awareness of the health risks, and the increasing demand, in volume and species, to feed a wildlife market that has become urban

and global. The most determining factor seems to be the phase of contact with wild animals, generated by hunting, keeping in captivity and preparing the carcasses to feed this market **(SHEET 1)**.

Factory farms allow the implementation of biosecurity measures; the risks of disease emergence are therefore less frequent, but when the emergence does occur, a disease can spread rapidly and, via trade, spread throughout the production chain, as the avian influenza epidemics have shown **(SHEET 1)**. Thus, the exponential development at the global level of livestock and poultry farms, where animals may have little specific diversity and reduced genetic diversity, generates a large target compartment for zoonoses and therefore favorable to epidemics **(SHEETSHEET 1)**.

There are many examples of pathogen spillovers from humans to domestic animals, pets and also to wild animals, including marine mammals and Antarctic birds. Great apes are also victims of measles epidemics and various respiratory infections caused by viruses of human origin. Increasing interactions between humans and wildlife can lead to complex interactions between anthroponotic and zoonotic transmission processes **(SHEET 1)**.

What recommendations can be made to minimize the risk of zoonotic diseases?

Maps showing areas at risk of emergence, i.e. where hazard, exposure and vulnerability of populations overlap, can be used to locate on a regional scale where this risk may occur, such as areas of tropical forests, areas with high mammal species richness and areas undergoing land-use change towards agriculture **(SHEET)**.
The identification of sentinel species that can act as an warning signal for the development of an infection could be considered for known cases, once the dynamics of the pathogen are documented **(SHEET)**.

Strategies to respond to the risks of emergencies must be developed from individual to collective levels. They can resonate with numerous recommendations to respect non-humans by default by encouraging, on the one hand, the preservation of their environment and their least disturbance and, on the other hand, by the preventive use of "protective measures" that avoids or reduce their manipulation to the strict necessary.

Faced with the expectations of certain populations worried about the health risks associated with the presence of species likely to cause zoonoses, considering the pure and simple elimination of a particular taxon, population or sub-population in a given area appears beyond the ethical problems it raises, to be very hard and above all may prove to be totally counter-productive, in view of the health objective sought **(**Error! Reference source not found.**)**, and extremely costly. Whenever possible, the vaccination of humans, domestic or farm animals and also wild hosts is a proven solution.
Rather than considering eradication, human populations, farmed animals and pets should be kept away from potential hosts of pathogens that may cause zoonotic diseases. The knowledge gained on the behavior of species causing zoonoses can be used to avoid providing them resources or habitats through certain human practices, which will help to guard against the risks of contamination.

There is a need to better understand the complex and highly diverse relationships that humans have with wildlife, depending on their location and social group. Recommendations that can be made should be based on a clear understanding of these relationships; otherwise they are unlikely to be implemented and followed by effects.
Secondly, investment in awareness-raising, education and co-construction is essential, provided that it is adapted to the cultural specificities of the different human societies concerned, which have developed complex and highly diversified relationships with wildlife. Local prevention measures must be based on accurate knowledge of these relationships in order to strengthen their implementation and achieve the desired effects. Education, especially of children, can help to reduce the risk of direct interactions with wildlife components by discouraging their manipulation and avoid negative reactions of some populations to species considered potentially dangerous.

The development of protected areas is a favored option for preserving wildlife habitats and reducing contact with humans **(**Error! Reference source not found.**)**. In protected areas, land-use change, particularly deforestation, can be strictly limited and human penetration and associated activities, including wildlife harvesting, can be reduced. From an ecological point of view, and even if there are elements of dissensus within the scientific community, the hypothesis that maintaining biological communities with high specific diversity within protected areas would prevent the emergence of major pathogens that could cause zoonoses reinforces the rationale for promoting protected areas **(**Error! Reference source not found.**)**.

A policy aiming at increasing the number of protected areas can be achieved through the creation of new areas, the expansion of existing ones or, above all, through dialogue with local populations, taking into account their knowledge and strengthening the level of protection afforded to these protected areas. However, the development of protected areas and the increase in their level of protection raises social, political and economic questions as well as pedagogical issues, given the growing concerns of human populations about the risks of zoonoses and epidemics; these concerns, in view of the existence of areas where wild animals can thrive, can both relate to the development of new protected areas or call into question the future of existing ones.

A strategy for the development of protected areas must be thought at the relevant territorial scales by promoting dialogue with local populations, who can be actors in the protection of biodiversity and the regulation of access to protected sites, without calling into question the dual imperative of protecting biodiversity and limiting the transmission of pathogens to humans, farm animals or wildlife.

However, better protection of biodiversity, particularly in the countries of the South, can only be envisaged and be sustainable if consumption pressures, particularly of external origin (imported deforestation), are significantly reduced.

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6. FILES

SHEET 1
Is the frequency of zoonotic diseases increasing, and if so, since when?

CONSENSUS:

Over the past 50 years, the number of epidemics worldwide has risen significantly with on average two to three new infectious agents emerging each year (Jones *et al.* 2008, Nature). An acceleration in the frequency of disease outbreaks, particularly of zoonotic origin, has been observed since the early 1980s (Smith *et al.* 2014, J R Soc Interface; and Morand *et al.* 2014, Plos One for a closer look at South East Asia). These trends are significant, even when taking into account the fact that the monitoring effort has been increased, which could confound these observations (Morand and Lajaunie 2017, ISTE Press Ltd.). After controlling reporting bias, we do observe an increase over this period of time in the number of epidemics, particularly of animal origin, with mortality varying greatly from one epidemic to another (a few dozen to 12,000 for SARS-CoV-1 and 20,000 deaths for Ebola virus diseases).
The emergence and spread of antimicrobial resistance is also becoming a problem worldwide. This has a major impact on public health as it helps the spread of infectious diseases. The effects of antimicrobial resistance on animal health and biodiversity are still poorly known, but its transmission pathways involve wildlife and the environment. An integrated (One Health) approach to antibiotic resistance is essential (Goutard *et al.*, 2017, BMJ).

DISSENSUS:

There may be some disagreement, not on the increase in the frequency of epidemics, but on the number of cases of illness that are caused by an emerging zoonotic disease (often only a few), on the use of different diagnostic tools at different points in time and on changing human demographics (the effects of population size on pathogen diversity and the spread of epidemic waves). There may also be a sampling bias, with previously known or major types of diseases or epidemic events receiving particular attention, and conversely, other diseases, whose exact etiological origin has not been established, being classified under generic terms such as "influenza syndrome" or "infectious pneumonia". There is also a tendency to underestimate co-infections, which has consequences for the recording of infectious agents in circulation, including those of animal origin (Razzauti *et al.* 2015 Plos NTD, Moutailler *et al.* 2016, Plos NTD).

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

There may be a bias in how these events are counted, especially if the etiological origin or mode of transmission of a pathogen is not known, as is the case at present for the SARS-CoV-2 virus responsible for Covid-19. In addition, although the discovery of new viral entities has increased since the second half of the 20th century, it is unclear whether these are indeed new species and whether they can be considered pathogenic to humans (Woolhouse *et al.* 2008, Proc Biol Sci). There is still confusion between the notion of microbe and pathogen, one not necessarily being the other. Furthermore, new microbes are nowadays mainly characterized by molecular sequencing, which does not inform on whether these particles or cells are viable and at what density they infect organs (the notion of inoculum) (Hosseini *et al.* 2017, Phil. Trans. R. Soc. B). Many endemic diseases, of which many are of zoonotic origin, do not sufficiently mobilise decision-makers and the public and private sector. These diseases affect nearly one billion people, especially in tropical countries (for Africa, see Hotez and Kamath 2009, Plos NTD). To reverse this trend, several of these diseases have been put on the WHO's "neglected tropical disease" list. Lack of data for these diseases also introduces a bias in the case count (under-reporting, confusion with other diseases).

NEED FOR RESEARCH:

It would be interesting to refine this trend by determining the proportion of zoonotic diseases that are transmitted by wildlife and by domestic animals, and assess the relative importance of these groups in disease emergence. In addition, improvement in diagnosis without a priori knowledge (exploratory infectiology) would make it possible to uncover new or underestimated infectious agents that may be responsible for specific outbreaks (the subject of attribution), whereas at present they are linked to outbreaks of syndromic origin.

SPECIAL CASE OF COVID-19:

Covid-19 is due to the emergence of a coronavirus-type infectious agent that belongs to a known viral family with previously identified risk factors (Cheng *et al.* 2007, Clin Microbiol Rev). However, the host species of origin and the modes of transmission of the virus causing this pandemic are not precisely known to date.

SHEET 2

Are there more contacts between humans and wildlife, and if so, why?

CONSENSUS:

Changes in land use, particularly the exploitation of forests in intertropical regions, bring humans in contact with microorganisms (Karesh *et al.* 2012, The Lancet, Jones *et al.* , 2013 PNAS, Combe *et al.* 2019, Emerg. Microbes Infect.). Recent assessments have shown an increase in deforestation in different parts of the world, with 100 million hectares of forest lost between 1980 and 2000 (IPBES 2019, IPBES Secretariat). Wildlife trade is also expanding, but the situation regarding poaching is harder to quantify because of the clandestine nature of this activity, which affects the poorest populations (Can et *al.* 2019, GECCO). In developed countries, urban greening, certain forms of rewilding , outdoor activities (Millins *et al.* 2017, Phil Trans, Kilpatrick et al. 2017, Phil Trans, Sandifer *et al.* 2015, Ecosyst Serv), as well as the demand for new species of pets (e.g. cases of Monkeypox in the United States, Bernard and Anderson 2006, EID) could promote contacts between humans, wildlife and infectious agents. These elements point to an increase in contacts between humans and wildlife (Symes *et al.* 2018, Nat Comm).

DISSENSUS:

Globally, biodiversity loss could ultimately reduce human/wildlife contacts, simply due to a lack of wildlife, although the situation may differ greatly from one region of the world to another. However, it is important to clarify what is meant by “biodiversity loss”, as this loss may benefit a small number of species (for example, certain human commensal species) that are potentially involved in zoonotic diseases. Nevertheless, the proportion of wild species without any contact with humans is undoubtedly decreasing, and exposure is on the rise.

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

Studies quantifying these contacts are lacking, particularly on a local scale. Studies of socio-ecosystems with limited contacts or few outbreak occurrences are also lacking (Duvall 2008, Landscape Ecol., Leblan 2017 EHESS Coll. “En temps & Lieux", Guégan et *al.* 2020, Env. Res. let.). Moreover, the notion of "contact" is relatively imprecise: in the literature, a distinction is made between "direct" contact (physical exposure to body fluids from an infected animal, but also exposure to aerosols) and "indirect" or "secondary" contact (via fomites, excreta or vectors sharing the same habitat as humans). In addition, the notion of "close contact" may refer to bodily proximity both with and without physical contact (Narat *et al.* 2017, EcoHealth). Knowledge is also lacking regarding the effects of spatial planning (of protected areas) on exposure risk (i.e. area size and shape influence the quantity of borders (fractal dimension of the fringes) and thus the amount of interaction with the wild) (Hosseini *et al.* 2017, Phil. Trans. R. Soc B).

NEED FOR RESEARCH:

Clearly, approaches that are similar to those proposed by Rulli *et al.* (2017, Sci Rep) and Olivero *et al.* (2017, Sci Rep), which consider the spatial topology of different environments (urban and peri-urban environments, agricultural and livestock areas, natural ecosystems), their interaction and their evolution, should be developed. Planning scenarios should also be analysed and interpreted in the light of the microbiological hazards present, and the level of exposure and vulnerability of individuals and populations. Studies that model land fragmentation and human/wildlife contacts (Faust *et al.* 2018, Ecol Lett, Bloomfield *et al.* , 2020, Landscape Ecology) could be followed up with an analysis of their impact on infectious risk.

SPECIAL CASE OF COVID-19:

Studies on the bats (flying foxes) responsible for transmitting the Hendra virus have been carried out (Plowright et al. 2011, Procs B). However, data is lacking for horseshoe bats, several species of which

could be involved in the emergence in China of the coronavirus causing Covid-19. It has already been shown that human presence constitutes a stress factor for bat colonies and induces changes in their social behaviour (Ancillotto, *et al.* 2019, LUP). Conversely, certain human socio-cultural practices may promote contact with bats (Ohemeng *et al.* 2017, Anthrozoös). Viruses that are phylogenetically close to the one that caused the Covid-19 crisis have been identified in horseshoe bats (Lau *et al.* 2005, PNAS, Li et al. 2005, Science, Hu *et al.* 2018, Emerg Microbes Infect, Zhou et *al.* 2020, Nature) and pangolins (Lam *et al.* 2020, Nature). The latter are sold in large numbers on Asian markets for food and pharmacopoeia (Challender *et al.* 2020 in « Pangolins », Elsevier), and are also "kept" on wild animal farms ('t Sas-Rolfes and Challender 2020 in "Pangolins", Elsevier), providing much opportunity for contact with humans and interaction with other species. These conditions facilitate the emergence of new viruses.

SHEET 3
What is the geography of emerging zoonotic diseases? How can it be explained?

CONSENSUS:

The different regions of the world do not present the same risk of emergence of infectious or parasitic diseases (Wolfe *et al.* 2007, Nature). Spatially explicit modelling predicts that there is a high risk of disease emergence in regions with tropical forests, high mammalian diversity and changes in land use related to agricultural practices (Allen *et al.* 2017, Nat Comm, Morse *et al.* 2012, Lancet). Infectious risk being determined by the combination of three components: hazard, exposure and vulnerability (of individuals and populations), it is greater in areas with high biodiversity and high human population density. Research has shown that areas with high mammalian species richness globally coincide with areas with high plant and microorganism species richness (Schipper *et al* 2008, Science). Furthermore, there is a correlation between mammal and bird species richness and the number of infectious diseases (Dunn *et al.* 2010, Proc. R. Soc. B., Morand and Lajaunie 2017, ISTE Press Ltd.). Macroorganism hotspots, and thus microorganism hotspots, pose a greater threat, or hazard, in intertropical regions. A correlation between the number of endangered species and zoonotic disease emergence has also been found (Morand and Lajaunie 2017, ISTE Press Ltd.). There are likely to be differences in exposure levels and exposure history between temperate and tropical regions; in the intertropics, exposure to wildlife and its infectious agents is increased due to deforestation and bushmeat consumption activities (Wolfe *et al.* 2005, EID, Karesh *et al.* 2012, The Lancet). Similarly, the threat posed by microorganisms, and their hosts and vectors, constitutes an infectious risk when it coincides with socio-economic factors that aggravate the chances of transmission to humans: e.g. greater exposure through enhanced contact with wildlife, and an epidemiological terrain that favours the spread of disease among dense, poor and unhealthy populations (Guégan et *al.* 2020, Env. Res. Let.). Thus, in temperate zones, the microbiological hazard linked to biodiversity hotspots poses a risk of zoonotic emergence that is lower (and also better detected and highly linked to antibiotic resistance, see Jones et *al.* 2008, Nature) than in tropical zones. In particular, this is due to the lower vulnerability of human populations in temperate regions, which is due to several factors including better public health and education systems and lower human population densities with fewer rapidly growing megacities (Neiderud 2015, Infect Ecol Epidemiol). This view may need to be re-examined in the light of the Covid-19 pandemic.

DISSENSUS:

Depending on the evolution of human factors that increase or decrease the vulnerability and exposure of populations, risk areas could change. For example, the epidemic events observed in South East Asia are linked to the high concentration of conurbations, combined with the presence of biodiversity hotspots and increased exposure through human practices (consumption of natural resources and occupation of natural ecosystems). A similar trend could be observed in the future in, for example, West or Central Africa, or in Mesoamerica or South America, with the development of cities that are in contact with diverse microbial reservoirs, and the growing exploitation of natural biomes and their biodiversity (Guégan *et al.* 2020, Env. Res. Let.). Research into the relationship between biodiversity and health is often designed by zoologists rather than public health experts so that all too often the notion of hazard is confused with that of risk. As a result, most maps produced nowadays represent hazards and not risks (Guégan and Simard 2015, Actualité et dossier en santé publique).

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

The use of biodiversity hotspot maps is not enough to assess a potential infection risk, since there may be other factors such as local resistance to treatments that could modify the epidemic potential in that particular area.
The possibility that geographical variations in zoonotic risk may be influenced by the link between the intraspecific genetic diversity of infectious agents and their emergence success may have been understudied compared to the link between interspecific pathogen diversity and emergence risk.

RESEARCH NEEDS:

Work on geographical areas that have received less attention would lead to a better understanding of the risk of disease emergence in these areas, particularly in Central and South America where there is high biodiversity and ongoing urban development, as well as in India, Africa and the Middle East (Han *et al.* 2015, PNAS, Guégan *et al.* 2020, Env. Res. Let.).

SPECIAL CASE OF COVID-19:

Although the origin of the virus causing the Covid-19 crisis is not fully established, the conditions surrounding the emergence of this epidemic are typical of this type of phenomenon: high biodiversity, exposure to infectious agents reinforced by the trade in live animals, high exposure through local or regional practices and customs, and enhanced vulnerability of dense populations with high poverty levels.

SHEET 4
Are certain human populations more at risk?

CONSENSUS:

The risk of infection is determined by the combination of three components: hazard (the presence of microbes, reservoir hosts or vectors, and their association), exposure of individuals and communities, and vulnerability of individuals and populations.
Hazard is determined by the occurrence of areas, often associated with biodiversity hotspots, where microbial agents, some of which may be pathogenic to humans, circulate (the concept of the enzootic cycle); exposure is determined by how often and to what extent populations are in contact with wildlife (see **SHEET 3**). For example, hunters are more exposed on an individual level to an infectious threat because of their practices (exposure within the community or occupational risk).
Vulnerability is in part modulated by the genetic makeup of populations (neutral and adaptive diversity, Quintana Murci 2019, Cell). However, genetic background does not appear to be the most important factor determining infectious risk (difficulty in clearly quantifying the contribution of this component in risk estimations: values range between 6% and 24%, seldom more). Vulnerability is also influenced by physiological factors such as stress, physical condition (immunosuppression, co-infections, being over- or underweight, Dobnet and Kaser 2018, Clin Microbiol Infect)) and by the resident microbiota, which varies between populations and affects susceptibility to infection (Pfeiffer and Sonnenburg 2011, Front Microbiol). Vulnerability is also determined by the socio-economic organization of the group in question and the structure of their productive system with its various components (agriculture, hunting, gathering, fishing, exploitation of forest products). Their conception of health, their living space, their environment (determined by human density, access to water and food, forms of well-being and care, education, etc.), their mobility (in particular contact with urban environments), threats to their territories (gold mining, timber exploitation, deforestation, etc.), their status within society nationally but also their capacity, when possible, to organise themselves in the face of a health threat, as well as the frequent lack of adequate health services, all play a major role in their vulnerability or resistance.

Depending on the evolution of human factors influencing the vulnerability and exposure of populations, risk areas may change. For example, the epidemic events observed in South East Asia are linked to the high concentration of conurbations combined with the presence of biodiversity hotspots. In the future, similar conditions could be found in Africa or Central America, for example, with the development of cities that are in contact with pathogen reservoir zones (microorganisms, not all of which are pathogenic at present) (Guégan *et al.* 2020, Env. Res. Let.).

Because of the persistence of transmissible diseases that perpetuate poverty, and in order to mobilise resources for the most vulnerable populations, the WHO has placed certain diseases on their "neglected tropical disease" (NTD) list, including several zoonotic diseases: *T. solium* cysticercosis, echinococcosis, leishmaniasis, rabies and the zoonotic form of African trypanosomiasis or sleeping sickness. Less formally, other zoonotic diseases (brucellosis, anthrax, bovine tuberculosis) are also considered as being neglected by other experts in the field. Finally, animal diseases should also be considered as being neglected given their socio-economic impact on vulnerable human populations (Roger *et al.* 2017, Plos NTD).

DISSENSUS:

The risk level of a population can be mitigated or aggravated by local perceptions of the causes of the disease that generate a range of responses, by the breakdown of the socio-political, cultural and subsistence organization within these populations, and by changes in mobility (Buchillet 2016, in Erikson P. (ed.) Trophées : études éthnologiques, indigénistes et amazonistes offertes à Patrick Menget, vol. 2 : Guerre, chamanisme et rencontres interethniques).

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

Research on alternatives to game consumption in populations that depend on it for food or socio-cultural practices should be carried out in order to fully apprehend the ecological, economic and socio-cultural dimensions of these practices. Studies need to discriminate between self-sufficiency practices and long-distance trafficking and trade practices.

NEED FOR RESEARCH:

Work on prevention measures aimed at reducing population exposure (relationship to the wild) and vulnerability (living conditions in the broadest sense) would help limit the risk for populations in contact with potential pathogens, but also limit the risk of epidemic or pandemic events that could result from these contacts, while taking into account cultural specificities. Although French laboratories are contributing to these fields and are recognised worldwide, research in anthropology, sociology and health economics, and in political science on the organisation of health systems (surveillance, care, etc.), in particular through multidisciplinary and multisectoral comparative studies, needs to be supported. It is important to study the relationship between populations and wildlife, in all its diversity and complexity. This relationship does not only concern the practices of hunting, consumption, etc., but also the knowledge that these populations have (or do not have) of wildlife and diseases.

SPECIAL CASE OF COVID-19:

In the case of Covid-19, although the origin of the virus is still uncertain, populations were exposed to the virus responsible for this disease before its emergence was discovered. This was also the case for the Ebola virus in central Africa, the Nipah virus in South East Asia and most likely for a very large number of cases. The measures taken by States worldwide have therefore focused on responding to the epidemic (containment measures, stopping population movements) rather than on prevention by reducing exposure (legislation against illegal hunting and live animal markets, prophylactic measures, etc.) or individual and collective vulnerability (increased protection measures and medical capacities, and educating on the risk factors as was done for the Nipah virus).

SHEET 5
What roles can co-evolutionary processes between humans and pathogens play?

CONSENSUS:

As on most living things, pathogens have exerted (and still are exerting) major selective pressures on the human genome and on immunity genes in particular (Hill 1998, Ann Rev Immunol; Quach *et al.* 2016, Cell) throughout human evolution (Karlsson et al. 2014, Nat Rev Genet; Chen et *al.* 2018 Plos Pathogens). Our immune responses to current infectious agents are in part determined by our responses to past selective pressures, with either positive or negative effects (e.g. immunopathology, maladaptation to new pathogens, see Graham et *al.* 2005, Ann Rev Eco Evo Syst). In parallel, our immune systems, but also our behavioural and cultural responses, can potentially exert selection pressures on pathogens (Weinstein et *al.* 2011. Med. Hyp.).

Co-evolutionary processes take time (determined by mutation rates and generation time); they begin once transmission from animal to human is completed (we refer to this as *spillover*). In many cases, for example Ebola in West Africa, the pathogen evolves very slowly in humans and remains relatively stable.
The virulence of newly emerged pathogens can be attributed to the absence of coevolution between humans and the infectious agent (e.g. symptoms caused by Hantavirus infections, Schonrich *et al.* 2008, Immunol Rev). Initial virulence seems to increase with the phylogenetic distance between humans and the animal host (Guth *et al.* 2019, Phil Trans, Longdon *et al.* 2005, Plos Pathogens). Co-evolutionary processes may lead to a decrease in pathogen virulence (the 'traditional wisdom' hypothesis, see May and Anderson 1983, Proc R Soc Lond B Biol Sci ; virulence/transmission trade-off), but also to its increase, when virulence and likelihood of transmission or competitiveness of the infectious agent are positively correlated, for example, due to short-term intra-host evolution (see for a review Levin 1996, EID) or to stochastic events associated with pathogen emergence (André and Hochberg 2005, Evolution). Thus, the tuberculosis agent *M. tuberculosis* seems to have evolved towards a potential for increased transmission and virulence despite a long history of coevolution with humans (Gagneux 2012, Phil Trans). Host changes may result in a breakdown ("disruption") of coevolution and thus favour the emergence of diseases with severe forms (Corvalan *et al.* 2019 Cancers; Jorgensen *et al.* 2019**.** Annu. Rev. Ecol. Evol. Syst.).

DISSENSUS:

None identified at this stage.

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

Studies analyse animal-to-human transmissions where pathogens persist long enough to be detected.
However, it is highly likely that many transmissions fail, for genetic/physiological reasons, or because non-adaptation/adaptability prevent the spillover of wildlife pathogens into humans. Spillover success is more likely when its "cost" is mitigated, i.e. when the nutritional, immunological, etc., background in humans is weakened.

NEED FOR RESEARCH:

Study the phylogeny of viruses to estimate the temporal and spatial changes in their genetic variability. Investigate the evolution of virulence in the field, even though this type of research is complicated by factors of heterogeneity (health system, population age structure, etc.). The link between health at the individual level and emerging infectious risk could be explored. Research also needs to focus on better understanding the spread of pathogens, the origin of disease emergence and its evolution in order to better predict and prevent the emergence and re-emergence of human infectious diseases (Jorgensen et *al.* 2019**.** Annu. Rev. Ecol. Evol. Syst.).

SPECIAL CASE OF COVID-19:

We are faced here with a true emergence (i.e. a new virus, unknown to humans). There can be no short-term co-evolutionary response on the human side of this interaction due to our long generation time (decades, on average) and the low selection pressure exerted by the virus (mortality mainly affects people who have already reproduced). The virus, however, has a much shorter generation time (a few days) and could theoretically mutate and be subject to selection pressures from the natural or medicalized immune system of humans or other animal species that may have served as intermediate hosts. It is worth noting the strong influence of genetic drift (i.e. evolution caused by random events) during disease emergence and pandemic events.

SHEET 6

Are certain taxonomic groups more likely to cause zoonotic diseases? If so, why?

CONSENSUS:

Certain groups of animals seem more likely to cause zoonotic diseases:

- Those that are genetically and physiologically close to humans (mammals - primates in particular - but also other homoeothermic vertebrates such as birds) (Davies and Pedersen, 2008, Procs Roy Soc B, Olival *et al.* 2017, Nature, Copper *et al.* 2012, Ecol Lett.).
- Species with a long history of cohabitation with humans: domestic animals (Suidae in particular), commensal species and game. The number of zoonotic viruses was found to increase with the age of domestication of a domestic species (Morand and Figuié 2016, QUAE eds) and with population abundance in mammals that have adapted to anthropized environments (Johnson *et al.* 2020, Proc Roy Soc B).

DISSENSUS:

The link between species richness and the ability to harbour a greater diversity of pathogens remains controversial.
According to Mollentze and Streicker (2020, PNAS), the number of viruses in different orders of mammals and birds is related to the number of species in that order. Moreover, the proportion of viruses that are zoonotic is homogeneous in different taxonomic orders of mammalian and bird reservoir hosts, and increases with the age of domestication of domestic species (Morand and Figuié 2016, Editions Quae). Thus, the number of observed zoonoses within animal orders increases with the species richness of the order. The number of zoonotic viruses within a species also scales positively with the abundance of that species (Johnson *et al.* 2020, Proc. R. Soc. B).
The alternative view is that certain groups of animals are preferential hosts for certain categories of pathogens because of particular features in their genome, immune system, ecology, life traits, or physiology. This hypothesis has been put forward for chiropterans and other groups of mammals such as primates, carnivores and rodents (Locatelli and Peeters 2012, Nature Education Knowledge; Han et *al.* 2015, PNAS; Olival *et al.* 2017, Nature; Schountz et al. 2017 Front immunol; Wells *et al.* 2019, GEB; Rossetto, 2020, PLos One; Luis et *al.* 2013, Procs). The following mammalian orders appear to harbour the highest proportion of zoonotic viruses: Rodentia, Chiroptera, primates, Artiodactyla, Carnivora, in descending order of importance (Han *et al.* 2016, Trends Parasitol.).

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

The particular interest given to certain taxa (chiropterans and rodents in particular) may cause a sampling bias, with over-representation of these taxa. These taxa are nonetheless important sources of zoonotic diseases.

NEED FOR RESEARCH:

There is a need to understand entire biological communities and develop broad taxonomic sampling efforts as well as reintegrate the notion of "**Pathocenosis**" in training courses and research practice.

SPECIAL CASE OF COVID-19:

There is a lack of scientific data to date, apart from evidence of high sequence similarity of the virus (a Betacoronavirus) in humans and bats from China belonging to the genus *Rhinolophus*. The hypothesis of the role of an intermediate host such as the Malayan pangolin *Manis javanica* is plausible but remains to be demonstrated, as does the possibility of recombination mechanisms that may have occurred (Hassanin *et al.*, 2020, Mammalia).

SHEET 7

What do we know about the processes that enable different types of human pathogens to cross the species barrier?

CONSENSUS:

In the living world, in which organisms are ever-evolving and in constant interaction, life must be seen as a set of networks, not as separate compartments. The notion of barrier therefore paints a false picture, except for saying that it is there to be crossed. Although this cannot not be quantified, it is very likely that humans are very frequently exposed to infectious agents from wildlife, but that infection success is extremely low (Wood *et al.* 2012, Phil Trans, Morse *et al.* 2012, Lancet).
The question of crossing the species barrier has been relatively well studied by British and North American researchers since 1995 (Woolhouse 1995, Vaccine, Antia et *al.* 2003, Nature etc.). This process involves different steps including cross-exposure to an infectious agent or contact between hosts, the capacity of the infectious agent to infect a new host, and possibly adaptation of the infectious agent to its new host, which may improve its capacity to jump from one host to another (see Parrish et *al.* 2008, Microb Mol Biol Rev for a review of the mechanisms).

Spillover is easier between humans and primates because of their biological proximity; this is true for different types of pathogens (viruses, bacteria, parasitic worms, ectoparasites, etc.) (see **SHEET 6**, Wolfe *et al.* 1998, Emerg Infect Dis). It is also promoted by close contact, especially with commensal (Han *et al.* 2015, PNAS, Davis *et al.* 2005, Vect Born Zoon Dis) and domestic species (Morand and Figuié 2016, Editions Quae).

This phenomenon is facilitated at different levels (see Parrish *et al.* 2008, Microb Mol Biol Rev for details on the mechanisms):

- Via ecological processes through enhanced contact or exposure, for instance in more fragmented landscapes (see Borremans 2019, Phil. Trans. R. Soc. B)
- Via cellular processes involving host receptors/anchor proteins of infectious agents (e.g. ACE2 receptors for coronaviruses). On a finer scale, there may be a loss of genes or gene functions (e.g. the human pertussis bacterium, of zoonotic origin). Many bacteria acquire "gene cassettes" and bacterial plasmids, for example.
- Via evolutionary processes involving the immune system and the genetic diversity of the potential host (the innate response could eliminate a large proportion of infectious agents crossing the host barrier), the genetic diversity of the infectious agent and its rate of evolution (mutation, recombination, re-assortment for viruses), etc.. Thus, RNA viruses have been identified as important pathogens that need to be monitored because of their high rate of evolution and their ability to adapt to new environments (Grenfell *et al.* 2004, Science). Some viruses replicate in the cell cytoplasm, not in the nucleus, and thus seem to be able to infect several species more easily (Pulliam *et al.*, 2009, J Infectious Diseases).

DISSENSUS:

The mechanisms underlying this phenomenon are relatively well-known for certain pathogens (e.g. RNA viruses), but remain more hypothetical for others.

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

This issue is very complex and multifactorial. There have been theoretical studies on this subject but the need for field studies remains great. In particular, a complete understanding of the phenomenon, combining the analysis of the dynamics of the infectious agent within its animal reservoir and outside its reservoir (survival in the environment, dispersal), is often lacking.

An analysis of the interaction between exposure, infectious dose and host immune response would help us better understand spillover events (Plowright *et al.* 2017, Nat Rev Microb).

The study of unsuccessful *spillovers* could also be very informative. To this end, a more exhaustive survey of the microbial agents circulating in wildlife (Anthony *et al.* 2014, mBio) would make it possible to better identify the characteristics of zoonotic agents that have crossed the animal-human 'barrier', compared to non-zoonotic agents that have not (yet) crossed this 'barrier'.

NEED FOR RESEARCH:

Research in evolutionary biology and modelling is needed to better address these issues. Understanding how the various barriers (exposure, human-infectious agent interaction, etc.) are linked and how the spatio-temporal variability of these barriers (seasonal fluctuations in pathogen dynamics, spatial variations in human population behaviour, etc.) affects spillover, would improve the development of approaches dedicated to modelling the ecology of zoonotic risk (Plowright *et al.* 2017, Nat Rev Microb).

SPECIAL CASE OF COVID-19:

Covid-19 most likely originated from contact between humans and wild animals carrying the SARS-CoV-2 virus or a closely related form. On the 12th of March 2020, the journal Nature published two scientific articles written by Chinese research groups that indicated, based on high genetic sequence similarity, that bats were potential reservoirs of the SARS-CoV-2 virus (Wu *et al.* 2020, Nature, Zhou *et al. 2020,* Nature). A sequence of the virus found in the bat species *Rhinolophus affinis* was 96% identical to that of SARS-CoV-2 (Zhou et *al.* 2020, Nature). Other animals could also have contributed to the emergence of this zoonosis (Wu *et al.* 2020, Nature); the hypothesis that consumption of the Malayan pangolin, *Manis javanica*, may have played a part seems relevant but still needs to be confirmed (Lam *et al.* 2020, Nature). Recombination has been observed in other coronaviruses, which has allowed them to adapt to new hosts. For example, the virus responsible for SARS in 2003 lost 29 nucleotides when it passed from civets to humans (Guan *et al.* 2003, Science).
In addition, work (virology, cell biology, phylogeny, etc.) is being carried out on the interaction between the coronavirus S protein and ACE2 receptors, which are the entry points for coronaviruses in host cells (Li *et al.* 2003, Nature, Li *et al.* 2006, J Virol). This should make it possible to better predict which coronaviruses can cross the species barrier (bats/other wild animals, domestic animals or humans) (Liu et al. 2020, J Med Virol, Zhou *et al.* 2020, Nature).

SHEET 8
Are intermediate hosts always critical for the emergence of zoonotic diseases?

CONSENSUS:

The intermediate host is an animal species that may allow the infectious agent to become pathogenic to humans, may allow it to multiply or may increase the exposure of humans to that infectious agent. Intermediate host species have specific life traits (diet, immune system, synanthropy - the adaptation of species to anthropized environments -, etc.) that allow it to act as a "go-between" reservoir species and humans, which would otherwise have rarely come into contact. They are also species that live in close proximity to human populations (livestock, and domestic and commensal animals). These hosts have an amplifying role by increasing exposure or through their ability to carry, multiply and transmit the pathogen. For many diseases, domestic or commensal animals (i.e. animals that live close to humans, such as rats, some insects) act as intermediate hosts (e.g. pigs in the Nipah virus epidemic). These animal communities, through their contact with humans, play an important and recurrent role in transmitting or 'humanizing' infectious agents.

However, zoonotic diseases do not always have an intermediate host and can be transmitted directly from the reservoir to humans. Examples include rabies, brucellosis, tuberculosis, Ebola, hantavirus fevers, leptospirosis. Furthermore, several species may associate to form a multi-host system (Webster *et al.* 2017, Phil. Trans. R. Soc. Lond. B).

DISSENSUS:

None identified to date.

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

Certain important functions are under-studied, in particular the role of omnivorous species (pigs, rats) in trophic transmissions, but also in airborne transmissions (e.g. Nipah) and transmissions in anthropized environments.

NEED FOR RESEARCH:

The relative importance of these intermediate hosts, or host networks, in increasing exposure, increasing the volume of infectious agents that come into contact with humans, and for the evolution of these infectious agents into "variants" with greater a capacity for human infection and human-to-human transmission should be clarified.

SPECIAL CASE OF COVID-19:

According to Cui *et al.* (2018, Nature Reviews Microbiology), the majority of coronaviruses that are transmitted to humans have an intermediate host (llama, civet, dromedary, pigs). This may be the case for SARS-CoV-2, but this remains to be scientifically demonstrated. The cramped conditions of captivity (of animals such as the Malayan pangolin *Manis javanica*) that lead to stressed, immunocompromised animals should be taken into account as a facilitator of transmission (Lam *et al.* 2020, Nature, Hassanin et *al.* 2020, Mammalia).

We lack hindsight to rule out the possible role of carnivores in disease transmission. Leroy *et al.* (2020, One Health) report cases of probable contamination of felines in an American zoo as well as sporadic cases of contamination of pets. The French national institute for health, food, environment and work security (ANSES) has indicated that experimental infections demonstrate the receptivity of some animal species to the virus (ferrets, hamsters and to a lesser extent cats, from human transmission, see ANSES Opinion Referral No. 2020-SA-0037). Taking these new elements into account, ANSES nonetheless

considers that there is currently no scientific evidence that show that domestic animals (livestock and pets) play an epidemiological role in the spread of SARS-CoV-2.

SHEET 9
What are the evidence-based links between zoonotic diseases and biodiversity loss?

CONSENSUS:

There is rising evidence that global environmental change, loss of biodiversity and its associated regulatory services and the emergence or increase in prevalence of infectious diseases are correlated.
The risk of zoonotic disease emergence and spread may be augmented by the erosion of biodiversity (at the species or genetic level) through ecological (habitat destruction and fragmentation, food chain disruption, pollution, stress), epidemiological (dilution/amplification phenomena associated with the disruption/reorganisation of ecological communities), adaptive (behavioural changes, the concept of synanthropic species – wild species that have adapted to anthropized environments) and evolutionary (disruption of co-evolutionary links between hosts and pathogens) factors.

Bibliography: Patz *et al.* 2000, Int. J. Parasiol; Suzan *et al.* 2009, Plos One; Keesing et *al.* 2010, Nature, Young *et al.* 2014, PNAS, Morand *et al.* 2014, Plos One, Aguirre 2017, ILAR J. Nava et al. 2017, ILAR J. , Ecke et al. 2017, Ecol. & Evol. Interface, J. R. Soc. Interface, McMahon *et al.* 2018, Zoonose Public Health, Ellwanger *et al.* 2020, An. Acad. Bras. Cienc, Rohr *et al.* 2020, Nature Ecol. & evol.

For more details, see fact sheets 10 (deforestation), 11 (infrastructure), 12 (urban development) and 22 (maintenance of species biodiversity and the dilution effect), which describe specific aspects of the link between zoonotic diseases and biodiversity loss and the underlying eco-evolutionary processes.

DISSENSUS:

There is no particular dissensus within the biodiversity science community.

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

Criticisms highlight a lack of evidence regarding the potential mechanisms linking biodiversity and disease. This needs to be addressed, while bearing in mind that it is difficult to carry out experiments at these levels.
In addition, it is important to distinguish the consequences of environment and habitat destruction from those of habitat conversion (forests converted for crop production or plantations).

NEED FOR RESEARCH:

Further research should be carried out:

- To better understand the ecological and evolutionary processes that can explain observed patterns.
- To assess the link between reduced population size in declining species and the risk of transmitting their microorganisms to domestic animals and humans.
- At the community level, and within the framework of the interaction between biocenoses and **pathocenoses** (Johnson *et al.* 2015, Science, Vayssier-Taussat *et al.* 2014, Front Cell Infect Microb).
- Integrating the diversity and role of microbiota (Trevelline *et al.* 2020, Mol Ecol, Trevelline *et al.* 2019, Procs Roy Soc).
- To assess the influence of different spatial scales on observed patterns (see Rohr *et al.* (2020, Nature Ecol. & evol.) for a detailed review of research perspectives and Johnson et *al. (2015*, Science) who argue in favour of community ecology).
- In historical ecology, to integrate the history and dynamics of biodiversity loss in the analysis of present day biodiversity patterns.

SPECIAL CASE OF COVID-19:

To date, there is a complete lack of scientific knowledge regarding the link between biodiversity and the emergence of Covid-19. However, it has been previously reported that serious damage to biodiversity, in particular to the integrity of ecosystems, in China has impacted the population dynamics/viability of certain species including bats.

SHEET 10
What are the links between biodiversity and zoonosis regulation?

CONSENSUS:

Pathogen regulation is one of the services provided by ecosystems listed by the IPBES. It relies on the dynamics, within an ecosystem, between species that regulate transmission and those that spread pathogens among individuals and even among species. Pathogens are regulated via various mechanisms, including the dilution effect (see sheet 22), the use of active principles against pathogens, and the exposure to a diversity of antigens that promote immunity. Some studies, which have used the EcoHealth approach, have shown that the more diverse ecosystems are, the less diseases are transmitted (Myers et al. 2013, PNAS, Johnson et al. 2013, Nature).

However, it is difficult to generalize the link between biodiversity and zoonotic diseases, in part because empirical evidence of a relationship between host competence (the ability to maintain and transmit infections) and animal community structure, comprising species with varying levels of competence, is difficult to obtain (Johnson et al. 2013, Nature). As an example, field data have shown that host diversity inhibits transmission of the virulent pathogen *Ribeiroia ondatrae* and reduces disease in amphibians. By revealing a link between species richness and community competence, these results highlight the influence of biodiversity on infection risk and emphasize the value of a community-scale approach to understanding infectious diseases (Johnson et al. 2013, Nature).

Most evidence of this regulatory effect comes from the corollary that the more degraded ecosystems become, the less biodiversity there is, the more easily diseases are transmitted and the less effective the regulatory service is (Gottdenker et al. 2014, EcoHealth, Keesing et al., 2010, Nature, Ostfeld and LoGiudice 2003, Ecology, Faust et al. 2018, Ecology Letters, Halliday et al. 2020, Ecology letters). Thus, Halliday et al. (2020, Ecology letters) demonstrated that the dilution effect was negatively correlated with biodiversity gradients associated with biodiversity loss, rather than positively correlated with biodiversity levels. Faust et al. (2018, Ecology letters) assessed different scenarios of land conversion and found that the highest risk of pathogen spillover from animals to humans occurs at intermediate levels of habitat loss, while the rarest, most important outbreaks in humans occur at extreme levels of land conversion. More recently, Gibb et al. (2020, Nature), through the analysis of 6,801 ecological assemblages and 376 host species worldwide, showed that wild species that harbor the most human pathogens are globally favored in degraded ecosystems (secondary, agricultural and urban ecosystems) relative to nearby undisturbed habitats.

There is a growing consensus that land use change increases the risk of human infection and disease emergence globally (see Fact Sheets 11-14). The most common types of land use change associated with disease transmission are:
- deforestation, forest fragmentation, habitat fragmentation;
- agricultural development, irrigation;
- urbanization, peri-urban development.

More than half (56.9%) of the studies reviewed by Gottdenker et al. (2014, EcoHealth), addressing how anthropogenic change influences the dynamics of infectious diseases, documented increased pathogen transmission; 10.4% of the studies reported decreased transmission; 30.4% reported variable and complex responses; and 2.4% detected no change. Commonly reported mechanisms by which land use change has impacted infectious disease transmission include disruption in vector or host ecology; alteration of the pathogen niche; changes in host and vector community composition; changes in behavior or movement of vectors and/or hosts; alteration of the spatial distribution of hosts and/or vectors; socioeconomic factors; and environmental contamination (Gottdenker et al. 2014, EcoHealth). On a practical level, this work suggests that maps showing areas of biodiversity loss, i.e. areas where pathogen regulation will be affected or impaired, will identify areas with an increased risk of zoonotic disease emergence (for example, see Rulli et al. 2020, Public and Global Health). By contrast, maps that

only show biodiversity levels do not indicate whether a dilution effect occurs in areas with the highest diversity levels.

DISSENT:

The question of the generality of the dilution effect is still debated in the scientific community (see Johnson et al. 2015, Ecology letters, Salkeld et al. 2013, Ecology letters, see SHEET 24).

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

Few cause-and-effect relationships have been demonstrated. Halliday et al. (2020, Ecology Letters) found a lack of correlation between species diversity (or more precisely, low levels of biodiversity loss) and zoonotic risk in experimental studies that considered rather artificial (i.e. not representative of real cases) species assemblages. These authors found a correlation by excluding these experimental studies from their analyses.

NEED FOR RESEARCH:

Accelerating rates of population collapse, species extinction and disease emergence highlight the importance of understanding how changes in biodiversity affect the occurrence and evolution of zoonotic diseases in the context of increasing human demographics and infrastructure development. Further work comparing the structure of host communities (including traits associated with community competence and host biodiversity) under a variety of factors influencing biodiversity in a variety of ecological systems is needed to assess whether the dilution effect can be generalized. There is also a need to understand the degree to which biodiversity influences disease risk among specialist and generalist species in the context of biodiversity loss (Halliday et al. 2020, Ecology Letters).

SPECIAL CASE OF COVID-19:

The hypothesis that the emergence of Covid-19 is due to the loss of pathogen regulation in Wuhan Province, China, is one of the strongest to date, although it remains to be formally demonstrated. Note that Rolli et al. (2020, Nature - research Square) showed that areas hosting suspected SARS Cov2 host populations (horseshoe bats) are biodiversity hotspots that are strongly affected by land conversion: high forest fragmentation, high presence of livestock and high levels of urbanization.

SHEET 11
What is the link between agriculture and the increase in zoonotic diseases?

CONSENSUS:

Different agricultural systems, ranging from intensive agriculture to more sustainable practices such as organic farming, have varying impacts on the emergence and spread of zoonotic diseases (Jones et al. 2013, PNAS). It is generally accepted that intensive agriculture has led to increased food production at the cost of homogenizing biodiversity and decreasing many ecosystem services, whereas small-scale extensive family farms and farming systems such as organic agriculture contribute to greater biodiversity, improved soil and water quality, and increased food nutritional value (IPBES, 2019). In particular, intensive domestic animal husbandry can create the conditions for the establishment of "pathosystems" when interactions occur with potentially pathogen-carrying wildlife. This point is specifically addressed in FACT SHEET 17 of this document.

Industrial agriculture is recognized as having major negative impacts on biodiversity. It influences and exacerbates each of the five direct drivers of biodiversity loss identified by the IPBES: land use change, direct resource extraction, climate change, pollution and invasive species. The consequences are twofold. First, these pressures contribute to negative effects on human health, such as pollution by various chemicals (which has a direct impact on farmers and an indirect impact via the environment and food, with consequences on the immune system), loss of food diversity and lower food nutritional quality. Second, they contribute to the loss of ecosystem services that humans derive from nature and among them, soil functioning, pollination and the regulation of pathogens affecting species that are useful to humans, humans themselves, or non-humans.

A synthesis of the literature by Rohr et al. (2019, Nature sustainability) suggested that, since 1940, agricultural factors have been associated with more than 25% of all infectious diseases - and over 50% of all zoonotic diseases - that have occurred in humans, proportions that will likely increase as agriculture expands and intensifies. Morand (2020, Biological Conservation) showed that the increase in infectious disease outbreaks affecting humans and those affecting livestock is associated with the growth of livestock populations. For example, the Japanese encephalitis virus, which is transmitted by mosquitoes of the genus *Culex*, has established a secondary cycle in domestic pig populations in Asia where it amplifies and spreads to human populations (Kock 2015, One health, Erlanger et al. 2009, Emerg Infect Dis, Misra and Kalita 2010, Progress in Neurobiology, Kaiser et al. 2005, Acta Tropica, Le Flohic et al. 2013, PLOS Negl Trop Dis, Van der Hurk et al. 2009, Annu. Rev. Entomol, Hasegawa et al. 2008, Am. J. Trop. Med. Hyg.). Expansion and changes in agricultural practices are also associated with the emergence of the Nipah virus in Malaysia (Walsh 2015, Trans Roy Soc Trop Med Hyg). Significant associations have thus been observed between animal husbandry, especially swine and poultry, and zoonotic diseases (Damayanti et al. 2017, Biomed Pharmacol J). A meta-analysis of 34 scientific publications (Shah et al. 2019, Nature Communications) showed that in Southeast Asia, people living or working on agricultural land are on average 1.74 times more likely to be infected by a pathogen than unexposed individuals, thereby suggesting that agricultural land use exacerbates many infectious diseases. For example, populations working or living in or near oil palm plantations are more likely to be infected with vector-borne and zoonotic diseases (leptospirosis and *Plasmodium knowlesi*), and exposure to rubber plantations increases the risk of being infected with all the pathogens investigated in the study (Tangena et al. 2016, Trends in parasitology, Chadsuthi et al. 2018, Epidemiology & Infection).

If wild birds are indeed virus reservoirs, the acceleration of viral transmission is clearly dependent on the increase in poultry production. Thus, the countries and regions that are most susceptible to avian influenza epidemics are those with high poultry production. This is confirmed by data from the World Organization for Animal Health (OIE), with Asian countries reporting the highest number of highly pathogenic avian influenza outbreaks between 2005 and 2020. The increase in the number and size of poultry farms is the result of the increase in demand and supply, reinforcing the role of the circulation of commercial poultry in viral transmission. A study published in 2020 confirmed that the spread of different

highly pathogenic avian influenza viruses is geographically associated with the intensity of the poultry trade in China (Yang et al. 2020, PNAS).

The destruction of natural ecosystems (see FACT SHEET 9) as a result of agricultural practices is now considered, based on multiple examples, to be one of the major explanatory factors for the increase in the number of emerging infectious epidemic diseases (Jones et al. 2013, PNAS, Faust et al. 2018, Ecology Letters, Murray and Daszak 2013, Current Opinion in Virology, Lambin et al. 2010, Inter Jour Health Geo, Gottdenker et al. 2014, EcoHealth, Patz et al. 2000, Inter Jour for Paras, Patz et al. 2004, Env Health Pers, Morand 2020, Biological Conservation). Deforestation and the associated environmental changes appear to facilitate the transmission of the malaria agent *Plasmodium knowlesi* (Brock et al. 2018, Proc. Roy. Soc. B), particularly in areas that have been deforested within the past five years (Fornace et al. 2016, Emerg Infect Dis). Guo et al. (2018, EcoHealth) and Faust et al. (2018, Ecology Letters) established that habitat fragmentation, and agriculture in particular, benefit host and vector communities and may therefore increase transmission risk by exacerbating pathogen prevalence via a highly context-dependent relationship influenced by multiple factors. For example, agriculture and rural development based on irrigation may expand the habitat of *Culex* mosquito vectors. Furthermore, an increase in *Leptospira* infections and deaths in Thailand has been observed in open habitats such as rice fields that are prone to flooding (Della Rossa et al. 2015, Epidemiology & Infection).

DISSENT:

There is strong disagreement regarding the strategies that should be implemented in human-nature relationships, ranging from those that favor the coexistence of humans and the rest of biodiversity within a shared space (land sharing) to those that advocate the protection of areas with little or no human activity (land sparing) (Narat et al. 2015, EcoHealth, Cibot et al. 2015, PLOS Negl Trop Dis), although in reality this dichotomy is not desirable from the perspective of producing multifunctional landscapes (see Law et al. 2015, Biological Conservation).
Questions persist regarding the influence of the design and size of livestock systems on the risk of zoonotic disease emergence, which can occur on both small-scale (Lowenstein et al. 2016, Am J Trop Med Hyg) and factory farms (Leibler et al. 2008, PPLPI Research reports). Another study predominantly identified intermediate-sized farms as posing a risk (Hosseini et al. 2013, PLOS ONE). The risk seems to vary with the type of farm considered, with traditional feeding systems increasing the risk of virus transmission from wild animals to humans, whereas intensive farms being more likely to be responsible for disease amplification due to high animal densities (Espinoza et al. 2020, Env and Res Eco).

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

Epidemics and health crises raise the problem of linking local events (emergence and early transmission) to global events (widespread transmission), which requires an understanding of epidemic processes at different spatial and temporal scales.
The generality of the relationship between zoonotic diseases and agriculture has not been assessed, despite the observed correlations. Evidence linking agriculture-induced land use change to infectious disease risk in humans has not been systematically assessed or quantified.
In addition, we lack data on the effect of low level chronic pollutants on health/susceptibility to infectious agents (not just in humans but also in livestock and wild reservoirs that live on or at the interface with these agricultural lands, such as birds or insect-feeding chiropterans).

NEED FOR RESEARCH:

Most research on the link between agriculture and disease has focused on the health effects of occupational exposure to pesticides, chemicals and heavy metals.

The consequences on human and animal health of nature-based solutions (implemented to mitigate climate change) and rewilding (biodiversity protection) need to be studied. In particular, dilution effects must be better documented.
It is also necessary to extend this research area with an interdisciplinary (OneHealth) approach in order to improve our understanding of the links, and the underlying mechanisms, between changes in land use and practices associated with agricultural development and the multiplication of zoonoses, as well as prevent zoonotic diseases by adapting agricultural and food practices (Cappelle et al. 2020, Bulletin of the WHO).

SPECIAL CASE OF COVID-19:

Rulli et al. (2020, Nature ResearchSquare) observed that rhinolophid populations, suspected of having participated in the emergence of SARS CoV2 because they harbor SARS coronaviruses, were located in areas of high biodiversity where forest fragmentation, increased agricultural intensification, livestock densities and human habitation are high.

SHEET 12

What are the evidence-based links between zoonotic diseases and deforestation (and the development of agriculture and monospecific plantations)?

CONSENSUS:

It is widely acknowledged that there is a link between deforestation and the increase in the number of zoonotic diseases in Asia, Africa and South America.
However, a number of explanatory factors related to deforestation could underlie this observation:

- Factors that are likely to reinforce the effects of deforestation **(climate change and extreme climatic events, changing seasonal and rainfall patterns**), affect human populations and potentially promote the proliferation of vectors,
- The effects of deforestation on landscapes and community ecology: reduction of biodiversity, especially predator diversity, disruption of community functioning (trophic interactions), habitat loss and fragmentation,
- Human activities associated with deforestation: increased human presence in forest habitats, particularly via communication infrastructures, and the development of hunting, poaching and bushmeat consumption,
- Changes at the interface between human populations, wild animals and domestic animals: increased human-wild animal and domestic animal-wild animal interactions at urban-forest interfaces and increased spillover.

There is also a consensus that land use changes related to agriculture, monospecific plantations, extractive activities, the development of hydroelectric and road infrastructures and urban development have resulted in an increase in the number of zoonotic disease outbreaks in previously forested areas, and more generally in areas previously unaltered by human activity.

Bibliography: Arevalo-Herrera *et al.* 2012. Acta Tropica, Rebaudo *et al.* 2014, Plos Neg. Trop. Dis. Morand *et al,* 2014, Plos One, Alarcón de Noya and Gonzalez, 2015, Acta Tropica, Ajesh *et al,* 2017, Zoon. Pub. Health, Morris *et al,* 2016, Sci. Adv. Nava et *al.* 2017 ILAR J. Erazo et al. 2019, Parasite Vectors, Ellwanger *et al.* 2020, An. Acad. Bras. Cienc, Olivero et al. 2017, Scient. Rep. Rulli et *al*, 2017, Scient. Rep. Singh *et al*, 2019, Vet. Quarterly.

The link between Ebola virus disease outbreaks in Africa and deforestation events is particularly clear, and illustrates the link between deforestation and the increase in the number of disease outbreaks (Olivero *et al.*, 2017, Scient. Rep., Rulli *et al.* , 2017, Scient. Rep.). Studies on the Nipah virus in Asia also illustrate how behavioural changes in species whose habitats have been disturbed or destroyed due to deforestation can lead to the transmission of pathogens to domestic animals and humans (Singh et *al.* , 2019, Vet. Quarterly).

DISSENSUS:

There is no dissensus within the biodiversity science community on the link, globally, between deforestation and zoonotic disease emergence. It should be noted, however, that there are a few examples where the effect of deforestation on infectious risk may be positive, negative or absent depending on the situation (Young *et al.* 2017 Phil Trans.).

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

There is a lack of case studies linking the emergence of pathogens, deforestation and the development of monospecific plantations.

NEED FOR RESEARCH:

Multiply the number of specific case studies, clarify the role of monospecific plantations, determine the specific effects of deforestation versus human intrusion to exploit resources.

SPECIAL CASE OF COVID-19:

No specific study has been carried out nor is any knowledge available to date. Deforestation is still ongoing in several Chinese provinces and neighbouring countries (notably Vietnam and Laos), where hosts of the viruses currently presumed to cause Covid-19 (fruit bats and pangolins) are found.

SHEET 13

What are the evidence-based links between zoonotic diseases and the development of human infrastructure (roads, etc.)?

CONSENSUS:

The unprecedented development of human infrastructure, in particular roads, dams, infrastructure related to mining activities and air and sea transport, is having a considerable impact on the environment. We can distinguish three major roles of infrastructure:

1) as a process that facilitates contact between human populations and zoonotic reservoirs, via the degradation of ecosystems (trophic interactions disrupted by landscape fragmentation, reduced functional connectivity), increased human incursion and activity in the habitats of pathogen reservoir species and by facilitating the movement of these species,
2) as a process that facilitates the spread of zoonotic diseases via the movement of reservoir hosts, intermediate hosts or human populations (human-to-human transmission), and their evolution into epidemics or pandemics via the movement of humans, their pets or domestic animals, or the movement of invasive species that are reservoirs of zoonotic agents (e.g. rats and mice),
3) as a process that allows the entry of new human groups (gold miners and others) that are likely to spread new pathogens to local populations.

The more connected a region is, in terms of the amount of infrastructure and the number of movements, either over long (air or sea) and short (roads or waterways) distances, the more likely it is to play a role in the spread of emerging pathogens with epidemic or pandemic potential and itself be the target of an outbreak. The establishment or expansion of transport networks can therefore facilitate the emergence and spread of zoonotic diseases.

Bibliography: Hosseini *et al.* Plos One, 2020, Maheu-Giroux *et al.* 2010, Acta Trop. , Cesario *et al.* 2011, Global Bioethics, Marsot *et al.* 2013, Plos One, Lucaccioni et al. 2016, Plos One, Puckett et al. 2016, Proc. R. Soc. B, Laurance and Arrea 2017, Science, Lana et *al.* 2017, Plos Neg. Too much. Say. Da Costa *et al.* 2018, Plos One, Djemai,2018, J. Health Econ. Douine et *al.* 2019, Malar. J. Ellwanger et *al.* 2020, An. Acad. Bras. Cienc.

DISSENSUS:

No dissensus within the biodiversity science community.

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

No major knowledge gap; the topic is well researched.

NEED FOR RESEARCH:

Vulnerable human populations in relative isolation are brutally connected to the rest of the world. Moreover, a major lever of development has been the diversification of human activities that impact the environment (building dams, roads - e.g. the opening of roads in the Amazon in the 1970s, the advances of agricultural colonization fronts as another form of infrastructure, but also the construction of railways, for example the Madeira-Mamoré railway at the beginning of the 20th century), which justify the need to develop socio-eco-epidemiological approaches more widely (Benchimol et Silva 2008, His Cien Saude-Manguinhos)).

SPECIAL CASE OF COVID-19:

If wild intermediate host species, consumed as bushmeat or used in traditional pharmacopoeia, are implicated, it will be interesting to identify their national, regional and international supply routes ("pangolin trafficking routes").

SHEET 14
What are the evidence-based links between zoonotic diseases and urbanization?

CONSENSUS:

We are currently observing a major development of the urban network, especially in developing countries and particularly in Africa (which has the highest rate of increase of urbanization in the world) and Asia, leading to major changes to pre-existing natural environments (buildings, roads, modification of waterways, vegetation reduction and fragmentation, constraints on river systems, heat islands, anthropogenic pollution). In a context of high human population density and often degraded health conditions for a large proportion of city dwellers in developing countries, zoonotic health risks are increasing. These risks are associated with rodents and insects, some species or populations of which thrive with the availability of food resources linked to a lack of waste management in many cities in developing countries and to new urban nature management practices (composting, for example) in developed countries, and with vectors that find suitable habitats. Urban centres can be both sites of disease emergence (e.g. arbovirosis, but also human trypanosomiasis) and of outbreaks where diseases spread because of high population densities (Ebola in Africa, plague in Madagascar, typhus in South East Asia, leptospirosis in Brazil, Covid-19 in China and then in many other countries).
A major distinction must be made between city centres and peri-urban areas where there is a transition between urban and rural land uses and which are more likely to be infection sites, in particular due to the presence of a great diversity of farm animals that are likely to come into contact with wildlife (SARS in Vietnam).
Some recent trends, such as 'urban greening' (especially if green spaces are connected to outlying natural areas), eco-tourism and trends that promote increased contact with nature could in some situations facilitate contact with infectious forest agents, in particular those that are transmitted in some countries by non-human primates (e.g. the resurgence of yellow fever and malaria in Brazil, but also Lyme's disease in temperate zones). In no way does this outweigh the benefits for human well-being of reconnecting with nature, or the benefits of increasing green spaces and wooded areas in cities.

Bibliography: Tshimungu *et al.* 2010, Méd. et Mal. Infect. Weaver, 2013, Trends Microbio. Tong et *al.* 2015, Int. J. Environ. Res. Public Health, Saksena *et al.* 2017, AsiaPacific Issues, Toledo et *al.* 2017, Rev. Saude Publica, Possas *et al.* 2018, Mem. Inst. Oswaldo Cruz, Munster *et al.* 2018, New Eng. J. Medicine, Cunha *et al.* 2019, Scient. Rep. Ahmed et al. 2019, Environ Urban, Oliveira *et al.* 2015, Rev. Inst. Med. Too much. Paulo.

DISSENSUS:

No dissensus within the biodiversity science community.

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

Little is known about the emergence of pathogens in urban environments from domestic animals, urban livestock and small synanthropic mammals.
What is the role of ubiquitous and invasive species that thrive in urban environments and are not regulated by predators, especially in developing countries where promiscuity with humans is very high?
What impact do control practices (vector control, rat control, etc.) and urban pollution (air pollution, light pollution, Navara and Nelson, 2007, J. Pineal Res. Bedrosian *et al.* 2011, Biol. Lett. Kernbach et *al.* 2019, Proc. R. Soc. B.) have on diseases? Are interactions between infectious agents, reservoirs and vectors, **pathosystems** and humans different in urban environments? How can we reconcile the importance of biodiversity with the need to minimize health risks, including in dramatically underdeveloped areas where priorities are far removed from these concerns even though the risk is potentially higher?

NEED FOR RESEARCH:

Research is needed to fill the gaps in our knowledge as listed above. Studies on urban biodiversity and ecology are needed, probably making a distinction between cities in "developed" and "developing" countries, and examining the special case of cities in emerging countries. The role of biodiversity in the control of disease vectors, particularly by their predators (regulation service), should also be studied.
There is a need to study the different ways urban populations apprehend nature (the different views on animals, waste management, forms of consumption, etc.), and to continue developing studies on the relationship to urban managed nature and associated practices (new uses of nature). The link between zoonotic diseases and urbanization should be analysed through the prism of socioeconomic inequalities, in city centres and at the city/periphery interface where the link between health and the environment is likely to be different, and therefore where quite different infectious processes could be at work.

SPECIAL CASE OF COVID-19:

The question of the role of wildlife markets is central to understanding the Covid-19 crisis, but scientific data are lacking to date. Are transmissions from humans to domestic and wild animals possible (human to animal transmissions have been reported for various carnivores, e.g. dogs, cats, mink)? If so, could these animals constitute possible sources that may cause an “epidemic rebound”?

SHEET 15

Is there a link between the increase in the number of zoonotic diseases, climate change and exceptional climatic events?

CONSENSUS:

Climate change is one of the factors that affect species and therefore certain zoonotic diseases. The behaviour, activity level, range, and the biotic and abiotic environment of certain species, including those carrying pathogens, may be modified by climate change (Alkishe *et al.* 2017, PLOS One). Several studies show that climate change can impact the transmission of pathogens by influencing their reproduction or survival, or impact their hosts by altering their distribution and mortality rate, or by changing the mode of transmission (Booth 2018, Advances in Parasitology, *Khan et al.* 2019, Int. J. Environ. Res. Public Health). However, the proportion of climate-sensitive pathogens and their characteristics are not known (McIntyre *et al.* 2017, Sci Rep), although four infectious diseases have been identified as climate-sensitive in northern regions (borreliosis, tick-borne encephalitis, bluetongue disease and fasciolosis, Omazic et *al.* 2019, Acta Vet Scand). In some cases, favourable climatic conditions for the vector and host are expanding with climate change (Lord *et al.* 2018, PLOS Medicine) or are expected to do so in the future (Thomassen *et al.* 2013, PLOS One, Shiravand *et. al.* 2019, J Dis Emerg Res).
Viruses and bacteria that have been trapped for thousands or millions of years in the ice can reappear as the permafrost thaws (Revich and Podolnaya, 2011, Global Earth Action, Revich *et al.* , 2012, Int. J. Circum. Health).
Indirectly, climate change is correlated with a set of factors that are more directly related to the risk of zoonotic emergence such as deforestation (Thomassen *et al.* 2013, PLOS One), the disturbance of soils and their microbial communities (Combe 2019, Emerging Microbes & Infections), and floods (Boyce et *al.* 2016, The Journal of Infectious Diseases). These factors may elevate the risk of zoonosis by increasing human population exposure or vulnerability, which are considered to be increasing according to assessments by the IPBES (2019, IPBES Secretariat) and the IPCC (IPCC 2019).

DISSENSUS:

Despite the undeniable influence of climate change on biodiversity and its functioning, dynamics and evolution, no causal link has been established between climate change and the multiplication of zoonoses, although the literature notes a parallel aggravation of these two phenomena. Some studies predict that the effects of climate change are expected to be more severe in developing countries where the difficulties related to a challenging socio-economic and political environment are exacerbated by a lack of epidemiological studies on zoonotic diseases (Naicker 2011, Arch of Clin Micro). However, a review of recent modelling studies shows there is no consensus on the impact of future climate variations on mosquito-borne diseases (Franklinos *et al.* 2019, Infectious diseases).

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

Coupling climate and epidemiological models of zoonotic infectious diseases remains a challenge, particularly because of the complexity of merging these models and their data (Bartlow *et al.* 2019, Vet Sci). Moreover, studies predicting the effects of climate change on the risk of vector-borne diseases tend to underestimate these effects by considering only the direct effects of climate on the ecology of a disease, while omitting the more indirect effects of climate change on the ability of societies to control and prevent these diseases (Odgen 2017, FEMS Microbiology Letters).

RESEARCH NEEDS:

The link could be established on a case-by-case basis, however this requires being able to determine the distributional ecology of any species involved in pathogen transmission, define the environmental conditions required for transmission and project this ecological niche onto geography (Estrada-Peña *et al.*

2014, Trends in Parasitology). The study of the geographical displacement of disease emergence could provide answers to this question.

SPECIAL CASE OF COVID-19:

The lack of data available to date on the origin of the Covid-19 crisis makes it impossible at present to link this specific event to particular climatic variables.

SHEET 16

What are the evidence-based links between zoonotic diseases and the development of bushmeat consumption and wildlife trafficking associated with traditional pharmacopoeia?

CONSENSUS:

The link between bushmeat consumption and trade and emerging infectious diseases has been established in several cases (such as the shift from SIV to HIV, Ebola and SARS) (Karesh *et al.*, 2005, Emerg Infect Dis, Swift *et al.* 2007, EcoHealth). The number of zoonoses related to bushmeat consumption is believed to be currently underestimated (Gomez and Aguirre 2008, Ann N Y Acad Sci, Kurpiers *et al.* 2016, Problematic Wildlife). The bushmeat chain poses a greater risk than the local meat chain (in the way carcasses are processed, meat is stored and consumed, etc.). However, bushmeat trade participants and consumers remain poorly informed about the health risks or do not comply with health management measures, thus extending the risk of infection to the entire meat chain (from hunter to consumer) (Greatorex *et al.* 2016, Plos One, LeBreton *et al.* 2006, An Cons, Kamins *et al.* 2015, EcoHealth). The bushmeat trade tends to be organized regionally in large urban markets (Edderai and Dame 2006, Oryx), and is now expanding internationally via air and sea trade routes (Brown 2004, Rev Sci Tech, Temmam *et al.* 2017, Transbound Emerg Dis). To meet this demand, wild game from a wide range of species is sold in very large volumes (Chaber *et al.* 2010, Cons Lett, Cronin *et al.* 2015, Plos One). These factors (high volume and diversity of species involved, high human density) provide favourable conditions for the emergence and transmission of pathogens (Karesh and Noble 2009, Mount Sinaï J Of Medecine).
However, the most important factor seems to be direct contact with wild animals when hunting, holding animals captive (sometimes) and preparing carcasses for the bushmeat trade. Stress conditions associated with the capture and holding of animals could also increase the risk of pathogen transmission.
The risks associated with traditional pharmacopoeia are reduced once living organisms have been caught and handled, because products are often highly processed (packaged, cooked or dried, reduced to powder, or only specific parts are processed).

Additional literature: Narat *et al.* 2017, EcoHealth; Nahar *et al.* 2020, EcoHealth, Kolodziej-Sobocinska and Miniuk 2018, Medycyna weterynaryjna, Mwangi et al. 2016, African J. of Wildlife Research, Greatorex et al. 2016, PLOS One, Nauman et *al.* 2017, in Trends in game meat hygiene.

DISSENSUS:

The traditional dimension of these activities has been questioned. The development and/or globalisation of these practices potentially scale up their impact; in particular, an increase in volume and rate of resource exchange may increase the number of pathogens. These commercial bushmeat chains can also weaken local populations by competing with them for their food.

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

Practices that may cause zoonoses, other than the consumption of bushmeat, are harder to investigate: taming wild species, consuming the same fruits (cultivated or wild), sharing habitats and having contact with body fluids and excreta (Narat et al. 2017, EcoHealth, Muehlenbein 2017, Am Journal of Phys Anthr). The trade in exotic pets, in particular the trade in new “pet” species to supply an increasingly frantic market, poses a real threat of introducing new microbial agents, including human pathogens, as was the case with the Monkeypox virus in Atlanta in the early 2000s (Smith et al. 2017, EcoHealth).

NEED FOR RESEARCH:

Research using economic and ethno-ecological approaches (in particular, the study of communities that practice hunting and wild game "preparation") could provide valuable insights. Systematic (i.e. non-targeted) virological and serological screening of animals sold on markets could provide a better estimate

of the risk. Increased surveillance of the main platforms for wildlife trade in cities could be an effective strategy to prevent the risk of disease emergence.

SPECIAL CASE OF COVID-19:

As the precise circumstances of the emergence of the coronavirus causing the Covid-19 outbreak have not yet been established, bushmeat consumption cannot be implicated with any certainty at this stage, although the latest data suggest that pangolin, which is intensively consumed in China and South East Asia, could be a potential intermediate host for SARS-CoV-2 (Xiao et al. 2020, Nature; (Hassanin et al., 2020, Mammalia).

SHEET 17

Is it possible to generalise the mechanisms of interaction between livestock, the environment and health?

CONSENSUS:

In many **pathosystems**, there are frequent interactions between wild animals, domestic animals and humans. The passage of a pathogen from one of these compartments to another is often aided by local environmental and cultural factors, as the following examples show:

The case of avian influenza

There appears to be two types of mechanisms for the emergence and spread of this disease in this pathosystem (Dhingra 2018, Front. Vet. Sci.): first, in countries where there has been a shift from backyard to intensive poultry production systems (characterized by multiple circulating viruses, multiple host species, frequent contact at live bird markets, limited biosecurity and frequent vaccination campaigns that impose selection pressures that lead to the emergence of new viral strains (through recombinant mechanisms). Thus, in these countries, family-run backyard poultry farms pose a greater risk than industrial farms. For example, studies of H5N1 avian influenza in Thailand, which affected approximately 1,700 small backyard poultry farms, have shown that the disease was maintained locally by chicken collectors who moved from farm to farm to take chickens to the local slaughterhouse (Paul *et al.* 2011, Acta Trop.). Studies of poultry houses in India and China have shown that it is the medium-sized poultry houses (and not the intensive farms) that increase the epidemic risk as a result of contact between semi-intensively raised birds and wild birds. The smaller the farm, the less densely populated it is, and because the risk of disease emergence and establishment is density-dependent, less densely populated farms are less likely to pose a risk. Management in these regions should therefore focus on the size of family farms so that they do not become too large (it is in fact both a problem of frequency of contact and density dependence).

In developed countries, this risk is correlated with intensive farming as demonstrated by Dhingra et *al.* (2018, Front Vet. Sci.). Indeed, the vast majority of outbreaks have occurred on poultry farms located in areas with high poultry density. Of the 41 documented cases, only two occurred on rural backyard farms, and even these outbreaks occurred in regions of intensive poultry production (Italy in 1997 and France in 2015).

The case of the Nipah virus epidemic

The epidemiological investigation showed that the 1997 outbreak in pigs and humans originated on a large intensive pig farm in northern Malaysia where Nipah virus-infected fruit bats came to feed on fruit trees planted around the farm. The virus spread to susceptible pigs through their consumption of fruit contaminated by bat saliva and urine. The spread of infection between pigs was facilitated by the high density of pigs on the farm and the high number of pig farms in the area, and by the transportation of pigs between farms to the main epidemic area in southern Malaysia. Pigs then served as amplifying hosts for human infection. Nearly all human cases came into contact with pigs; there is no evidence of direct bat-to-human or human-to-human transmission (Kurup 2002, IDCP, Jones *et al,* 2012, PNAS).

DISSENSUS:

The interactions between agriculture and the environment are complex and difficult to generalise from one system to another.

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

Interdisciplinary research in agriculture and health is rare.

NEED FOR RESEARCH:

The evolution of zoonotic risk within the context of greener farming practices (e.g. where animals are more in contact with the outside world and thus with wildlife) also needs to be explored.

SPECIAL CASE OF COVID-19:

Too recent, no evidence available to date.

SHEET 18

What is the link between zoonotic diseases and the development of large-scale livestock farming, the reduction in the number of farmed species and the genetic homogenization of these species?

CONSENSUS:

Numerous studies have established a link between the risk of infection and the intensification of livestock production. There seems to be consensus on several known risk factors:

- close spatial coexistence of livestock and wildlife;
- animal crowding and the hypothesis that an increase in human, crop and livestock densities has the potential to increase both the incidence and severity of infectious diseases (Rohr 2019, Nature Sustainability);
- loss of genetic diversity in livestock species;
- stressful farming conditions.

In factory farms, however, biosecurity measures are easier to implement and reduce the risk of infection but are probably not the global standard.

Like human populations, livestock/poultry populations have increased exponentially in recent decades. Compared to wild mammal and bird populations, they constitute a much bigger and thus more favourable compartment for infectious outbreaks, especially with the development of large-scale transportation of animal products and live animals (Trovão and Nelson, 2020, Plos Path.).
Intensive farming is characterised by high density and stress, and low genetic diversity. However, the implementation of biosecurity measures reduces the access of pathogens to these farms. Emergence risk is therefore less frequent, but when emergence does occur, disease can spread rapidly due to a combination of these vulnerability factors (density, stress and low genetic diversity) (Drew et *al.* 2011, Rev Sci Tech). The persistence of viruses is also sometimes observed on intermediate-sized farms (Hosseini *et al.* 2013, PLOS One).
Moreover, many industrial farms produce a single species with reduced genetic diversity, which increases the chances of runaway propagation of a pathogen in the event of an emergence.
In past avian influenza epidemics, for instance, the role of wildlife in the spread of the disease has always been ruled out (Awada *et al.* , 2018, Trans. Emerg. Dis.): amplification occurred on poultry farms.

This phenomenon is probably better studied in crop pathogens, and strategies to alleviate the risks of disease outbreaks associated with monocultures and intensive farming are starting to be put in place (use of different rice varieties in China, for example).

DISSENSUS:

In the case of avian influenza, it appears that the effect of genetic homogenization has not been investigated.

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

Human societies that do not keep livestock but raise young wild animals as pets have received little attention.

NEED FOR RESEARCH:

The links between agriculture, the intensification of animal and plant production and health, in all its dimensions, must be studied on a global scale. For many diseases, there is a serious lack of research and evidence.

SPECIAL CASE OF COVID-19:

Too recent, no evidence available to date.

SHEET 19

What is the risk posed by human epidemics to wild species (e.g. primates) and pets?

CONSENSUS:

There are many examples of pathogens that have been transmitted from humans to domestic animals, pets or wildlife, including marine mammals and Antarctic birds. The spread of antibiotic-resistant strains of *Staphylococcus aureus* of human origin to great apes, and more generally to primates, is a classic example. Great apes are also subject to outbreaks of measles and various respiratory infections caused by viruses of human origin. Increased interaction between humans and wildlife can lead to complex interactions between anthroponotic and zoonotic transmission processes, as is the case for *Listeria* infections in American black bears and *Plasmodium* infections in humans and gorillas. In the case of the Ebola virus, the natural reservoir is still not identified, but it appears that humans and apes may be exposed to the pathogen within their respective environments. Ecological disturbances of anthropogenic origin, including simplification of communities, introduction of invasive alien species, and growing human intrusion into preserved areas (e.g. eco-tourism) may facilitate the transmission of pathogens from humans to wildlife.

Bibliography: Acosta-Jamett *et al.* 2010, Prev. Vet. Med. Prugnolle *et al.* 2010, PNAS, Medina-Vogel 2013, Microb. Spectrum. Baily et *al.* 2015, Mol. Ecol. Schaumburg et *al. 2015*, Clin. Microbiol. Infect. Leendertz *et al.* 2017, Mam. Rev. 2017, Grützmacher *et al.* 2016, Am. J. Primatol. Scully et *al.* 2018, Emer. Inf. diseases, Parsons *et al.* 2019, Microb. Biotechnology.

DISSENSUS:

No dissensus within the biodiversity science community.

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

The impact of pets on the transmission of pathogens to wildlife needs to be better assessed.
It is important to be aware of the bias associated with relying solely on the similarity of molecular sequences.

NEED FOR RESEARCH:

Accurately assess the reality of anthroponotic transmissions.

SPECIAL CASE OF COVID-19:

Cases of pets (cats and dogs) and wild felines (tigers and lions) in captivity contaminated with SARS-CoV-2 have recently been reported. These cases suggest the possibility of contamination of pets or zoo animals by owners or caregivers. Further studies should be conducted to better estimate the risk of transmitting the virus to pets and the subsequent risk that infected pets could in turn be a source of infection for humans (Leroy *et al.* 2020, One Health).
For a recent comprehensive review of pathogen transmission from humans to non-human primates, see Devaux *et al.* 2019, Front. Pub. Health.

SHEET 20

Should we develop zoonotic disease prediction methods (and models), and on what basis, or should we prioritise the monitoring of weak signals of potential zoonoses?

CONSENSUS:

Different types of models and methods for predicting zoonotic risk exist, and are used for making geographical predictions (identifying where zoonotic agents are likely to emerge and circulate) and for identifying potential reservoirs and infectious agents. However, pathogen emergence must be distinguished from disease emergence because there are many pathogens in wildlife that are potentially dangerous to humans (see the PREDICT programme, USAID), but this does not necessarily mean that a disease will develop into an epidemic (or pandemic).
Mapping areas at risk of emergence, i.e. where hazard, exposure and vulnerability of populations overlap, makes it possible to locate this risk on a relatively fine scale. This risk is greater in tropical forest areas, areas with high mammal species richness and areas linked to variables related to changes in land use (natural habitats converted into agricultural land) (Han *et al.* 2015, PNAS, Han et al. 2016, Trends Parasitol, Allen *et al.* 2017, Nature Communications, Guégan *et al.* 2020, Env. Res. Let.).
Predictions are made (i) on the zoonotic potential of certain microorganisms based on meta-analyses of their biological characteristics (Pulliam 2008, EcoHealth, Olival *et al.* 2017, Nature) as well as molecular and experimental analyses (Russell *et al.* 2012, Science) and (ii) on the range of potential reservoirs of zoonotic agents using meta-analyses (Mollentze and Streicker 2020, PNAS) or machine-learning algorithms (Babayan *et al.* 2018, Science).
Combining these predictive approaches may be useful for effectively targeting the surveillance of geographic areas and organisms (Morse *et al.* 2012, Lancet). Spatial multi-criteria assessment methods are useful for prioritising areas for surveillance, particularly in areas where epidemiological data are difficult to collect (Aenishaenslin et al. 2013, BMC Public Health, Paul *et al.* 2016, Nat. Scient. Rep. Tran et *al.* 2016, Plos NTD).

DISSENSUS:

Monitoring weak signals that would indicate an infectious risk is difficult and unreliable, as the emergence of an infectious agent is an event of extremely low probability resulting from a combination of independent events, which are themselves of low probability. These events may also be subject to high spatio-temporal and non-synchronous variability.
This is nonetheless the objective of international programmes such as PREDICT (Mazet *et al.* 2015, EcoHealth, Joly *et al.* 2016, Int J Inf Dis). Furthermore, mapping emergence zones remains difficult because most of the parameters that are taken into account are associated with hazard rather than exposure (see Chavy *et al.* 2019, PLoS Negl Trop Dis) or vulnerability (Guégan *et al.* 2020, Env. Res. Let.). Thus, so-called emergence risk zones are often spatially over-estimated or poorly identified. These observations also apply to the relationship between climate change and infectious diseases, including vector-borne diseases.

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

Modelling efforts are ongoing but lack development to produce usable results in terms of predictive power. At the very least, they can guide surveillance strategies and identify priorities requiring further attention.

NEED FOR RESEARCH:

Research on the presence of hosts, human commensal species, and more generally species that are closely associated with humans (synanthropic species), as well as the location of areas where there are disruptions in the balance of ecosystems (natural, agricultural and urban environments), would make it possible to better locate potential infectious risk (Han *et al.* 2015, PNAS). The historical context of

epidemics also needs to be taken into account in order to understand how these outbreaks, and their warning signals, have been interpreted by different groups (populations, State services, etc.). Local populations should also be included in eco-epidemiological participatory research approaches (providing information on the local history of epidemics, on changes to the ecosystem, the hydrological system, the behaviour of animals, insects, etc.), and should contribute to the establishment of local observatories.
It is essential to develop, in parallel with biodiversity conservation, surveillance systems that can detect weak signals that could signify the start of an epidemic in humans or domestic animals (Holmes *et al.* 2018, Nature), as well as generic surveillance systems that can detect other anomalies (clinical, epidemiological, etc.). Surveillance must be based on research and methodological developments at the interface between health sciences, social sciences and biodiversity sciences. Integrated ("**One Health**") surveillance should be developed at the interface between human and animal populations and the environment (Bordier et *al.* 2018, Prev Vet Med).

SPECIAL CASE OF COVID-19:

Previous research has identified the possibility of emergence of a coronavirus-induced SARS (Cheng *et al.* 2007, Clin Microbiol Rev). In a context as that of Covid-19 (i.e. animal markets, hunting of certain species and large-scale trade) predictions are not required. Hunting and wildlife trafficking should have provided early warning signals.
To help prevent future epidemics/pandemics such as Covid-19, Daszak *et al.* (2020, Biosafety and Health) have proposed a programme based on the surveillance of wildlife that are likely to be reservoirs for zoonotic agents and of human populations at high-risk of contact with wildlife.

SHEET 21
Is it possible to identify sentinel species?

CONSENSUS:

The identification of sentinel species, which could be used to detect disease emergence risk by providing advance warning, may be possible in certain known cases once the dynamics of the pathogen are understood. Certain life traits of host species harbouring potential human pathogens may justify prioritising the surveillance of these species, in particular species that are increasing in abundance and expanding their range by adapting to anthropized landscapes (Johnson *et al.* 2020, Proc. R. Soc. B.).

DISSENSUS:

No notable dissensus to date.

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

It is difficult to generalize this approach, as it will depend on the zoonotic infection in question. It may be difficult to detect new pathogens in this way.

NEED FOR RESEARCH:

This type of approach is conceivable but requires more knowledge of the characteristics of a particular species in its ability to warn about potential risks, as well as of the dynamics of different pathogens.

SPECIAL CASE OF COVID-19:

The origin and mode of transmission of the pathogen responsible for the Covid-19 crisis are not yet fully established, making it difficult to monitor potential future emergences. However, monitoring species that are known to harbour viruses of the coronavirus family can help identify potential risks.

SHEET 22

Could the management or eradication of wild species or populations that are likely to cause zoonoses be an alternative? How can we avoid the negative reactions in certain sections of the population to species seen as potential sources of zoonotic diseases and epidemics?

CONSENSUS:

The first question refers in part to previous sections (**SHEET 6** and **SHEET 8**) on the taxonomic groups (excluding invertebrates) that are likely to be sources of zoonotic diseases or act as potential intermediate hosts. This question only makes sense from a scientific point of view if we can accurately identify which higher taxonomic groups, possibly even species, are most likely to be involved in new outbreaks of zoonoses. This is not always possible, although there is consensus as to the potential role of certain higher groups (e.g. Rodentia, Chiroptera, primates, Artiodactyla, Carnivora, in descending order of importance) for the transmission viruses, and in certain specific cases where the species responsible for the outbreak has been clearly identified. However, scientists are not the only ones with a say on this issue, especially when the press, the public or political figures start blaming particular taxa, such as bats, which then become the object of rejection by affected populations who will demand the removal or elimination of these animals.

The pure and simple elimination of a particular taxon, entire populations or sub-populations in a given area, beyond the ethical problems it raises, is problematic and raises the question of the impact the loss of this population would have on the ecosystem. This solution can only be envisaged in the case of invasive species. Nonetheless, drastic reductions in host populations are regularly proposed. Yet, beyond the fact that this practice is increasingly seen as unacceptable by society, it may be counterproductive in terms of health objectives. In certain specific cases, reducing host population density has significantly helped resolve a health crisis: for example, the culling of wild boars has contributed to the management of African swine fever outbreaks in Europe. The elimination of individuals can also contribute, alongside other methods, to controlling local outbreaks of, for instance, tuberculosis in badgers or brucellosis in ibexes. In other cases, the large scale indiscriminate elimination of individuals often has a disruptive effect which increases disease risk. This has been shown for instance for rabies and echinococcosis. The relative failure of badger culls in England in reducing the prevalence of bovine tuberculosis is very illustrative at this level and has just led the British government to abandon this practice, which was not well accepted by the public. In Uganda in 2008, a local population of flying foxes (bats) was almost completely exterminated, and the caves that sheltered them were sealed off, following cases of haemorrhagic fever linked to the Marburg virus. This resulted four years later in a serious epidemic, caused by the Marburg virus, associated with the return of a bat population that was much more infected than the one that was present in 2007-2008.
The use of genetic control methods (genome editing, gene drive, CRISPR-Cas-9) in mammalian populations to locally eradicate host populations of pathogens will also have to be limited, considering the risk of spreading these genetic modifications in the wild or transferring them into other species, and the ethical issues raised by these prospects.

When it is possible, the vaccination of humans, domestic or farm animals but also of wild hosts is an effective solution (e.g. rabies in Europe and the New World, foot and mouth disease in South Africa, Kyasanur forest virus, Nipah virus, etc.). Vaccination is considered an option for Ebola in great apes, particularly in "habituated" populations (scientific and tourism activities) and for reducing the transmission of bovine tuberculosis (bTB) by badgers in Great Britain. Vaccination of wild boars in Spain and brushtail possums in New Zealand is also being considered to control bTB. The best example of successful wildlife vaccination remains the eradication of terrestrial rabies in Western Europe through the vaccination of foxes.

Rather than considering culling wild animals, human populations should keep away from potential hosts of zoonotic diseases and ensure the same, as far as possible, for farmed animals and pets. This includes hunting, handling and consuming wild species that are potential hosts for pathogens. The knowledge acquired on the behaviour of these hosts can be used to limit their access to resources or habitats and protect against the risk of contamination (e.g. bats of the genus *Pteropus*, which are sources of the Nipah virus in Asia). Better waste and food resource management can help avoid attracting wildlife close to human habitations and thus reduce the risk of transmission. Education, especially of children, can help reduce the risk of direct interaction with wildlife by teaching them to not handle these animals.

In order to avoid negative reactions in certain populations to species perceived as potentially dangerous (or conversely species seen as totemic, sacred, untouchable), investment in raising awareness and education is essential. This investment has to be adapted to the cultural particularities of different human societies. In particular, it should be stressed that although an animal can, under particular circumstances, spread a pathogenic agent, this does not alter its role in the functioning of an ecosystem and thus in the maintenance of the major life cycles that are indispensable to humans. Scientists have a role to play here to avoid contributing to the stigmatization of certain taxonomic groups.

Bibliography: Kikuti *et al,* 2011, Zoon. Pub. Health, Harrison *et al,* 2011, Biol. Conserv. Amman *et al.* 2014, Em. Infec. Dis. Thanapongtharm *et al.* 2015, BMC Vet. Res. , Ajesh et *al.* 2016, Zoon. Pub. Health, Leendertz *et al,* 2017, Mam. Rev. De Vos *et al.* 2016, Ecol. Velasco-Villa et *al. 2017*, Antiviral Res. Sutherland et *al*, 2018, TREE, Carter et *al,* 2018, Plos One, Singh et *al,* 2019, Vet. Quarter. Parsons *et al,* 2019, Microb. Biotech. Ham et *al*, 2019, J. Appl. Ecol. ANSES, 2019, Prentice *et al,* 2019, J.R.S.Interface, Miguel *et al,* 2020, Nature Comm Biology).

DISSENSUS:

No dissensus apart from the fact that it is difficult to attempt to specifically regulate species or populations without (i) being certain that they are involved in a zoonosis and (ii) without placing this strategy within a wider approach that considers the functioning of biological communities and the interactions that take place within them.

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

It is difficult to have a clear idea of the consequences of management/regulation strategies, given the complexity of ecosystem interaction networks. There are a few studies on the eco-epidemiological consequences of management/regulation strategies (although this topic could be better documented); there is, in particular, a significant lack of studies on the evolutionary consequences (e.g. evolution of virulence; impact on genetic and immunogenetic diversity, impact on the immune response...) of these strategies. (Sarrazin & Lecomte 2016, Science, Jorgensen et *al.* 2019, Annu. Rev. Ecol. Evol. Syst).

NEED FOR RESEARCH:

There is a need to develop studies on the evolutionary consequences of wildlife management strategies. Investment in the dissemination of scientific knowledge is also needed so that human practices can evolve to take into account the ecology of animals that are likely to spread pathogens.

SPECIAL CASE OF COVID-19:

Reduce illegal wildlife trade, end bushmeat consumption including the consumption of species that are potentially involved in zoonoses, implement reasoned and science-based population management of these species.

SHEET 23

Can the development of protected areas help reduce the risk of zoonotic diseases? What are the processes involved and what would be the required level of protection?

CONSENSUS:

If we consider that there is a link between biodiversity degradation and the occurrence of zoonoses (see fact sheets 9-12), and that it can be explained, to a large extent, by increased contact between humans and wildlife, either from increased human presence in natural habitats or the destruction of these habitats through land use changes (e.g. deforestation), then the option of reducing these contacts by establishing protected areas, where both land use and human incursions into natural habitats, and associated activities including wildlife harvesting, are strictly limited, makes sense.

In addition, from an ecological point of view, and even if there is some disagreement within the scientific community, the hypothesis that maintaining biological communities with high species-level diversity within protected areas would prevent the emergence of major disease-causing pathogens reinforces the importance of having protected areas (**Error! Reference source not found.**).

Such as policy promoting the development of protected areas can be achieved by creating new areas, expanding existing areas and, above all, increasing their protection level (i.e. by further reducing human activity), even though the current trend worldwide is to reduce actual protection levels.

Still, we face multiple and complex challenges. Protecting biodiversity implies that we are effectively also protecting potential sources of zoonoses. It also means managing the interface between protected areas and peripheral areas of human activity, where contacts occur, in particular between domestic animals and wildlife, and paying particular attention to urban expansion near protected areas. At this level, a fractal dimension of boundaries should be minimized.

Protecting biodiversity also means limiting resource extraction and exploitation, while taking into account and managing the need of certain populations for bushmeat. It also means better regulation of tourism and recreational activities that are a source of contact between humans and wildlife, and of reciprocal pathogen transmission, even though these activities provide an income for local populations and contribute to different aspects of human well-being.

We are therefore faced with issues of social acceptability, political and economic constraints and the need to educate the public given the growing concerns surrounding the risk of zoonoses and epidemics; there may be concerns over the establishment of new protected areas and the future of existing ones may be called into question. Clearly, this type of strategy, beyond the conceptual evidence in support of it, must be implemented at the appropriate territorial scale. This means encouraging dialogue with local populations, who may play a role in protection and access regulation (sacred or community forests), all the while acknowledging the dual imperative of protecting biodiversity and limiting the transmission of pathogens to humans, farm animals or wildlife.

Bibliography: Aubertin 2015, Forests, Trees and Livlihoods, Bauch et *al.* 2015, PNAS, Cohen *et al.* 2016, PNAS, De Vos *et al.* 2016, Ecol. 2016, Ecol. & Soc. *2017,* Terraube et al. *2017,* Cur. Envir. op. Sust. Sust., Kilpatrick et *al.* 2017, Phil. Trans. R. Soc. B, Adams *et al.* 2019, Nature Sust. Geldmann et al. 2019, PNAS, Golden Kroner et *al. 2019,* Science, Naidoo et *al.* 2019, Sci. Adv. Veldhuis et al. *2019*, Science, Yergeau, 2019, World Dev. Halsey 2019, Nature Evol. & Ecol. Ecol. 2020, Tran *et al.* 2020, Biol. Cons. Leberger et *al.* 2020, Biol. Cons. 2020, Biol. Cons. Mammids, 2020, Biol. Cons. Selwood and Zimmer 2020, Biol. Cons. Corlett *et al.* 2020, Biol. Cons. Rohr et *al.* 2020, Nature Ecol. & Evol. Mokany et *al.* 2020, PNAS.

DISSENSUS:

There is a recurring debate within the scientific community as to whether the development of protected areas should be prioritised over other approaches of biodiversity conservation that may also lead to an improved management of the relationship between humans and wildlife. These dissenting views are related in part to the ongoing debate between land sharing (Leblan 2017, EHESS Coll. "In Time & Place") and land sparing (Oates 1999, Univ Cali Press) and do not directly address the issue of zoonoses. As indicated above, the hypothesis that maintaining biological communities with high species diversity would prevent the emergence of major disease-causing pathogens remains controversial (see the dilution effect hypothesis - i.e.the negative correlation between host richness and host infection levels, see fact sheet 22- *versus* the amplification hypothesis). These two hypotheses are certainly not mutually exclusive and may depend on the spatial scale of analysis. Overall, it is likely that the relationship between biodiversity and disease risk is not linear.

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

Current knowledge of the mechanisms underlying the emergence patterns of zoonotic diseases is still too patchy to accurately estimate the benefits that can be derived from different strategies of large-scale biodiversity conservation.

NEED FOR RESEARCH:

Research is needed at different levels, from understanding the mechanisms linking biodiversity, pathogen diversity, the prevalence of pathogens in their respective hosts and zoonosis risk, to a better assessment of the health benefits that can be expected from having protected areas (and the impact of different protection levels, up to the highest), without neglecting the cost-benefit aspect of these measures compared to other modes of public health interventions. The **EcoHealth** paradigm could be associated with the concept of resilience and landscape-level epidemiological data. A major investment in research is needed, both nationally and internationally.

SPECIAL CASE OF COVID-19:

There is no specificity associated with the Covid-19 phenomenon at this level. Choosing a strategy with the dual objective of preserving biodiversity and reducing the risk of zoonoses, and informed by scientific evidence and work that is needed to fill the gaps in our knowledge, should make it possible to partly reduce the risk of new occurrence of such pandemics.

SHEET 24

Does maintaining high species/genetic biodiversity prevent or limit the emergence of zoonotic diseases? How generalizable is the dilution effect?

CONSENSUS:

Following on from previous work, Schmidt and Ostfield (2001, Ecology) put forward the hypothesis of a "dilution effect". According to Morand and Lajaunie (2018, Iste Editions), this hypothesis "suggests that host species richness and diversity play a protective role in the spread of pathogens". The dilution effect depends on the state of the ecosystem. It is assumed that ecosystems under low anthropogenic stress, whose functioning and dynamics are closer to a natural state, should have higher levels of biodiversity. These 'undisturbed' ecosystems harbour species that vary in their ability (competence) to transmit pathogens: some species would have a high parasitic/bacterial/viral load, and others would be unable to transmit pathogens. Thus, in a species-rich ecosystem, the latter species, unable to transmit a pathogen, would dilute its transmission. If there really is a dilution effect, this would be beneficial to both humans and ecosystems. High biodiversity within communities can also imply greater diversity within different trophic levels, in particular with the presence of predators that control the density of reservoir species, as seen with foxes, rodents and Lyme's disease (Hofmeester *et al.* 2017, Proc Roy Soc B). Conversely, the introduction of alien species can affect (positively or negatively) reservoir populations (Morand and Lajaunie 2018, Iste Editions).

In parallel, populations with low genetic diversity appear to be more susceptible to the emergence of zoonoses. This is the case, for example, for recently established genetically depleted populations of the gastropod *Biomphalaria* and the zoonotic agent responsible for bilharziosis (Campbell *et al.* 2010). Theoretical and experimental models support the link between low genetic diversity (for genes associated with pathogen resistance) and emergence risk (Chabas *et al.* 2018, Plos Biol).
Once the species barrier has been crossed (spillover), it is generally well-accepted (based on theoretical, empirical and experimental studies) that populations with high genetic diversity have greater resistance to infectious agents and are better able to adapt to new pathogens (see King and Lively 2012, Heredity). The relationship between genetic diversity and susceptibility to infection does not appear to be related to inbreeding depression (Spielman *et al.* 2004, PNAS, Ebert *et al.* 2007, J Roy Soc Interface), but to the diversity of the genes involved in immunity or the presence of particular alleles/genotypes associated with pathogen resistance. The numerous immunogenetic studies conducted on *MHC* (major histocompatibility complex) genes in natural populations have also highlighted the link between the presence/absence of alleles and infection risk, but only very rarely between the latter and heterozygosity (Sarri *et al.* 2016, Plos One). Although there are some counter-examples (Springbett *et al.* 2003, Genetics, Yates *et al.* 2006, Proc Biol Sci, Nath *et al.* 2008, J Anim Sci), a recent meta-analysis (Ekroth *et al.* 2019, Proc Roy Soc B) has shown that low genetic diversity in populations is correlated with increased parasite success (infection prevalence and load), although only for microparasites, not for macroparasites.
Finally, many empirical studies have shown that new pathogens displayed reduced adaptive capacity and evolved less virulence when they were introduced into genetically diverse host populations (see references in Signe White *et al.* 2020, Biol. Let.). Indeed, high genetic diversity in the host population leads to an evolutionary trade-off (antagonistic pleiotropy) in the infectious agent, whereas low genetic diversity reduces this trade-off and favours the specialization and expansion of virulent pathogens.
These studies are important because they show that populations/species with low genetic diversity are more susceptible to infections, and that their infectious agents are more likely to evolve into highly virulent forms (e.g. the microbiota of the last hunter-gatherers was richer and more diverse than that of present-day urban westerners). These findings may guide reintroduction/rewilding strategies, by paying particular attention to potential infectious risks and by advocating the translocation of organisms within their native range over assisted colonisation (IUCN 2013).

DISSENSUS:

Recent meta-analyses seem to corroborate the dilution effect hypothesis (Civitello *et al.* 2015, PNAS, Johnson *et al.* 2015, Ecol Lett, Johnson *et al.* 2015, Ecol Lett), unlike the results from Salkeld *et al.* in 2013 (Ecol Lett). In addition, this effect has been observed for several vector-borne diseases (Morand and Lajaunie 2018, Iste Editions, Ezenwa 2006, Proc Biol Sci). More work is needed to understand the mechanisms at play, since the way this effect has been formulated has itself been highly criticized, and this has led to different interpretations of sometimes contradictory data (Randolph and Dobson 2012, Parasitology, Hosseini *et al.* 2017, Phil Trans R Soc Lond B Biol Sci). Nevertheless, some general principles seem to have emerged. The dilution effect only works if the least competent species, also assumed to be the least abundant, are the first to disappear when biodiversity decreases, and if their importance is measured in terms of frequency rather than prevalence/abundance. The dilution effect also seems robust for biodiversity gradients when there is an erosion of biodiversity (Halliday et *al.* 2020, BioRxiv). Besides, some experts emphasize that high levels of biodiversity will protect against an epidemic/pandemic but much less against an emergence; high biodiversity levels increase microbiological hazard but not necessarily infectious risk ("hazard *vs* risk").

As to the role of genetic diversity in preventing outbreaks, there may be cases where high host genetic diversity may increase the likelihood that an infectious agent with low diversity meets a susceptible host (Boomsma and Ratnieks 1996, Phil Trans Roy Soc B, Van Baalen and Beekman 2006, Am Nat).

LACK OF KNOWLEDGE OR ANALYTICAL BIAS:

Although the dilution effect seems fairly generalizable, the conditions required for this effect remain to be determined. Much basic data on infectious systems are still lacking today (e.g. host competence, trophic preference of vectors, link between reservoir and vector abundance).

Many studies have been carried out on the link between genetic diversity and disease emergence in invertebrates, but there is a lack of empirical data on vertebrate/pathogen systems. The existence of an acquired immune system could influence the results previously obtained in invertebrates.
In addition, the genetic diversity of vertebrate animal populations has mainly been inferred from *MHC* genes. *MHC* variation does seem to reflect the potential for population viability and pathogen resistance (Radwan *et al.* 2010, Biol Cons, Sommer 2005, Front Zool). However, genome-wide studies or the study of other immunity genes are needed to confirm this trend.

RESEARCH NEEDS:

Given the issues that have fuelled the debate on the dilution effect (formulation, confounding factors), it would be necessary to theoretically identify the conditions required for seeing a dilution effect and the circumstances under which these conditions are met (and identify gaps in our knowledge), for example by combining and analysing data from published case studies.

Concerning the importance of population genetic diversity in preventing zoonotic disease emergence risk, we need to better understand the relative influence of genetic diversity versus population density, as these characteristics may be strongly correlated.

It would be particularly interesting to analyse whether there is a minimum threshold of genetic diversity that guarantees resistance to the introduction of infectious agents, and to define how these thresholds of genetic diversity vary according to reservoir traits, geographical area, etc. (Lively *et al.* 2014, Am Nat).
Another element of intraspecific biodiversity that should be taken into account when studying the relationship between biodiversity and pathogen emergence is the microbiota. Numerous empirical and experimental studies have shown that it influences the susceptibility of hosts to infectious agents (Knutie *et al.* 2017, Nature Com, Koch and Schmid-Hempel 2012, Ecol Lett). However, the relative influence of the genetic characteristics of the host (immunogenetics, diversity), of its microbiota (composition, diversity) and of their interaction on the link between biodiversity and zoonosis emergence is not yet known (Trevelline et *al.* 2020, Mol Ecol).

SPECIAL CASE OF COVID-19:

In the case of the Covid-19 crisis, there is insufficient knowledge on the ecology of the animal communities that are presumed to harbour the coronavirus reservoir animals (fruit bats and pangolins) to formulate working hypotheses.