Programme et équipements prioritaires de recherche – PEPR

PREZODE - Preventing Zoonotic Disease Emergence

Preventing zoonotic disease emergence

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PEPR Preventing Zoonotic Disease Emergence (PREZODE)

Summary

Since the last decades of the XXth century, the occurrence of new infectious diseases of animal origins, some of which turned into pandemics (AIDS, influenza viruses, Covid-19), has been a stark reminder that zoonotic emergence is a major threat to human populations. While zoonoses represent more than 75% of emerging infectious diseases in humans, the links between the increasing level of pathogen circulation in animals and the major global changes induced by human activities (*e.g.,* deforestation, agriculture, wildlife market, climate change, etc.) raise fears that we are entering an era with ever increasing frequency and burden of epidemic outbreaks and pandemics of zoonotic origins.

To escape this era, working on the mitigation of human-to-human transmission is crucial in order to avoid large scale and massive spread. However, it is not enough and to improve our ability to prevent such pandemics, we must also **understand how to mitigate these risks before these infectious microbes begin to infect humans, *i.e.,* through understanding the drivers and the mechanism of zoonotic emergence at different scales**. Importantly, we also need to turn this knowledge into concrete strategies, easily adaptable by local stakeholders around the world.

With this in mind, this PEPR ("*Programme et Equipements Prioritaires de Recherche*") aims to provide the necessary knowledge and tools to enable France to play a pivotal role in the prevention of zoonotic disease emergence. Thus, it will represent a major academic contribution from France to the international PREZODE initiative. This PEPR program is structured around five main work packages that have been designed to put France in a leading position regarding knowledge on drivers and mechanisms of zoonotic emergences and innovative prevention strategies against the emergence of zoonoses. **Three calls for proposals on different aspects of these strategies will be launched** (1/ understanding the drivers and mechanisms of zoonotic disease emergence, 2/developing research on sustainable strategies to prevent zoonosis emergence and 3/ developing innovative methods to improve surveillance). A call on equipment structures will also be launched to strengthen French capacities to detect potential zoonotic pathogens. Finally, scientific coordination will seek to foster national and international scientific animation as well as prospective studies to support decision makers.

This program is perfectly complementary to the program developed within the PEPR MIE, which focuses on the human aspect of the emergence of infectious diseases. Moreover, a common scientific animation will be carried out with the ANRS-MIE and committees of each PEPR will reciprocally participate in the project selection committee of each other.

Table

Definitions

Aerosolization: Inhalation, contact with respiratory droplets (e.g., Brucellosis, *Chlamydia psittaci*)

Direct contact: transmission of pathogens through contact with saliva, blood, urine, mucous, feces, or other body fluids (e.g., Rabies, Ebola)

Emergence (WHO): Emerging infectious diseases are those due to newly identified and previously unknown infections, which cause public health problems either locally or internationally. Re-emerging infectious diseases are those due to the reappearance and increase of infections which are known, but had formerly fallen to levels so low that they were no longer considered a public health problem.

Foodborne transmission: transmission *via* milk, meat, eggs, fruits, vegetables contaminated by a pathogenic agent from an animal or human or environmental source (e.g., Salmonellosis, Brucellosis) or human/animal recombinants bugs (e.g., *E. coli* O104:H4)

Indirect contact: Coming into contact with areas where animals live and roam, or objects or surfaces that have been contaminated with germs (*e.g.,* Q fever *Coxiella burnetii*, Influenza, Coronaviruses).

Nature-based solution: Actions to protect, sustainably manage, and restore natural and modified ecosystems that address societal challenges effectively and adaptively, simultaneously providing human well-being and biodiversity benefits.

One Health (US CDC): Approach that recognizes that the health of people is closely connected to the health of animals and our shared environment.

Socio-ecosystems: A coherent system of biophysical and social factors that regularly interact together.

Pathogen spillover: an event occurring when a reservoir population with a high pathogen prevalence comes into contact with a novel host population. The pathogen is transmitted from the reservoir population and may or may not be transmitted within the host population.

Surveillance: Systematic, continuous or repeated, measurement, collection, collation, analysis, interpretation and timely dissemination of health-related data from defined populations to the relevant stakeholders to ensure risk mitigation actions.

Telepidemiology: consists of studying human and animal diseases which are closely linked to climate and the environment (transmitted by water, air or vectors), using data from remote sensing. Earth observation satellites provide geographic, meteorological, hydrological information, etc. related to the mechanisms of emergence and development of pathogens or their hosts causing disease. The Earth observation satellite contributes to the surveillance of these diseases by providing dynamic environmental measurements (time and space) crucial for the surveillance of these diseases.

Vector-borne pathogen: Pathogenic agent transmitted by the bite of an arthropod vector like ticks, mosquitoes, flies, flea, culicoids, lices, bedbugs, for instance (*e.g.,* Yellow fever, plague, West Nile fever, Lyme disease, Rift valley fever…)

Waterborne transmission: transmission by drinking or coming in contact with water that has been contaminated by an infected animal or human (*e.g.,* amoebae, Hepatitis E virus, leptospirosis, schistosoma...)

Zoonotic disease (US CDC): Zoonotic diseases (also known as zoonoses) are caused by germs that spread between animals and people.

Abbreviations

AAPs	Appels à Projets
AFD	Agence Française de Développement
ANR	Agence Nationale de Recherche
ANSES	Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'environnement et du travail
CBD	Convention on Biological Diversity
CNFCG	National Committee on Global Change
COVID-19	Coronavirus Disease 2019
ENSTBB	École nationale supérieure de technologie des biomolécules de Bordeaux
FAO	Food and Agriculture Organisation
FAIR	Findable, Accessible, Interoperable and Reusable (data)
GALVMED	Global Alliance for Livestock Veterinary Medicines
HCSP	High Council for Public Health
IAEA	International Atomic Energy Agency
ICAHS	International Conference on Animal Health Surveillance
IDRC	International Development Research Center
IPBES	The Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services
ISESSAH	international society of economics and social sciences in animal health
ISVEE	International Symposium of Veterinary Epidemiology and Economics
MESRI	Ministère de l'enseignement supérieur, de la recherche et de l'Innovation
MIE/EID	Maladies infectieuses emergentes/Emerging Infectious Diseases
NERC	Natural Environment Research Council
NIH	National Institutes of Health
OFFLU	OIE-FAO global network of expertise on animal influenza
OHHLEP	One Health High Level Expert Panel
OIE	World organisation for animal health
PCR	Polymerase Chain Reaction
PEPR	Programme et Équipements Prioritaires de Recherche
PNACC	French national Plan for Climate Preparedness and Responses
PREZODE	PREventing ZOonotic Disease Emergence
SBSTTA	Subsidiary Body on Scientific, Technical and Technological Advice

SGPI	Secrétariat general pour l'investissement
SVEPM	Society of Veterinary Epidemiology and Preventive Medicine
UNEP	United Nation Environment Programme
US-AID	United States Agency for International Development
WHO	World Health Organisation

1. The PEPR PREZODE within the PREZODE Initiative

The **PREZODE initiative aims, especially through a co-construction approach, to increase our knowledge on zoonoses emergence in order to implement prevention and epidemiological surveillance strategies able to mitigate the likelihood of future pandemics.** Initiated by the French President Emmanuel Macron, PREZODE is an international initiative that has received the support of the tripartite+ (composed by the WHO, the OIE, the FAO and the UNEP) and of the European Commission. It will be closely working with the One Health High Level Expert Panel (OHHLEP) and the other international One Health initiatives. In this context, the **PEPR PREZODE** represents a **major academic contribution from France** to this international initiative.

2. Articulation between the PEPR PREZODE and the PEPR MIE within the national strategy of acceleration on emerging infectious diseases and NRBC threats

The national strategy of acceleration for emerging infectious diseases and chemical, biological, radioactive and nuclear risks (NRBC) aims to reinforce the understanding, prevention, and preparedness for infectious diseases emergences and re-emergences. It relies on integrated, interdisciplinary and cross-sectoral approach, involving human, animal and environmental health actors, both in research and in the field (*e.g.,* politicians, policy makers, veterinarians, doctors, civil society actors, etc...). Indeed, the environmental, societal, economic, ethical and political factors that characterize a socio-ecosystem influence the emergence of zoonotic infectious diseases. Understanding, preventing, anticipating and better preparing for the emergence of infectious diseases require to gain knowledge on the complex mechanisms leading to infectious disease emergences which implies integration of these different determinants at the animal and human level.

The PREZODE and MIE PEPR take place in the national strategy with different but complementary objectives within national EID research priorities.

The **PEPR MIE is situated on the emergence phase of pathogens in human populations**, but also aims to improve the "preparation" phase and epidemiological response. In addition to the important human aspects, this PEPR will implement a One Health approach to understand the transition from animal species to humans with a particular focus on pathogen adaptation allowing dissemination in human populations. It will use comparative approaches to animal health research that are easily transferable to human health research so that each sector can feed off other. The PEPR MIE thus aims in particular to understand the mechanisms of transmission of zoonoses to human populations and thus prevent them at this stage.

The **PEPR PREZODE includes its research in the pre-emergence phase with a clear scope on prevention strategies**, with on the one hand the identification of the risks of emergence linked to local and global changes, the development of sustainable prevention strategies through livestock and/or ecosystem management and the development of early warning systems from local to global, especially through a participative approach with and by local actors to reduce risks. The PEPR PREZODE, through a One Health approach, thus aims to develop a research program to understand macro processes leading to infectious disease emergence in a context of global changes, including through the study of socio-environmental

mechanisms that brings humans and animals together, in order to minimize the exposure of human populations and to ultimately foster prevention of zoonotic disease emergence.

Based on different parts and at different level of the emergence processes of zoonoses, the two PEPR PREZODE and MIE also involve different scientific communities that each need to be structured in France. In order to harmoniously articulate these two programs, joint scientific events (e.g., via annual conferences) will be organized. Some members of the PEPR PREZODE committee will also be involved in the ANRS-MIE agency. Finally, the selection committee which will evaluate the responses to the calls in one PEPR will involve members of the other PEPR in order to guarantee consistency and coherence in the selection procedure at a national scale. The joint scientific expertise will lead to a common multidisciplinary prospective analysis that will provide key information to the strategic committee of the national strategy on EID and NRBCs and enable public policies and society to prevent pathogen emergence.

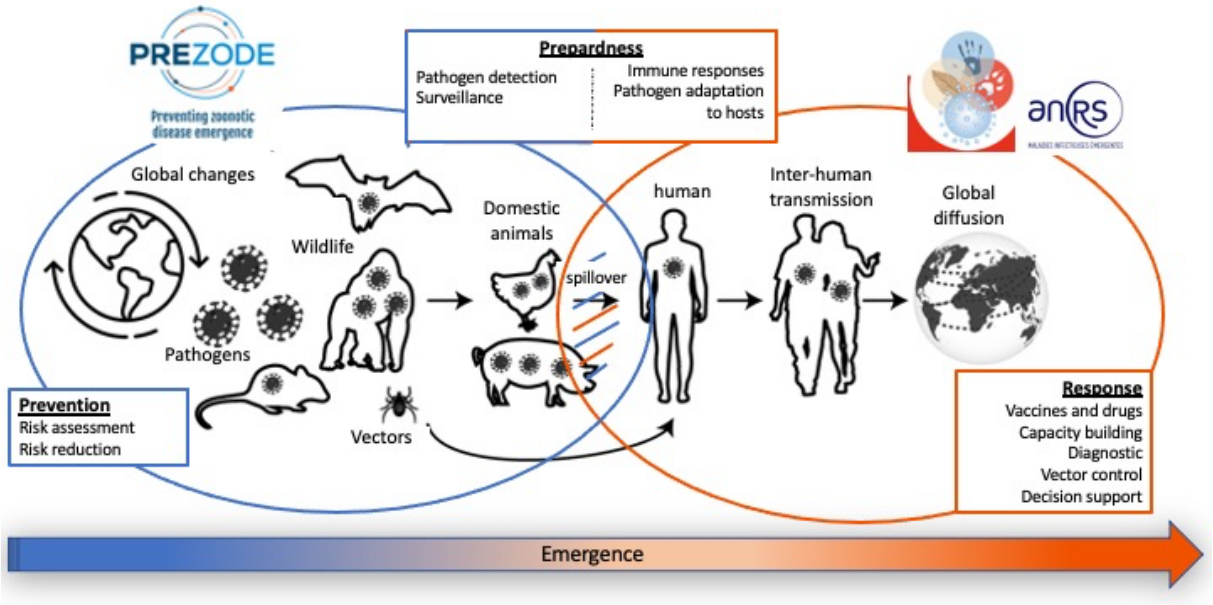


Figure 1. Articulation between the PEPR PREZODE and the PEPR MIE – Figure modified from "*Zoonoses, ces maladies qui nous lient aux animaux*" (1st Edition). Vourc'h G., Moutou F., Morand S., and Jourdain E. (2021) Editions Quae.

3. Scope and data issues

3.1. Scope of this program

The objective of the PEPR PREZODE is to understand what are the risk factors associated with zoonotic disease emergence, the underlying ecological and epidemiological mechanisms involved, how to mitigate these emergences and how to detect such events as early as possible. The factors of emergence are numerous and will be considered in a context of global changes (*e.g.,* biodiversity decline, climate change, livestock intensification, development of free-range breeding systems, interaction of backyards and free ranging animals with wildlife etc...). The PEPR will seek to foster systems-based approaches in order to better integrate processes at

local and global scales. The capture of fine and complex interactions at local scale and the further integration with large scale change can avoid the risk to attribute to global variables observed patterns that are in reality explained by local processes.

To achieve its goals, the PEPR will focus on zoonotic pathogens that could emerge (because of their characteristics such as host shifts or antibiotic resistance, increase of pathogen circulation within the ecosystem and/or the human-animal interface in which they circulate), those that have already emerged (i.e., such as hantavirus, Lyme disease agents, West Nile Virus, etc...) and/or those that could re-emerge (e.g., schistosomiasis).There will be no restriction on the type of pathogens that can be addressed. They could come from wildlife, domestic animals or livestock, from terrestrial or aquatic environments, and circulate on all continents. Similarly, all the different transmission pathways between animal species and human populations (e.g., through vector, food, environment, direct contact with infected animals etc...) will be considered.

3.2. Data interoperability and accessibility within the PEPR PREZODE

In the system-based, up-scaling from local to global, and multidisciplinary approaches that the PEPR is embracing, many ethical issues about data property and confidentiality will have to be addressed. At the same time, the "open science" movement is receiving a lot of support, from both research and authorities, allowing research data to be reused, processed multiple times and interoperated. Therefore, to manage such heterogeneous data, with all the care that it deserves, the PEPR PREZODE will rely on the FAIR[1] (findable, accessible, interoperable and reusable) data principles and the Nagoya protocol[2] for genetic resources. All consortium applying to the different call for proposals should then engage on the following requirements:

1. All genetic resources and associated traditional knowledge that are covered by the CBD and the benefits arising from their utilization will be covered by the Nagoya Protocol
2. All (meta)data produced (e.g., zoonotic pathogens life-history traits and ecosystems, genetics, socio-economics activities, biodiversity monitoring, geographic data) at regional, national and international levels should follow the FAIR data principles:
    a. (Meta)data are clearly identified (e.g., using a global, unique and persistent identifier) and well described (detailed provenance, data usage license)
    b. (Meta)data are registered or indexed in a searchable resource (e.g., the FAIRDataPoint, a data repository that provides (meta)data in a FAIR way)
    c. (Meta)data are accessible and retrievable (an authentication and authorization procedure might be implemented where necessary)

[1] https://www.go-fair.org/fair-principles/

[2] https://www.cbd.int/abs/

d. (Meta)data should follow community standards or best practices for data archiving and sharing (e.g., ISO 19115-1:2014 for geographic information, netCDF for climate data, EML for ecological sciences…)

4. Scientific and societal challenges

4.1. Emerging zoonotic diseases cause a major health burden

One of the greatest burdens on human health and livelihoods, amounting globally to about 1 billion cases of illness and millions of deaths every year, is caused by epidemic and endemic zoonoses that are persistent regional health problems around the world (Karesh *et al.* 2012, Morens and Fauci 2020). Zoonoses are a substantial threat to global health and global security and they have caused economic damages exceeding hundreds of billions of US dollars in the past 20 years (Smith *et al.* 2019) and this number will still rise during the COVID-19 pandemic, which has already a cost estimated at more than 11,700 billion dollars. Zoonotic agents also represent the largest number of infectious disease agents in humans (Murray *et al.* 2018), and the projections indicate that their number might significantly increase in the future (Anthony *et al.* 2013).

Thus, it is now time to act upstream of epidemic and pandemic crises by implementing ambitious scientific programs dedicated to the prevention of zoonotic diseases emergence and spread, before they have reached human populations, allowing to design "science-based prevention policies".

4.2. Early detection system and surveillance strategy

One major requirement for the implementation of "science-based prevention policies" is to have robust and sensitive surveillance and early detection systems of pathogens. This allows rapid response to emerging zoonotic diseases at source (Zinsstag et al. 2020) and therefore increase its efficiency. However, many surveillance systems may fail to grasp early enough signals at the interface of wildlife, domestic and human populations and may be a challenge to maintain functional on the long term. For example, passive zoonotic disease surveillance might lead to underreporting and biases while field surveys are very expensive while still lead to low coverage (Hattendorf et al. 2017). Moreover, implementation of rapid detection methods, surveillance and health system infrastructure could be improved at a local scale, which would shorten delays detection of emerging pathogens and increase our ability to prevent their potential to become epidemic and pandemic (Bird & Mazet 2018).

While French research teams have demonstrated their ability to develop innovative surveillance systems, such as epidemiological surveillance platforms, surveillance of antimicrobial resistance in animals, early warning systems through syndromic surveillance on low pathogenic and potentially emerging avian influenza viruses in domestic and wild birds, development of environmental DNA screening approaches (see for example Goutard et al. 2015; Calba et al. 2016 ; Delabouglise et al. 2016; Schulz et al. 2016; Bordier et al. 2018, Faverjon et al, 2017), there is a need of strengthening sustainable, continuous and effective surveillance systems for a broader range of pathogens and involving different reservoir and

vector species. While it is therefore crucial to capitalize on these first developments, their scope has to be opened widely, regarding their spatial scale and/or the pathogens that can be monitored, thanks to participatory approaches, to models that take into account heterogeneous data and to innovating easily to use tools.

#Research gap 1 – Innovative surveillance methodology from local to global

- Need for inexpensive rapid detection methods of pathogens from wildlife and environment and environmental health indicators.
- Strengthening integration of local, regional, national and global surveillance systems.
- Need for developing participative approaches with citizens to improve population and stakeholders engagement.
- Need to develop models that can integrate heterogeneous data
- Need to transform current epidemiological surveillance networks to risk-based surveillance system

4.3. Emerging zoonotic diseases, indicators of our relationship with animals and the environment

The emergence of zoonoses has been strongly linked to a consequence of pathogen ecology and evolution, where microbes have exploited new niches and adapt to new hosts (Gibb *et al.* 2020, IPBES, 2020). In addition, changes in reservoir host populations and communities can disrupt natural dynamics of microbes. For example, the transmission of pathogens from animal species to human populations, such as influenza virus, Hantavirus, Rift Valley fever virus, bacteria causing Lyme disease, leptospirosis, Q fever and many other pathogens, is a direct product of our relationship with the animals and the environment. The underlying causes that create or provide these new opportunities for pathogens are mediated by human action in most cases. These include changes in land-use (*e.g*. deforestation, urbanization, agricultural practices, homogenization of habitat, extraction of natural resources), animal production systems (highly intensive domestic or wild animals production systems, mixing traditional backyards and intensive animal production, development of free ranging production due to societal demand for animal welfare…), modern transport and global trade (Smith & Guégan, 2000) as well as our lifestyle with the increase in outdoor activities. These changes could increase the risk of transmission of infectious diseases between animals (enzootic/epizootic) and from animals to humans (zoonosis) and from human to animals (creating potential reservoirs) in the near future.

The emergence and spread of zoonoses does thus not only depend on the characteristics of the causative agents. Rather, it mostly reflects the dynamics across scales within socio-ecosystems, which include humans, biodiversity and evolution, microbes and potential agriculture activities (Lancet special series on zoonoses 2012, Morens and Fauci 2020, Lancet Editorial 2020). While infectious diseases are necessarily caused by microbial agents (or related agents in case of prions), disease emergence and spread, *i.e.* epidemics and pandemics, are also significantly determined by complementary factors related to hosts (vertebrates and vectors when it comes to vector-borne disease), hosts-environmental interactions and *in situ* human activities and practices (Engering et al, 2013).

Nevertheless, we are seeing an increasing number of zoonotic outbreaks over the last 30 years even after controlling for confounding effect of reporting (Smith *et al.* 2014, Vourc'h *et al.* 2021). This suggests that opportunities for zoonotic pathogen to infect human populations increase, implying that human behaviors and practices may have reached a tipping point in their relation with nature. Moreover, as Dobson *et al.* (2020) have recently written, these global conundrums need to be better understood at the local and regional level as disease control methods and treatments through drugs and vaccines are unlikely to be the only way to prevent an increasing number of zoonotic outbreaks and further on, the next pandemics.

4.4. Set of complex relationships and interactions

Emergence, spillover and spread of infectious diseases are a complex set of relationships and interactions, most of which are typically non-linear, and they often also show threshold effects and feedback loops. In general, much that is relevant to infectious disease emergence and spread is not reproducible to simple cause-and-effect relationships, and although the laboratory approach is necessary, it is not sufficient to understand this complex mechanism of emergence. In addition, as suggested by Hulme (2020), it is easier to generate scientific knowledge in understanding the ways humans are altering world ecosystems than to re-orient current human actions to act on their detrimental impacts.

Systems-based approaches have been increasingly used in ecology, climatology, agriculture and epidemiology, and they provide insights into key pathways and processes, critical tipping points and optimal conditions for intervention. Nonetheless, they have been very rarely used to analyze the interfaces between wildlife, ecosystems, agriculture and human health. Exceptions are, for instance, the demonstration of Hantavirus and Nipah virus disease risks in human as an outcome of complex interplay between predator-prey relationships, weather and climate variability conditions, seed and fruit production, host reservoir population dynamics, pathogen life-cycle and disease agent properties, agriculture organization and human settlements and activities in the concerned regions (Daszak *et al.* 2013). All these components can be studied separately by different disciplines, but a system-based approach can ideally bring this diverse information into dialogue, and even to include uncertainty and imprecision of several elements (see WHO Technical Report 2013). Ideally, synthetic figures, as used by experts of the Intergovernmental Panel on Climate Change (IPCC) that aggregate climate-change-related impacts and risks to various systems and sectors (Zommers *et al.* 2020), could be adapted and developed to show changes across different regions of the world in the assessed level of emerging risks to humans and ecosystems as a function of land-use changes, wildlife-domestic animals contacts and climate change in space and time (Figure 2). Thus, there is an urgent need to implement data sharing methodology and mechanisms of data exchange between the various countries, region, area and scientific domains involved.

On a higher more aggregated level, it is therefore crucial to study the trade-offs between food production, rural activities (e.g. employment), biodiversity, climate change adaptation and mitigation and the reduction of zoonotic emergence.

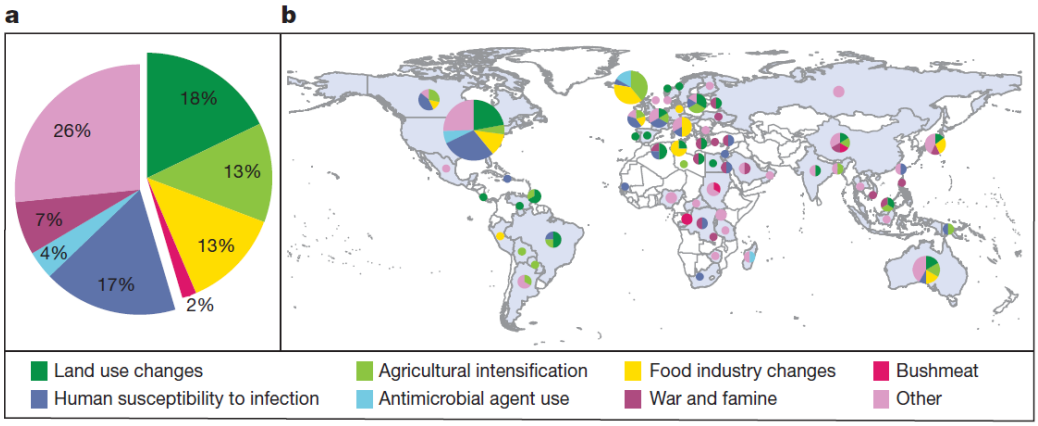


Figure 2. Drivers and locations of emergence events for zoonotic infectious diseases in humans from 1940-2005. a) Worldwide percentage of emerging disease events caused by each driver; b) Countries in which the emergence events took place, and the corresponding identified drivers of emergence per country. The size of the circle represents the number of emergence events. Scaling down this global observation in order to better understand locally the interactions between different disease emergence drivers is paramount to minimize and even avoid new disease threats. From Keesing *et al.* (2010).

#Research gap 2 – Strengthening our knowledge on potential reservoir populations and of system-based approaches to understand zoonotic diseases emergence in a changing environment

- Need to better characterize on potential zoonotic reservoir hosts (including their life-history traits, their morphological data and/or their geographic distribution among others...) to understand their potential roles
- Need of systemic and comparable data (e.g., epidemiological, ecological, genetic) at local level in different contexts to describe the risk of zoonotic disease emergence.
- Need to quantify/infer transmission network, including vector transmission responsible for hundreds of known and as yet unidentified zoonotic diseases.
- Need to improve our knowledge about how spatial and temporal scales may affect the relationship between biodiversity loss and pathogen circulation.
- Need to improve our knowledge about the climate change impacts on vectors, migratory birds, search for food for wild species by modifying ecosystems.
- Need to improve our knowledge about the impacts of new breeding and agricultural practices, mix of traditional and intensive agriculture, questions raised by the agroecological transition, biosecurity, human intrusion in protected areas, intensive urbanization

4.5. Human activities are recognized as one of the main drivers for zoonotic disease emergence

Among the different drivers of zoonotic disease emergence, spillover and spread (Woolhouse and Gowtage-Sequeria 2005), land-use changes, agricultural practices and human encroachments, increased contacts between wildlife and domestic animals and global changes have been recently highlighted as major drivers of new zoonoses by the

recent International Panel on Biodiversity and Ecosystem Services' report on Biodiversity and pandemics (IPBES 2020). These determinants can act separately or be combined together most of the time, which makes the study of their interactions and spatio-temporal dynamics even more urgent in today's world with growing demography and high demand for resources.

Typically, agricultural activities act through several mechanisms. First, they might alter important natural habitats, notably in tropical forests and cause the loss of ecosystem services and functions (Rockström *et al.* 2009, Venter *et al.* 2016, Weinzettel *et al.* 2018). Second, the increasing mass of domestic animals raised for food offer ever more opportunities for pathogens to encounter animals in human modified environments (Slingenbergh et al, 2018). Third, intensive food production is the largest stress to biodiversity through habitat destruction and nutrient pollution, threatening >70% of birds and mammals with extinction, which impact ecosystem functions and thus microbe dynamics within wild communities. Demands for space and food supplies have led to increasing contacts between humans, wildlife, and domestic animals, creating in turn opportunities for inter-species pathogen transmission within these new ecological settings (Craft 2015). In particular, numerous case studies support a link between agricultural land-use or land-use change and infectious disease risk outcomes in humans (Patz *et al.* 2004, Jones *et al.* 2013, Gottdenker *et al.* 2014, Murray and Daszak 2014, Morris *et al.* 2016, Faust *et al.* 2018, see IPBES 2020 and World Conservation Society 2020 for recent reports) even if the evidence has not been systematically evaluated (see Figure 2). In Europe, the agro-ecological transition which is underway, favors the existence of diversified breeding systems, with more animals raised outdoors, with more contact with wild fauna and under less controlled environmental conditions. While the production of animals in buildings allowed the implementation of biosecurity measures; new farming methods, in a context where we use less and less antibiotic and climate change affecting vectors distribution and possibly bird migratory routes, might lead to new infectious risks that we will need to understand in order to prevent them.

It is therefore essential to make the interfaces between ecosystems, biodiversity and agriculture practices more sustainable in the post COVID-19 era in different regions of the world. A key-step towards this goal is to assess the costs and benefits of contrasted agro-socio-ecosystems by simultaneously considering farming practices, social and economic well-being, various environmental impacts and emerging disease threats. For instance, recently Clark and collaborators have identified that dietary transitions towards greater consumption of healthier food would concomitantly improve environmental sustainability (Clark *et al.* 2019), but we do not know if the same holds true for the reduction of zoonotic risks (Roche et al, 2020). Such examples are lacking in the scientific literature, although they are required to guide agricultural transitions and sustainable development pathways by minimizing the risk of new emerging threats. Because current international agriculture and its development could impose both locally and globally new threats to animal health, human health and the environment (World Bank 2009), it is relevant to ask whether various agricultural system strategies will lead to different trajectories of human health impacts, social and cultural consequences and wide-ranging environmental issues.

#Research gap 3 – Increased knowledge to understand how to redirect human actions to stop their impacts on the emergence of zoonotic diseases.

- Scientific, socio-economic and societal complexity prevents the development of One Health territories where human, animal and environmental health is fully taken into account across all human activities (with local and global impacts).
- How can we reduce our impact on ecosystems in order to reduce the transmission of pathogens through wildlife?
- How can we meet increasing food demand and reduction of poverty while reorienting agricultural systems to reduce the risks of pathogen transmission?
- Need to increase intersectoral collaboration between human, animal and environmental health
- Integration of social aspects in understanding risk of emergence in Human population
- Need to understand how to transform political engagement into concrete participation requires understanding the architecture and multi-scalar nature of governance.

5. The present research proposal within the international context

In the light of an important increase of One Health initiatives worldwide to address the relationship between human health, the health of animals and the state of ecosystems in which humans and animals depend, we are strongly lacking of systematic and comprehensive overview of what is really done and not done. An in-depth bibliometric analysis revealing these weaknesses is described below, as well as the national and international funding that was available (section 8).

To this extent, a meta-analysis based on 2430 search results (Khan *et al.* 2018) identified 116 One Health networks (86 formed after 2005) in Asia, Africa and Europe with most of networks (64%) operating nationally or regionally, but not across regions or continents (only 2% operating across all three regions of interest). One-third of One Health networks analyzed only human and animal health, without including the environmental component which generally constitutes the Achilles's heel of these initiatives, 78 networks involved academic bodies and 78 governmental entities (section 10). The private sector was involved in only 23 networks and community group participation in only 10. Only 4 networks were collaborating together in the developing world, and 15 reported monitoring and evaluation information. Overall, and even if the majority of One Health networks worked on supporting communication, collaboration, information sharing and capacity building, a majority of these networks suffered from poor stakeholder representation, monitoring that is lacking or deficient in terms of sampling strategy, lack of evaluation structures and potential duplication between local and regional actions. One Health networks and collaboration led by developing countries are increasingly interested in environmental studies, an important pillar of One Health which is still often lacking but is essential.

5.1. France needs to reinforce capacities on health prevention and increase funding research targeting risk prevention

National strategy on public health

So far, France has invested in health promotion and disease prevention, which includes developing strategies at the interface between animal and human compartments in a context of changing environments, less than other European countries. Indeed, spending on prevention of emergence causes accounted for less than 2% of health and care expenditure, which is lower than the EU average of 3.1%, but this percentage only includes funding for prevention programs (European Commission 2019). This is mainly due to an historical approach of building curative capacities first. To this extent, the national French Strategy on Health 2018-2022 highlights the importance of prevention but prevention investments still remain modest (Ministère de la santé et des Solidarités, 2017). However, the COVID-19 pandemic crisis has also shown that relying solely on curative development has an extremely high cost, both in terms of deaths and economic growth.

Understanding how disease emergence, spillover and spread may intervene throughout the organization and evolution of socio-agro-ecosystems must participate in this necessary development of prevention if we do not want to suffer from new pandemics. Definitely, prioritizing research and research funding on determinants and risk factors responsible for disease emergence and spillover is paramount, and associated costs of preventive efforts are also very substantially less than the economic and mortality costs of responding to pandemics (Dobson *et al.* 2020). This is even more important when we consider that a low-level pandemic would globally reduce production by almost 1% of gross domestic product, a moderate pandemic by almost 2% and a serious pandemic by almost 5%, which would result in a serious economic recession (World bank, 2020)

Overseas territories: an urgent need to reinforce health system capacities

The situation in the overseas territories is a stringent illustration of the need to seek for integrated prevention strategies that would mitigate emerging risk. Indeed, the natural environmental conditions may undergo important variation that increase the risk of infectious disease transmission (*e.g.* abnormal climatic events in Saint-Barthélémy and Saint-Martin). In addition, higher levels of precarity prevent part of the population from having access to the information and care they need (e.g. Mayotte and French Guiana faced shortage of basic healthcare products), and lifestyles (particularly dietary for economic, social and cultural reasons) do not sufficiently encourage health-promoting behaviours. The COVID-19 pandemic highlighted weaknesses of health systems in these territories that are particularly exposed to EID (e.g. Chikungunya, Dengue).

Moreover, oversea territories are located in areas of exceptionally high biodiversity. Therefore, there is an urgent need to develop synergies between environmental strategies and investments to reinforce health system capacities through the development of One Health platforms. To this extent, the platform that will be developed in French Guiana as part of the Health Plan 2025 represents an emblematic example about what the national strategy for EID/NRBCs and PREZODE can gather research actors from different academic sectors around EID. Moreover, these One Health platforms will rely on existing technical facilities (sequencing

capacities, insectariums, database systems, etc...) that could be reinforced through the different projects that will be initiated within the work package 4 of the PREZODE PEPR.

6. Detailed plan of actions implementation

In order to develop a coherent scientific program, the writing committee has identified five work packages that have to be developed over the next 5 years for a total budget of 30 million euros. The expected results of this program are to enable French research teams to develop innovative programs in different fields throughout the World.

Work package 1: Developing a research program on the links between human activity and zoonotic emergence and re-emergence

- Action: Call for proposal for projects or targeted projects focusing on the impact of human activity (e.g., deforestation, afforestation, or reforestation in Europe, urbanization, climate change, agricultural practices in the context of agro-ecological transition, impact on breeding systems on plant protein demand, relocalisation of agriculture etc...), human direct or indirect relationships with wildlife and domestic species (such as hunting, meat consumption, veterinary practices, animal work, meat farming, recreational uses, etc..) on the risk of zoonotic emergence through considering the whole chain of events (from ecosystem alteration to human exposure through re-organization of reservoir and vector communities, including social perceptions of human/animal).
- Implementation: This will be implemented in two phases. First, a call for expression of interest will be launched to identify consortia able to fill the work package expectations and to ensure a good representativity of the different human activities. Second, pre-selected projects will be invited to submit a full proposal that considers the selection committee's recommendations. After this call, if important priority research gaps have still not been addressed, targeted project might further be funded in a second call.
- Target: Medium to large consortium - projects up to 3 million euros each.
- Expected results: Significant impact led by French teams on the impact of the main global changes (e.g., climate change, urbanization, deforestation- afforestation or reforestation in Europe, Agricultural practice, etc...) for risk assessment and prevention of zoonotic emergence.
- Originality/Specificity: Projects will focus on the common drivers of zoonotic emergence rather than the specific drivers for a given pathogen as it is usually done. The originality will be to study the whole chain favoring zoonoses emergence (from the global change to its impact on ecosystems and the consequences for human exposure to zoonoses) at a biotope scale and encompassing all the different dimensions of such events (biological, epidemiological, sociological, etc...). This will lead to an integration of our knowledge of the biological and ecological processes involved at each step.
- Budget: 9 million euros

Work package 2: Developing a research program on sustainable strategies to prevent zoonoses emergences relying on innovative approaches based on ecosystem management and/or wildlife/livestock contact reduction (e.g. adapted biosecurity approach such impact of free-range breeding on potential emergence due to contact with wildlife).

- Action: Call for proposal for projects or targeted projects focusing on envisioning sustainable strategies (e.g., sustainable agriculture, environmental protection programs) on a single territory to reduce the risk of zoonotic emergence at a local scale.
- Implementation: This will be implemented in two phases. First, a call for expression of interest will be launched to identify consortia able to fill the work package expectations. Second, pre-selected projects will be invited to submit a full proposal that considers the selection committee's recommendations. After this call, if important priority research gaps have still not been addressed, targeted project might further be funded in a second call.
- Target: Medium to large consortium - projects up to 2 million euros each.
- Expected results: Test of numerous sustainable and integrative strategies to reduce zoonotic emerging risk on a biotope scale.
- Originality/Specificity: Projects will focus on finding pro-actively sustainable solutions to reduce zoonotic risk emergence rather than screening the possible threats and trying to predict the most likely ones. These projects will involve a significant dimension to understand the sociological drivers of the possible adoption of these solutions by the different actors of the society.
- Budget: 8 million euros

Work package 3: Developing a research program to develop innovative methods to improve surveillance of pathogens and national and regional networks for epidemiological surveillance in animals and at the animal/human interface

- Action: Call for proposal for projects or targeted projects focusing on improving networks of epidemiological surveillance in animals and at the interface animal/humans through innovative methodologies (e.g., participative approaches, vulnerability assessment tools, digital access, viral presence in sewage, vector and high throughput vector-borne pathogens surveillance for early vector control, etc...).
- Implementation: This will be implemented in two phases. First, a call for expression of interest will be launched to identify consortia able to fill the work package expectations and to ensure a good representativity of the different human activities. Second, pre-selected projects will be invited to submit a full proposal that considers the selection committee's recommendations. After this call, if important priority research gaps have still not been addressed, targeted project might further be funded in a second call.
- Target: Small to medium consortium - projects up to 1 million euros each.
- Expected results: Test of numerous methodologies to improve epidemiological surveillance, including alert and continuum to response.
- Originality/Specificity: Projects will focus on innovative methodologies to engage stakeholders and perpetuate over a long-term efficient epidemiological surveillance.
- Budget: 8 million euros.

Work package 4: Strengthening French capacities to detect and study potential zoonotic pathogens from wildlife, domestic animals and environmental samples

- Action: Improving the availability of platforms with the capacity of developing innovative methods allowing high throughput, with or without a priori, detection of nucleic acids from putative zoonotic pathogens and assessing their zoonotic potential through *in vitro*, *in vivo and in silico* biological models.
- Implementation: Call for expression of interests targeting platforms to improve their capacity for identification and study of potential zoonotic pathogens (from nucleic acid detection to isolation and in vivo study using target wild or domestic animals).
- Target: platforms and infrastructures – projects up to 1 million each
- Expected results: Ability to fix some of the most recurrent methodological issues to perform accurate detection and isolation of putative zoonotic pathogens.
- Originality/Specificity: This equipment work package will rely on existing facilities (such as the national infrastructure EMERG'IN) but will extend its capacity to detect zoonotic pathogens through methodological developments to fix current caveats.
- Budget: 3 million euros

Work package 5: Scientific coordination on zoonosis emergence prevention at national and international scale

- Aim: In order to put the French research teams at the forefront of the zoonosis emergence prevention, this work package will support the scientific coordination of the research developed within this PEPR with the other French research teams (especially of the PEPR MIE), the whole PREZODE initiative, the other One Health initiatives (e.g., Zodiac, Pandora, Stop-Spillover, Star-Idaz, OneHealth EJP, etc...) and the One-Health High Level Expert Panel (OHHLEP, set up by the WHO-FAO-OIE-UNEP). In addition, this work package aims at proposing prospective studies to support decision makers.
- Action 1: National scientific animation (annual conference involving the two scientific communities) will be organized with the PEPR MIE to strengthen the links between these two scientific perspectives.
- Action 2: Assessing the impact of the PEPR program and of its projects impact pathways based on Asirpa real-time methodology.
- Action 3: International scientific animation will be organized, through international working group involving the largest One Health initiatives in order to share the latest advancements.
- Action 4: Identifying the most likely scenarios (e.g., development of sylvo-pastoral agriculture, stronger legislation on deforestation, improving hygiene measures inside livestock facilities, etc...) within the international working-group and developing an assessment of these scenarios in order to provide decision-makers quantitative support and qualitative impact evaluation for long-term policy.
- Action 5: The funded projects of different WPs including the activities conducted in WP5 are expected to use and generate a wealth of data. Data management, interoperability, and accessibility will be addressed here.
- Implementation: Implementation by the pilot institutions

- Expected results: (i) Improved collaborations at national and international scale on the topic of zoonotic emergence prevention, (ii) Quantitative socio-economics and sanitary prospective regarding the main orientations that can be taken today, combined with sociological studies to apprehend their conceptual background, political and regulation framing, implementation model, acceptability and potential adoption.
- Originality/Specificity: Implementing sustainable strategies, including nature-based solutions, to reduce zoonotic emergence risk will face inevitable trade-offs between some socio-economic activities and health threats. Without obvious solutions, the society has to decide which scenario must be chosen. These produced prospective, as a result of an international consultation implemented by the projects developed within the PREZODE PEPR and the MIE PEPR, will represent the quantitative background for societal debate.

Budget: 2 million euro

Some of these actions will be partly funded through other mechanisms of the national strategy on infectious diseases (in particular the 3rd measure on pre-maturation of projects and measures 4 to 6 of the 2d axis – Innovation and counter measures development)

7. Planning and project calls

We are planning to organize 1 call (AAPs) per work package, starting with work packages 1 and 3 during the second semester of 2022, then work packages 2 and 4 on the first semester of 2023. The budget of the work package 4 (3 M€) will be dedicated to equipment and infrastructures through an AMI process and the budget for work packages 1, 2 and 3 to AAPs and targeted projects.

Work Packages		M€	2022	2023		2024		2025		2026		2027
			Sem. 2	Sem. 1	Sem. 2	Sem. 1	Sem. 2	Sem. 1	Sem. 2	Sem. 1	Sem. 2	Sem. 1
1	Human activity and zoonotic (re) emergence	9										
2	Innovative approaches based on ecosystem management and/or wildlife/livestock contact reduction	8										
3	Networks for epidemiological surveillance in animals and at the animal/human interface	8										

4	Equipment	3										
5	Scientific coordination at national and international scale	2										

Opening the call/AMI	Project selection	Implementation

The content for each call for proposal will be proposed by the programme committee. More specifically, the PEPR pilots will draft and submit the call to the Joint Directory Board (cf Gouvernance) which is composed of PREZODE and MIE PEPR representatives. This will address potential overlaps, ensure a good articulation and define, when needed the funding responsibilities between the two PEPR. Regular exchanges will be encouraged as well as reciprocal participation of PREZODE and MIE members in the selection and evaluation committees of the proposals. Finally, PEPR pilots will submit the call for validation to the CPM.

The AAPs and the composition of the selection committee will need to be validated by the CPM.

Obviously, the selection criteria, besides those classically set by the ANR (Excellence and scientific ambition, Quality of the consortium, resources mobilized and governance, impact and benefits of the project), will have to be discussed with the whole programme committee and may differ for one call to the other. At least five preliminary indicators (that are in line with PEPR MIE criteria) could be used:

- Innovation dimension
- The project should address at least two components of the One Health framework for zoonoses (human/environment or human/animal). Addressing the three components will be considered as a bonus.
- Implication of decision-makers, non-academic stakeholders and patients associations/communities, when relevant
- The scientific knowledge produced during the project will have to contribute to envision prevention strategies against zoonosis
- Coherence with the national strategy

Moreover, call for joint projects will be established on a middle-term (upon the first evaluation by the CSTP) on the topic at the interface of the two PEPR such as pathogen host jump, where complementary expertise of each PEPR teams can be mobilized to answer this major question using interdisciplinarity approaches, mixing biological, ecological and sociological disciplines. This will be under the responsibility of the Joint Directory Board.

Several possible interactions have been identified between the two PEPRs. First, through the WP1 of both PEPRs where the two programmes aimed at the understanding of ecological and molecular drivers and processes of emergence. The ecological drivers will be covered by PREZODE while the understanding of molecular mechanisms of EID will be covered by MIE.

The MIE WP#3 will focus on strategies to enable public policies and society to cope with epidemic crisis and is linked to Prezode WP2 and WP3. Through WP3, PREZODE will aim at developing innovative approaches to engage stakeholders in long-term efficient epidemiological surveillance; this action aims to engage actors into surveillance and will contribute to the involvement of a large range of actors, as presented in the PEPR MIE. In WP2, on the identification of sustainable strategies to prevent zoonotic disease emergence, a specific action aims to understand the sociological drivers involved in the adoption of these solutions by the different actors of the society. This will in turn help promoting free adherence to proposed measures as planned in the WP#3 of the PEPR MIE.

Synergies have also been identified through innovation in diagnostics which is included in (i) MIE WP#3 which aims at establishing a diagnostic capacity compatible in between medical and veterinary field and (ii) PREZODE WP4 which aims to strengthen the French capacity in detecting zoonotic pathogens from wildlife, domestic animals and environmental samples.

Finally, both PEPR have a coordination and scientific animation work packages (WP#4 for MIE and WP5 for PREZODE) that will be in constant interaction through the implementation of coordinated animation actions.

8. Innovation

Finally, a last point will be developed in the framework of this PEPR through several innovation challenges. The objective of these challenges will be to foster collaboration with the private sector in order to develop innovative methodologies:

1/ for non-invasive detection such as environmental DNA (to characterize terrestrial and aquatic environmental biodiversity) or diagnostics adapted to wildlife, unbiased early detection (*e.g.,* viroma from mosquito saliva), flying syringes (to characterize biodiversity and circulating pathogens) and/or extraction of pathogens from feces,

2/ for early detection of zoonoses (event-based surveillance systems through the analysis of formal and informal information from the web, socio-environmental satellite-based surveillance, etc.), including remote sensing, i.e., informal and formal signs from the web, modelling), decision support system for actors in charge of the epidemiological surveillance and response (including GIS- and model-based risk assessment and forecast solutions), participative surveillance.

3/ for promoting actual interactions between the scientific community, field actors, public/private sectors, civil society, and therefore effective inter-sectoral collaborations (public, private, civil society) to modify risk management practices by limiting risk factors (*e.g.,* participatory modelling, serious games on rabies or on Ebola (Alert game, BioViva).

For an additional budget of about 10% of the total PEPR, such challenges can rapidly open up a commercial niche in France with an important potential given the demands by the entire PREZODE initiative on a global scale.

These actions will benefit from several funding mechanisms within the national strategy that are organized to allow a continuum:

- from the PREZODE PEPR for basic research and early development;
- through the 3rd measure of the strategy to support the selected research projects with a view to industrial transfer (setting in place the tools, methods and support in order to create value and protect the initial results);
- and to the 4th and 5th measures that will allow research project maturation with support from the Office of Technology Transfer (OTT) and funding of ambitious partnership projects.

The idea is to initiate and fund some of the actions through the PREZODE PEPR segment and to very quickly link them to other axes of the National strategy focusing on industrial transfer, prematuration and maturation.

9. Existing international funding

In the past decade, various activities were funded at international level, either at a multi-regional dimension or at a regional dimension.

These programs were/are financed by national funding agencies or government (AFD, ANR, UK government, US government, IDRC), the European Union, International Organizations or the World Bank among others. They were/are carried out by universities, operational organizations… In particular, at the European level the Horizon Europe program will fund several projects on this broad topic in the coming years (Fig. 3).[3]

[3] HORIZON-HLTH-2021-ENVHLTH-02-03: Health impacts of the costs of climate change and benefits of action and inaction, Type of project: RIA / Total budget: 60M euros / Number of funded projects: 6
HORIZON-HLTH-2021-MALADIE-04-06: Building a European partnership for pandemic preparedness
Type of project: CSA / Total budget of the CSA: 2M euros

HORIZON-HLTH-2022-MALADIE-07-02: Preparing for a pandemic
Type of project: RIA / Total budget: 10M euros / Number of funded projects: 3

HORIZON-CL6-2021-BIODIV-01-11: What else is there? Explore the link between biodiversity, ecosystem services, pandemics and epidemic risk
Type of project: RIA / Total budget: 12M euros / Number of funded projects: 2 or 3

HORIZON-CL6-COO-2021-00-00: A health approach for food security, nutrition and sustainable agriculture (FNSSA)
Type of project: RIA / Total budget: 18M euros / Number of funded projects: 3

HORIZON-CL6-GEO-2022-00-00: Environmental observation solutions contributing to “One Health” challenges meetings
Type of project: RIA / Total budget: 10M euros / Number of projects funded: 2

HORIZON-CL6-2022-FARM2FORK-02-03-two-stage: Ecology of infectious animal diseases
Type of project: RIA / Total budget: 12M euros / Number of funded projects: 2

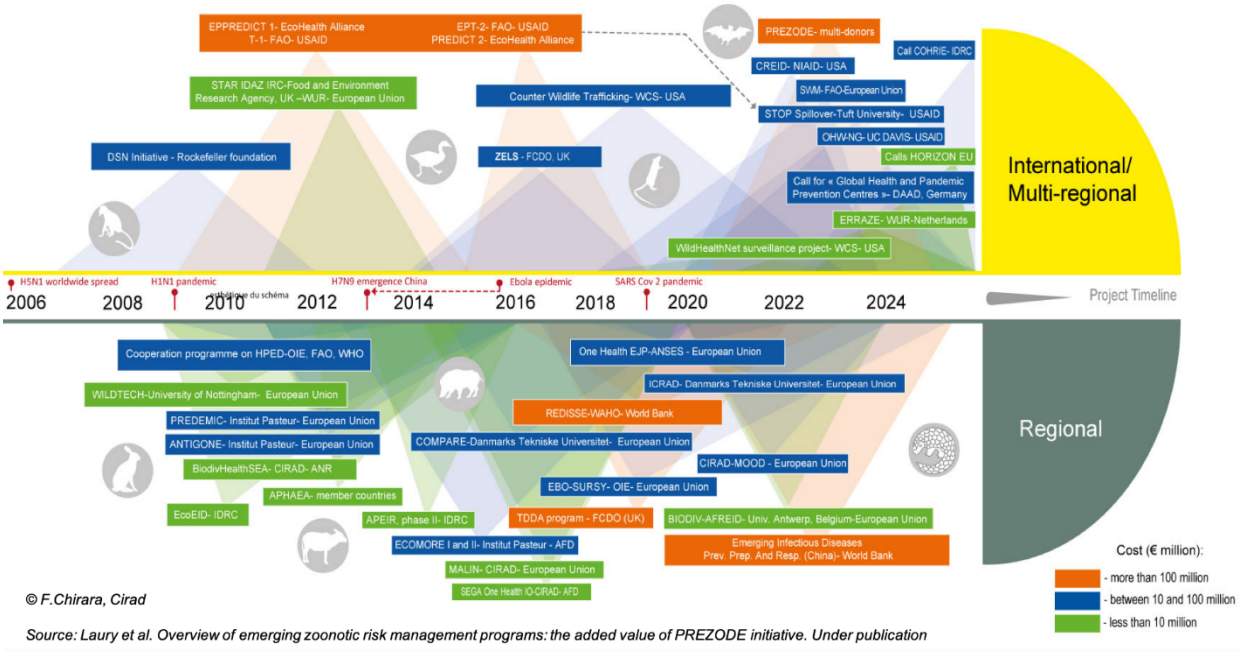


Figure 3. Mapping of the initiatives related to the prevention of zoonotic emerging diseases (from Laury et al, in prep)

The PEPR PREZODE, as the French academic contribution of the whole PREZODE initiative, is therefore unique in several ways (fig. 4).

- The PEPR PREZODE is focusing on a pro-active way to reduce zoonotic emergence risk, while most of the large projects aim to screen these potential threats and aims to anticipate their emergence, which will be complementary with:
    - PREDICT from US-AID, USA
    - Global Viriome Project from US-AID, USA
    - What else is out there? European Commission
    - Environmental basis for the prevention of zoonotic pathogen emergence, NERC, UK
    - Network for prevention and control of zoonoses, EU
    - STAR-IDAZ from the European Commission
- The PEPR PREZODE does not focus also only on threats from livestock, but on all the different global change that can play a role on zoonotic emergence risk. Therefore, PREZODE will complement research performed by
    - ZELS from the NERC, UK
    - CEEZAD, Department of Homeland Security, USA
    - the Emerging Infectious Diseases Prevention, Preparedness and Response Project for China, World Bank
- The innovative aspects of surveillance strategies that will be developed within the PEPR PREZODE, notably through participative approach, also do not fall into the current existing programs which mostly focused on technological innovation
    - ZODIAC, IAEA, AS
    - ERRAZE@WUR, The Netherlands

- The PEPR PREZODE does not focus only on rapid reaction when zoonotic microbes land into human populations, but before that stage. Therefore, this will be highly complementary with other initiative such as:
    - PANDORA, Zambia

Initiatives	Engagement and enpowerment	Prevention & Biodiversity	Prevention & Self solution	Prevention & Early detection	Capacity building	National & Regional surveillance systems	International surveillance system
Global health security agenda							
PREZODE							
CREID							
ZODIAC							
EPT-2							
STOP Spillover							
One Health Workforce-NG							
PREDICT							
SWM							
DSN Initiative							
ZELS							
Counter Wildlife Trafficking							
WildHealthNet							
OH intelligence Hub							
EU call Biodiversity/pandemics							
EU call Animal Disease Ecology							
IDRC COHRIE Call							
ERRAZE							
Total	26	29	31	32	49	33	15

Source: Laury et al. Overview of emerging zoonotic risk management programs: the added value of PREZODE initiative. Under publication

Figure 4. Analyses of the proposed priorities for the various initiatives related to the prevention of zoonotic emerging diseases (from Laury et al, in prep)

10. International scientific animation

As mentioned under work package 5, the animation of this program goes beyond the scientific pilotage of the projects that will be launched. It is a crucial part to ensure the strong mobilization of a large multidisciplinary community of domestic and international actors. In particular, there is a strong need to strengthen coordination between the other national, including the PEPR MIE, regional or international initiatives, throughout the duration of this program. It will therefore imply activities such as organization of symposia, meetings, but also the development of prospective studies (work package 5), the follow up of the impact of the program, etc. that will all be supported by the scientific pilots and the coordination of the programme. Collaborative platforms, such as klaxoon, will be opened at the beginning of the programme and project coordinators will use this tool and additional that will be discussed by the community. Furthermore, impact of the programme will also be evaluated thanks to a validated methodology, as highlighted in the same work package.

Finally, PhD students funded by both PEPRs, and if possible by other relevant ones, will be included in a “PhD Club” in which they will present their respective projects and exchange ideas.

11. Governance scheme

The **pilot institutions (INRAE, IRD, CIRAD)** are in charge of coordinating the PEPR implementation (Figure 5). The 3 pilots will work within the **programme committee**, which will be composed by one scientific member of each of the French research institute involved. This **programme committee** will establish the strategic document of the program, shape the call for proposals, as well as organize the coordination of the PEPR and share with the ANR all information useful for the implementation of a national coordination in the field of emerging infectious diseases, which best serves the interests of French research, and will ensure regular reporting to the SGPI.

The organization and implementation of the call for projects and projects evaluation will be done by the ANR through an independent an international evaluation committee.

The **Institutional strategic committee**, which will be composed by one institutional representative of each research institute, will meet once a year to provide consultative recommendations about the match between institutionnal's strategies and the directions adopted by the PEPR. The experts serving in the **evaluation committee** for each call for proposals will be jointly selected by the programme committee and the National Research Agency (ANR).

The Ministerial Steering Committee (Comité de Pilotage Ministériel, CPM) ensures that CSTP's recommendations have been implemented, validates the Call For Proposals (CFPs) and the jury composition.

Therefore, the scientific pilots of the PEPR PREZODE propose to the General Secretariat for Investment the designation of each project that could be funded and the amount that could be allocated to them. The Prime Minister, after consulting the SGPI, decides on the beneficiaries and the funding granted. Each project is the subject of an agreement between the ANR and the institution coordinating the project, detailing the reciprocal obligations of each party.

The members of the **evaluation committee**, as well as the external experts called upon, undertake to respect the rules of ethics and scientific integrity established by the ANR. The ANR's code of ethics is available on its website. **The evaluation committee will be composed by multidisciplinary experts having expertise in One Health approaches and with specific experts according the calls. Moreover, we will encourage reciprocal participation of PREZODE and MIE members in selection/evaluation committees for projects submitted following calls.**

The ANR ensures strict compliance with the rules of confidentiality, the absence of links of interest between the members of the committee or external experts and the project leaders and partners, as well as the identification of conflicts of interest. for committee members and external experts. In the case of a proven breach, the ANR reserves the right to take any measure it deems necessary to remedy it. The composition of the selection committee will be displayed on the publication site of the call for projects at the end of the selection procedure.

The **CSTP** (*Permanent Scientific and Technical committee*) will serve as an international scientific board that will provide a scientific and PEPR evaluation two years after the beginning of the program. Similarly, **the Stakeholder committee** will provide an evaluation about the impact of the programme on the different facets of the society.

Finally, there will be two common committees with the PEPR ANRS-MIE:

- The Data Sharing Committee will be created in order to monitor the respect of the ANR rules and especially ensuring data sharing and interoperability while safeguarding equitability of partnerships. This committee will have two roles:
    - Before and during the projects' implementation: proposing tools and support for ensuring that the FAIR data principles are applied
    - After the projects' implementation: provide guidance on metadata handling, accessibility and utilisation (including intellectual property component).

Implementation of the DSC proposals might require additional funding under WP5 that will be discussed during mid-term evaluation of the program. This committee will be composed by national and international specialist in big data management, PEPR MIE and PREZODE representatives and can be solicited upon request by data owners.

- The Joint Directory Board will be in charge to ensure a good synergy and avoid overlap between the two programmes. This board will also identify the key results to be communicated through the "Stratégie d'accélération" actions.

In addition to these two committees, communication and coordination tools, such as collaborative platforms (e.g. Klaxoon), will be used between the two programmes to ensure real time collaboration. Moreover, the ANRS-MIE is currently working on setting up a cross-cutting, high-level project management tool. This tool should be operational within eighteen months, then shared and used by PREZODE and will then contribute to establishing synergies between the two PEPRs. Finally, PhD students funded by both PEPRs, and if possible by other relevant ones, will be included in a "PhD Club" in which they will present their respective projects and exchange ideas. Prezode experts will also participate to the One Health experts group that will be set up by the ANRS to promote exchange of information and the search for complementarities within its scientific animation system, however the articulation between both PEPRs will be ensured by the JDB.

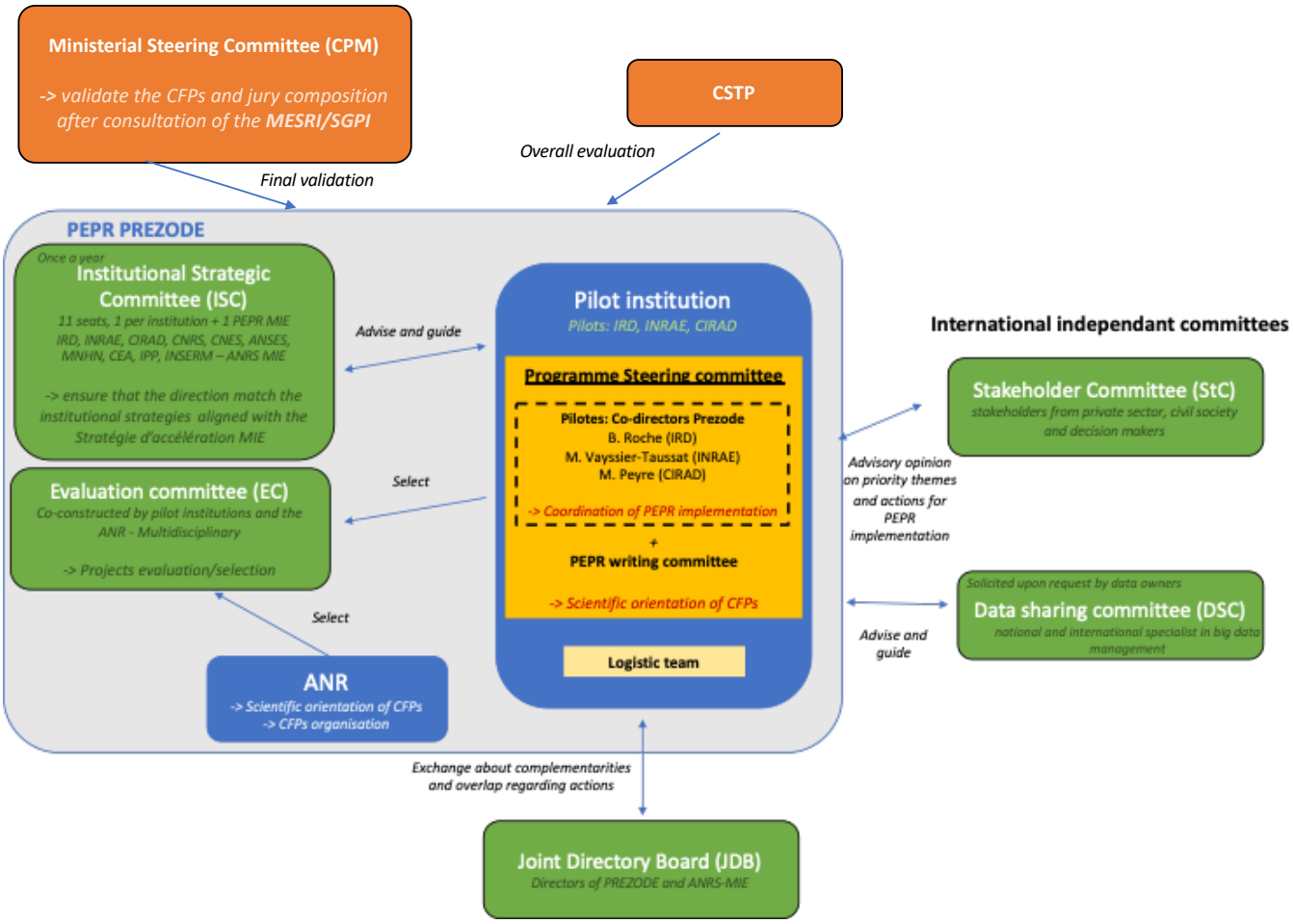


Figure 5: summary of the governance scheme of the PEPR PREZODE.

12. Conferences and events

Conferences or webinars and events will be organized each year on the themes of the PEPR with complementary approaches. They could take two forms:

The first type of conference will be an international scientific conference, aiming to bring together the international scientific community on a specific research topic to exchange on the front of science. It will ensure the international impact and recognition of the program.

The second type will be events between researchers, representatives of the civil society, professionals and politics that could take the form of roundtable or, when possible, of field visits. It will foster a stronger dialogue between science and society and maximise the impact on public policies of the program.

At least one event will be organised every year in strong collaboration with the PEPR MIE. Other events will be organized following the coordination scheme exposed in work package 5.

13. Expected impacts

In terms of expected impacts, the outcomes of this program will be strategic for two reasons.

First, this ambitious program, combined with the PEPR MIE that will focus more on the zoonotic emergence in humans, can put France at the forefront of innovative strategies for zoonotic threats. Second, it will ensure the pivotal place of France in the whole PREZODE initiative (with complementary funding from other funders such as AFD or the European Commission).

In scientific terms, our understanding on the impact of main global changes for risk of zoonotic emergence will be greatly improved, and numerous sustainable and integrative strategies to reduce them will be tested locally in combination with innovative methodologies for epidemiological surveillance). The French capacities to apply meta-genomic approaches without *a priori* will be greatly improved as well as an innovative data system connecting the existing databases between them will be developed.

Moreover, the impacts of the PEPR program and of its projects will be assessed and monitored throughout its course, by building expected "impact pathways" based on Asirpa real-time methodology.

The approach that will be implemented is based on an important literature (Joly et al., 2015; Matt et al., 2017; Joly et al., 2017) and on more than 50 case studies concerning the analysis of the societal impacts of agronomic research developed within INRAE (Asirpa ex-post Project).

The main principles of the method that will be deployed are as follows:

- Identification of the expected transformations and impacts, for 2030 (shortly after the end of the program) and for 2050 (long term) This identification will be made at the program level but also at the level of the various funded projects;
- Alignment of the research objectives and expected research results with the expected transformations and impacts
- Representation of ecosystems (program and projects): identification of facilitating / limiting factors; identification of the actors and their potential role towards the expected transformations;
- Construction of an expected impact pathway at the program and project level: deduce the main meeting points and the anticipated follow-up elements (in link with work package 5);
- Determination of intermediate stages, results and expected action plan
- Iteration of this process.

In this approach, the periodic assessment and monitoring is participatory. Its primary objective is to improve on-going learning. It is complementary to foresight activities and is based on an identification of scientific results and their possible first effects as well as on monitoring transformations in the environment of the program. The evaluation will thus follow-up the impacts of the program and help with its governance.

14. Bibliometric analysis of the French teams regarding the international scientific community

The French scientific community is quite active on the topic of zoonoses, with more than 200 papers published in 2020 (equation search: TOPIC=(zoonose* OR zoonosis OR zoonotic) AND AuthorAddress CONTAINS France)).

This number of publications is increasing constantly since the beginning of the 2000s, showing the awareness of the French community of this important topic, consistently with the international dynamic.

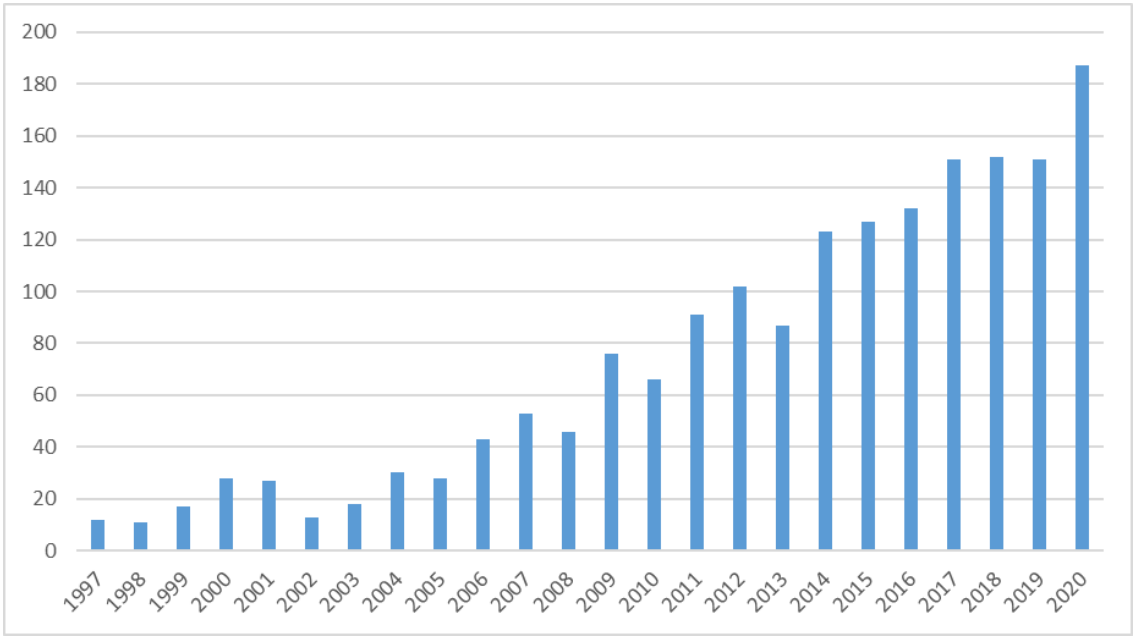


Figure 6: Number of publications on the topic of zoonoses (y-axis) through time (x-axis) with at least one author based in France.

From a topic perspective

Nevertheless, it is clear that this topic is so far, studied mostly by medical and veterinary researchers, but quite rarely by researchers working in ecological sciences of environmental health. This illustrates that the French academic community has mainly a "microbe-centered" approach, mostly in a reactive way when the zoonosis has started to spread rather than a "driver-centered" approach, which is key to develop efficient prevention strategies.

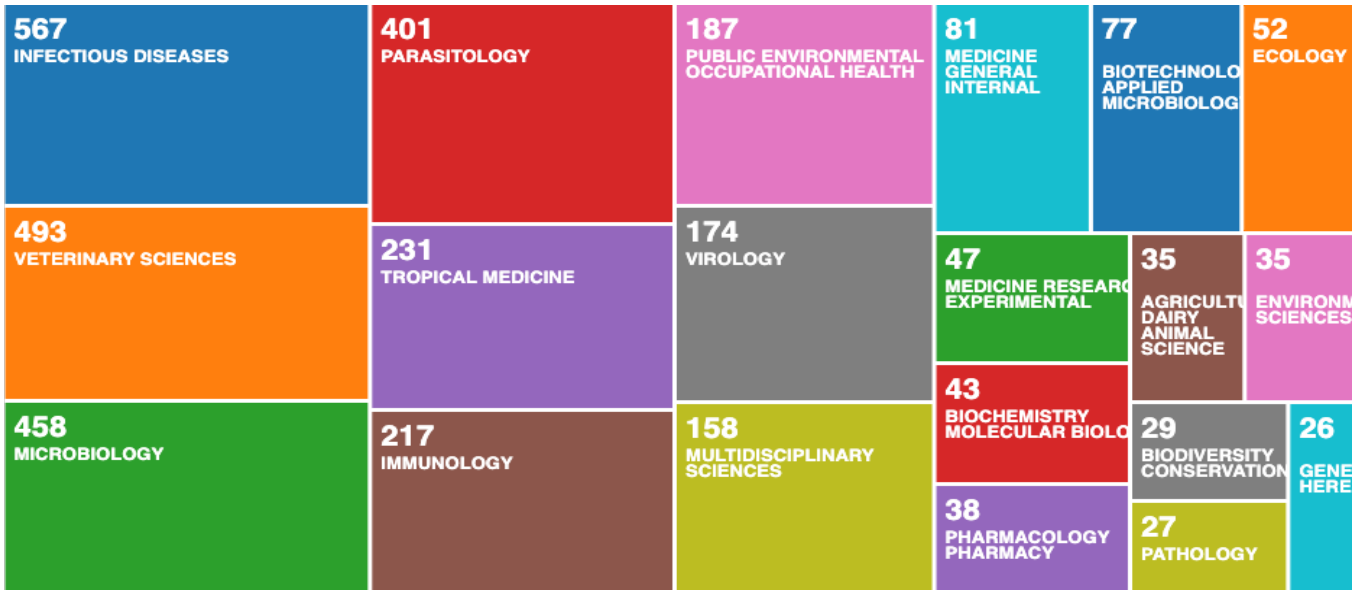
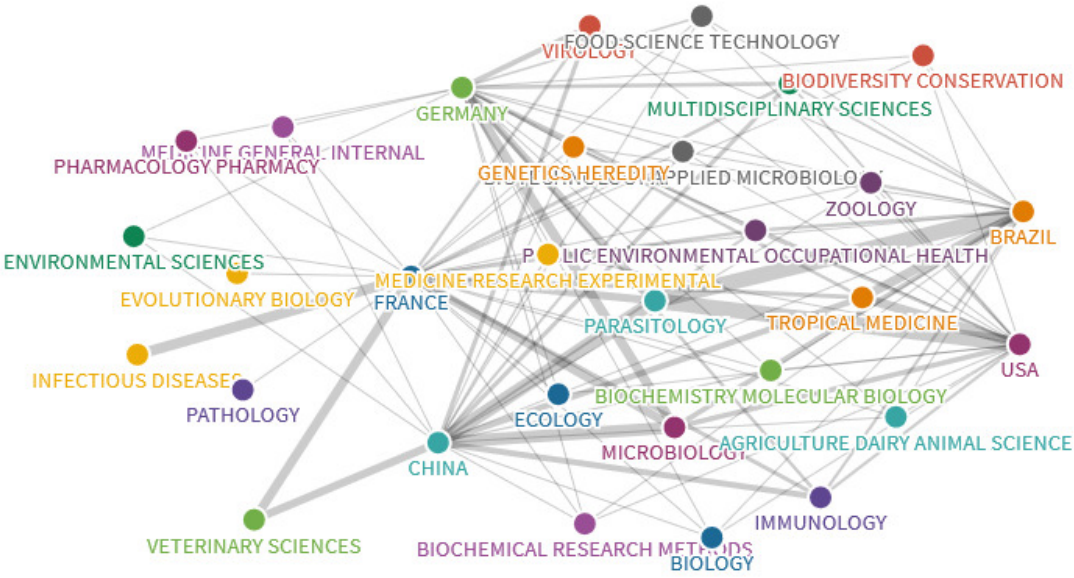


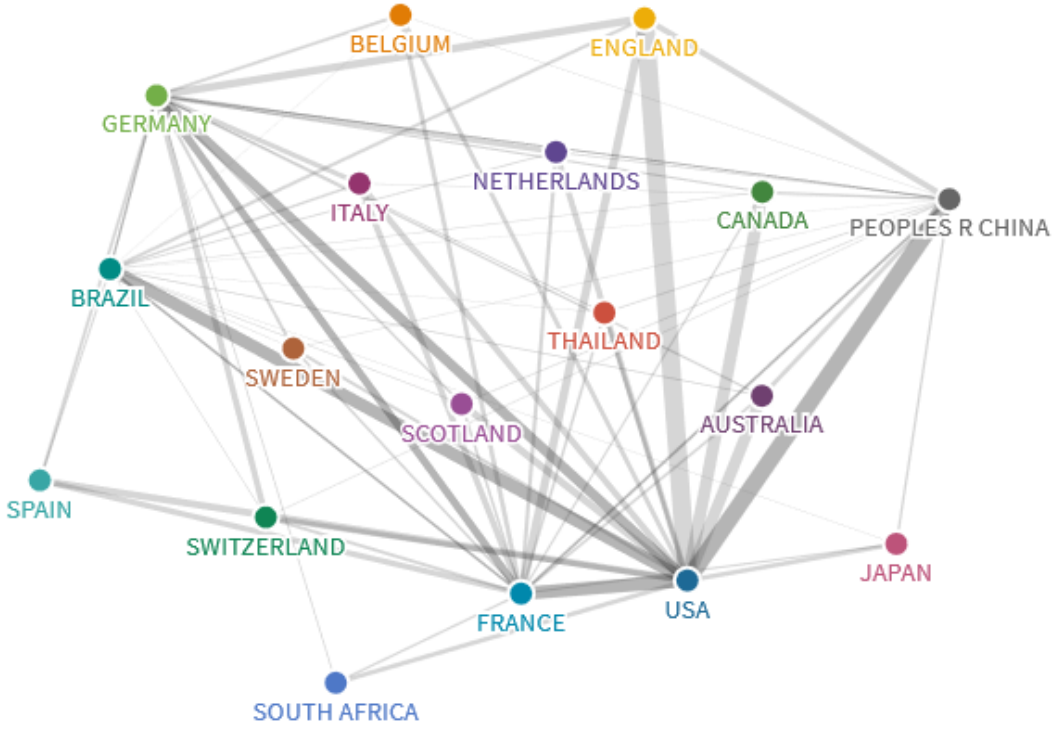
Figure 7: Number of publications for each Web of Science category on the topic of zoonoses with at least one author based in France.

The situation is not very different for the main other actors, even if topics such as “Ecology” or “Public environmental occupational health” are more strongly associated respectively for China and Brazil/USA.

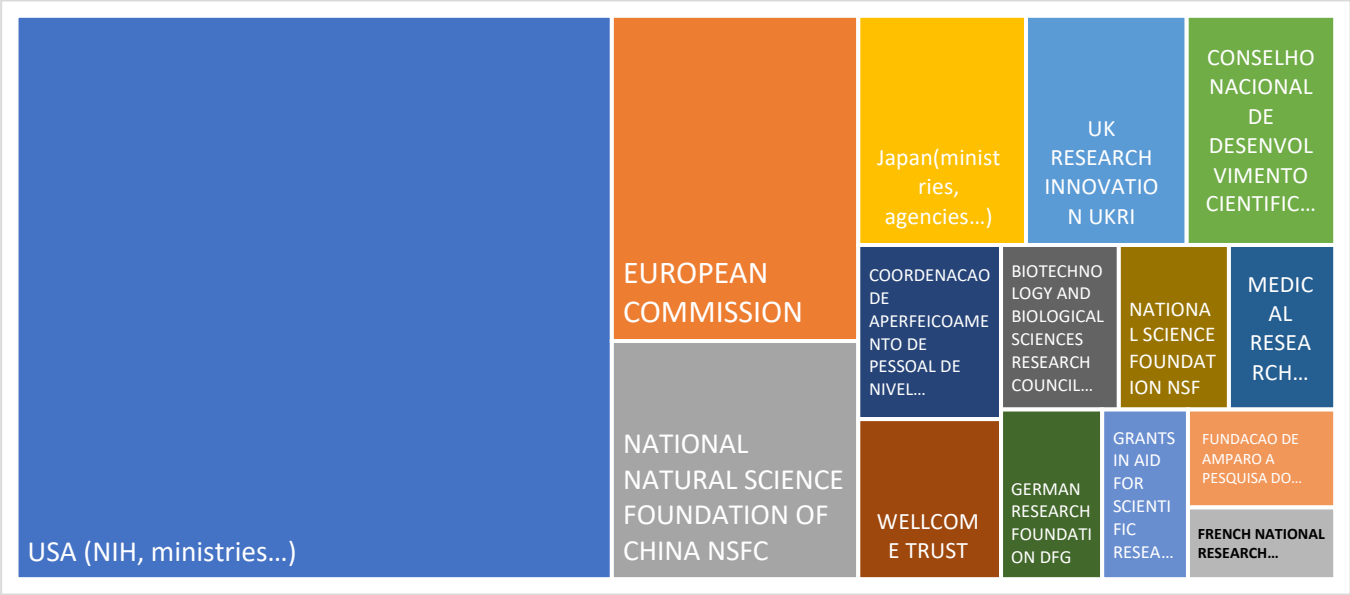


In terms of international activities

The USA are by far the most active country with almost 25% of all related publications on these topics. China, England, Germany and Brazil are the next most active countries followed by France, Italy, Austria and Spain. France is mostly partnering with the USA and its European neighbors, with little connections with the other main international actors.



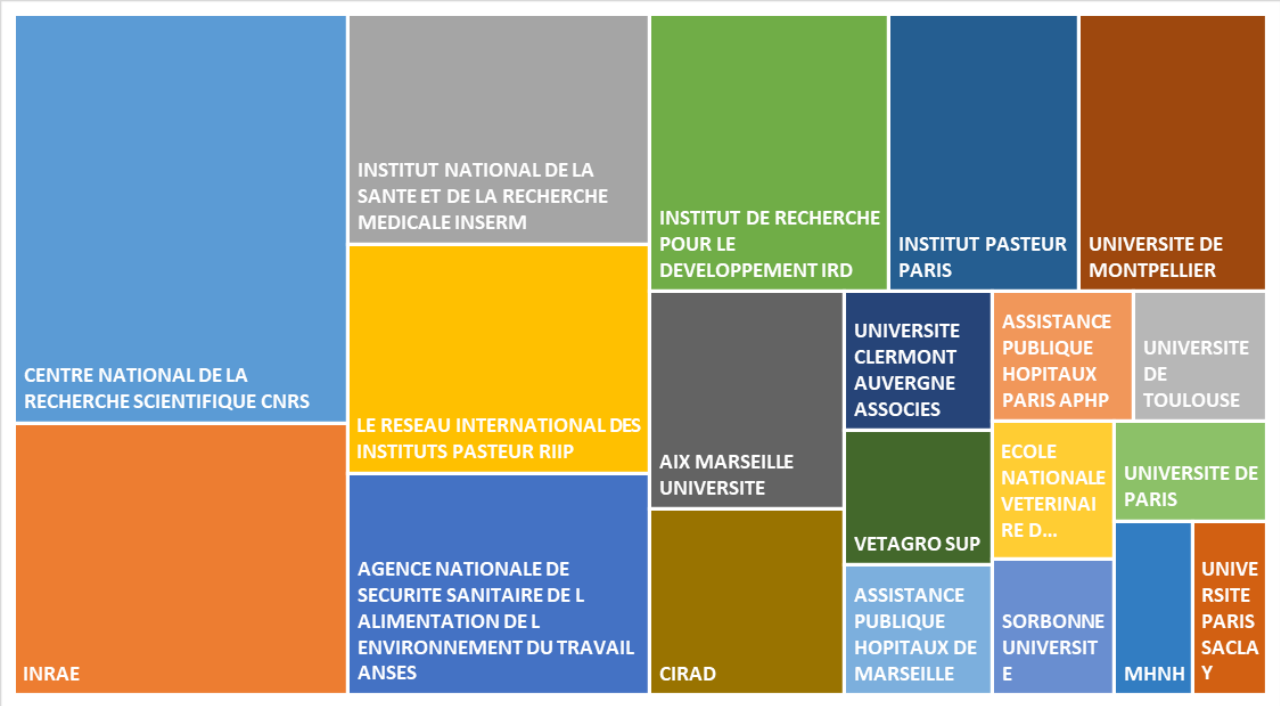
These figures can be associated with the level of funding from national ministries or funding agencies, where American, European, Japanese, Brazilian or UK sources are far above French ones.



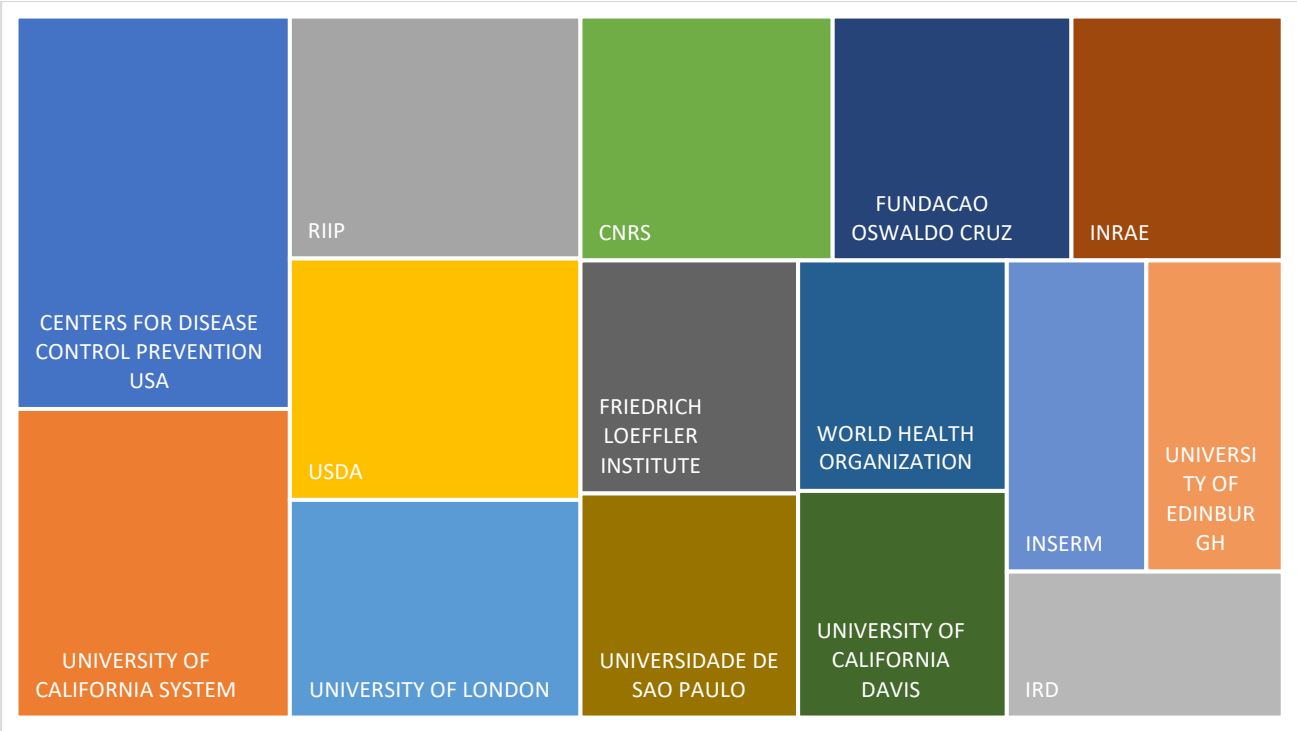
In terms of research organization

Regarding the different French institutes and universities working on this topic, the three largest ones (CNRS, INRAE, INSERM) have the most publications. While the analysis of publications from the CNRS is difficult to analyze (because covering a broad range of topic), the high presence of international Pasteur network and IRD, despite their lower size compared to CNRS, INRAE or INSERM in terms of staff population size, illustrates that study of zoonoses is mostly done overseas in Southern countries or peripherical European regions. Similarly, the presence of ANSES highlights the importance of both veterinary research and disease safety on this topic in France[4].

[4] Details of the research units in appendix



From an international perspective, even if American organizations are the most actives in the field, France benefits from some of the leading institutes and networks on these topics.



Finally, the analysis of the most frequent journals is also intriguing. Among the top journals are *PLoS Neglected Tropical Diseases*, *Microbes and Infection*, *Infection, Genetics and Evolution*.

Despite of a high quality, these journals are quite modest regarding their impact factors. Regarding journals with highest impact factors, only 5 papers published in *Nature*, 1 in *Science*, and 9 papers in *The Lancet* journals during the last 20 years. Regarding the threat posed by these zoonoses and the large research community working on this topic in France, our researchers clearly need to access specific grants on this topic in order to produce data that can allow them to publish in the most prestigious journals. To this extent, this PEPR PREZODE can play a pivotal role.

15. CV of the program PIs

Benjamin Roche

Benjamin Roche is a Research Director at the French National Institute for sustainable Development (IRD), as well as an associate professor at the National Autonomous University of Mexico (UNAM). After graduate studies in computing sciences (Conservatoire National des Arts et Métiers, Paris) and in Biomathematics (University Pierre and Marie Curie, Paris), he has completed his *Ph.D.* in ecology and evolutionary biology in 2008 from the University of Montpellier (France) and got his Habilitation to Supervize Research (HDR) in Medicine and Public Health in 2017 (University Pierre and Marie Curie, Paris). He has carried out his postdoctoral studies at the University of Georgia (Athens, GA) and Michigan (Ann Arbor, MI), has been an associate researcher at the *Ecole Normale Supérieure*, is affiliated to the Research Unit *Infectious Diseases and Vectors: Ecology, Genetics, Evolution and Control (MIVEGEC)*, and is the co-director of the *Centre for Ecological and Evolutionary Research on Cancer (CREEC).*

His research is focusing on understanding what key inter-disciplinary insights can be gleaned from bringing together the fields of evolutionary ecology and public health. To do so, he has studied how host and pathogen diversity may affect infectious disease transmission and may lead to zoonotic diseases emergence. To this extent, he is also conducting field research to characterize how environmental protection may risk this emergence probability. Finally, he has also worked to understand the interactions between ecological and societal processes in pathogen propagation. While deeply rooted in fundamental research, these projects also offer translational opportunities that are investigated to improve public health strategies, especially against vector-borne diseases in European and low-income countries. The unifying goal for all these research projects is to gain a better understanding of, and ideally find ways to help improve, public health strategies, especially in low-income countries.

He also took national and international responsibilities. He is the “One Health” scientific advisor of the CEO of the IRD. In 2020, he has been the only French researcher to take part of the IPBES workshop on Biodiversity and Pandemics, where he was a section leader as well a spokeperson. He is also a member of scientific committee of Public Health France and a member of expert group of the One Sustainable Health foundation.

With more than 4 million euros of grants directly managed during the last 6 years, he has authored more than 100 articles in international journals (*The Lancet*, *Ecology Letters, PLoS Biology*, *PNAS*, *PLoS Pathogens*, *Trends in Parasitology, eLife, Philosophical Transactions of the Royal Society* among others), edited 3 books and has been invited more than 50 times to give communications in national and international conferences

Muriel Vayssier-Taussat

Muriel Vayssier-Taussat is research director at the French National Research Institute for Agronomy and Environment (INRAe). She is a microbiologist with experience in both human and animal infectious diseases. After her PhD in 1997, she spent 3 years as a post-doc at Cochin Institute in France and in Harvard Medical School in the US. In 2001, she got a position at INRAE and came back in France to launch a team working on vector-borne pathogens. She has published more than 100 original articles and reviews in international journals on this topic.

She is now the director of the animal health division at INRAE (20 research units and 1024 agents). Since January 2020, she is also the director of the Carnot Institute France Futur Elevage. In 2020, during the coronavirus pandemic, she was part of the Research and Expertise Analysis Committee (CARE), bringing together 12 scientists to advise the French government on treatments and tests against SARS-CoV-2.

She is member of the French Veterinary Academy.

Marisa Peyre

Marisa Peyre (Eng. , Ph.D., HDR) is a senior epidemiologist specialized in the evaluation of surveillance and control programs in animal health and One Health. She is currently the deputy director of ASTRE, the integrated health research unit in CIRAD. After graduating in 1998 in biotechnology engineering (ENSTBB, Bordeaux, France), she obtained her PhD in 2005 in human health Immunology (London, UK), and her habilitation to direct researches (HDR) in the field of health evaluation in 2019. She has been working for CIRAD (French Agricultural Research Centre for International Development) since 2006, based in Vietnam for 6 years and contributed to the development of evaluative epidemiology and health economics research fields. She has been professionally trained in epidemiology, health evaluation, health economics and participatory approaches. She is a professional trainer in participatory epidemiology. She has developed and coordinated one health economic training modules for different Master degree programs in France and South East Asia. She is a member of the OFFLU OIE, FA, WHO expert network on animal influenza; of the GALVMED board meeting where she represents Cirad. She provides expertise for international organizations such as OIE, FAO, World Bank, and Galvmed. She is a member of SVEPM and ISVEE scientific societies; and a member of the ISESSAH and ICAHS scientific committees. She has organized multiple international workshops on one health including 2 international conferences: One Health in Action (Hanoi, Vietnam, 2014- 100 participants) and Innovation in Integrated Health Surveillance (InnovSur - Montpellier, France, 2018- 250 participants).

She has worked for the past 15 years on the evaluation of animal and zoonotic diseases surveillance and control both in developed and developing countries, especially on emerging zoonotic risks such as animal Influenza, Ebola, MersCov and more recently SARS-Cov2 and on the strengthening of public-private partnership. Her key expertise is on design and evaluation of health systems (surveillance and control) including wildlife and integrated surveillance systems; animal health economics; participatory epidemiology and public-private partnerships. Her work has contributed to improving our understanding of animal health surveillance challenges, especially regarding the socio-economic drivers impacting disease reporting and for

the optimization of resources allocated to these systems. She has been promoting the implementation of an integrated approach to health evaluation, taking into consideration social, cultural and economic issues, to provide relevant and adapted solutions for all the stakeholders. Her work aims to improve awareness of researchers, decision makers and private actors on health systems issues and needs and to provide tools for to better assessment of such systems. She has been promoting the needs to move from a top-down t o a bottom- up approach in the definitions of health policies and the implementation of impact evaluation (based on theory of change) as a planning tool for co-development and better engagement of all the actors in the health system processes.

She has published more then 60 articles in peer reviewed rank A scientific journals; edited a book on "Principles and methods for health surveillance evaluation"; authored 10 book chapters in integrated health and written-up more than 10 technical expert reports for international organizations. In the past 10 years she has supervised 7 PhD students and more than 25 Msc students; set up and coordinated more than 10 research projects ranging from 100k€ to 3,5 million €. In the past year she has been leading the development and writing up of the PREZODE initiative from Cirad side.

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18. Appendix

18.1. Tentative Inventory of France research unites in the scope of the PEPR

Agroecologie	AgroSup Dijon, CNRS, INRAE, Univ Bourgogne
Anses LSAl	ANSES
Anses LSAn	ANSESANSES
Anses LRFSN	ANSESANSES
Anses Lyon	ANSES
Anses PPN	ANSES
ASTRE	CIRAD, INRAE
BioEPAR	INRAE, ONIRIS
BIOGECO	INRAE, Université de Bordeaux
BioSP	unité propre INRAE
BIPAR	ANSES, ENV Alfort, INRAE
BREED	INRAE, Univ Paris-Saclay, ENVA, Univ Versailles
CBGP	INRAE, CIRAD, IRD, Montpellier SupAgro
CEEM	CNRS, INRAE, Montpellier SupAgro, Univ Montpellier
CEFE	CNRS, Université de Montpellier, Université Paul Valéry Montpellier, SupAgro Montpellier, INRAE, EPHE, IRD
CEFS	Unité propre INRAE
CEPED	Université de Paris, IRD
CESAER	AgroSup Dijon, INRAE
CESBIO	NCES, CNRS, IRD, Univ Paul Sabatier, USC INRAE
CESCO	MNHN-CNRS-Sorbonne Université
Chronoenvironnement de Besançon	CNRS, Université de Franche-Comté, USC INRAE
DIADE	IRD, Université de Montpellier
Dynafor	ENSAT, INRAE, Purpan
ECOFOG	AgroParisTech, CIRAD, INRAE,Univ Guyane
EDB	Université Paul Sabatier - Toulouse 3, CNRS, IRD
EFNO	INRAE
EGCE	IRD, CNRS, Université Paris Saclay

ESPACE-DEV	IRD, Université de Montpellier, Université de Guyane, Université de la Réunion, Université des Antilles
EPIA	INRAE, VetAgro Sup
GABI	INRAE, AgroParisTech
G-Eau	AgroParisTech, CIRAD, BRGM, INRAE, IRD, Montpellier SupAgro
GET	CNRS, IRD, CNES, Université Toulouse 3, OMP
IEES-Paris	Sorbonne Université, CNRS, INRAe, IRD, UPEC
IGE	CNRS, Grenoble INP, IRD, Université Grenobles Alpes
IHAP	ENV Toulouse, INRAE
IHPE	CNRS-INEE, Ifremer, Perpignan Univ, Montpellier Univ
INTERTRYP	IRD, CIRAD, Université de Montpellier
IRISSO	INRAE, CNRS, Dauphine Université Paris, PSL
IRSD	INRAE, INSERM, ENVT, UT3 Paul Sabatier
ISEM	CNRS-INEE, IRD, CIRAD, EPHE, Montpellier Univ
ISYEB	MNHN-CNRS-Sorbonne Université-EPHE-Université des Antilles
ISP	INRAE, Univ Tours
ISPA	Bordeaux Sciences Agro, INRAE
IVPC	INRAE, Univ Lyon
LBBE	CNRS-INEE, UCB Lyon 1, VetAgro Sup
LEM	CNRS, INRAE, Université de Lyon, VetAgroSup
LETG	CNRS, EPHE, Université d'Angers, UBO, Université Caen-Normandie, Université de Nantes, Université de Rennes 2
LISC	UR INRAE
LISIS	CNRS, ESIEE Paris, INRAE, Univ Gustave Eiffel
LPED	IRD, Université Aix-Marseille
MaIAGE	INRAE, Univ Paris-Saclay
MARBEC	IRD, IFREMER, CNRS, Université de Montpellier,
MCAM	MNHN-CNRS
MEDIS	INRAE, Univ Clermont-Auvergne
MICALIS	INRAE, AgroParisTech, Univ Paris-Saclay
MIVEGEC	CNRS, IRD, Univ Montpellier, USC INRAE
MOSAR	INRAE, AgroParisTech
PatriNat	MNHN-CNRS-OFB- IRD

Paval	UGA, USC INRAE
PEGASE	Agrocampus Ouest, INRAE
PHMI	CIRAD, INRAE, IRD, SupAgro Montpellier, Université de Montpellier
PIMIT	Université de la Réunion, INSERM, CNRS, IRD
SADAPT	AgroParisTech, INRAE, Univ Paris-Saclay
SELMET	CIRAD, INRAE, Montpellier Sup Agro
smart lereco	INRAE, Agrocampus Ouest
STLO	INRAE, Agrocampus Ouest
Territoires	INRAE, Univ Clermont-Auvergne, VetAgro Sup, AgroParisTech
TETIS	AgroParisTech, CIRAD, CNRS, INRAE
TRANSVIHMI	IRD, INSERM, Université de Montpellier, Université de Dakar, Université de Yaoundé I
UMRH	VetAgro Sup, INRAE
UMTS	CEA, Université Paris-Saclay, INRAE, UMR 0496
URZootechniques	unité propre INRAE
Unité de Modélisation mathématique des maladies infectieuses	Institut Pasteur Paris
Groupe à 5 ans - Algorithmes pour les séquences biologiques	Institut Pasteur Paris
Collection et Centre de Ressources Biologiques de L'IP	Institut Pasteur Paris
Laboratoire de Découverte de Pathogènes	Institut Pasteur Paris
Unité de Recherche et d'Expertise Arbovirus et Insectes Vecteurs	Institut Pasteur Paris
Unité à 5 ans - Anthropologie et Ecologie de l'Emergence des Maladies	Institut Pasteur Paris
Unité Ecologie et Evolution de la Résistance aux Antibiotiques	Institut Pasteur Paris
Groupe à 5 ans Biologie moléculaire des Trypanosomes	Institut Pasteur Paris
Unité Interactions Virus-Insectes	Institut Pasteur Paris
Unité de Recherche Yersinia	Institut Pasteur Paris

Unité de Biologie des Infections	Institut Pasteur Paris
Unité de recherche et d'expertise Environnement et risques infectieux	Institut Pasteur Paris
Unité Biologie des Spirochètes	Institut Pasteur Paris
Unité de Génomique évolutive des microbes	Institut Pasteur Paris
Unité de Virus et interférence ARN	Institut Pasteur Paris
Groupe à 5 ans Génomique évolutive des virus à ARN	Institut Pasteur Paris
Unite de Parasitologie moleculaire et Signalisation	Institut Pasteur Paris
Unité de Génétique moléculaire des virus ARN	Institut Pasteur Paris
Unite de Génétique et Génomique des Insectes Vecteurs	Institut Pasteur Paris
Unité de recherche et d'expertise des Bactéries pathogènes entériques	Institut Pasteur Paris
Unité de Lyssavirus, épidémiologie et neuropathologie	Institut Pasteur Paris
Unité Biodiversité et Epidémiologie des bactéries Pathogènes	Institut Pasteur Paris
Laboratoire des Interactions Virus-Hôtes	Institut Pasteur de la Guyane
VIM	INRAE, Univ Paris-Saclay
VITROME	IRD, APHM, Service de santé des armées, Université Aix-Marseille
VIRO	ANSES, INRAE
Plusieurs Unités	Réseau International des 32 Instituts Pasteur