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EMERGING INFECTIOUS DISEASES Inserm

«Programme et équipements prioritaires de recherche-PEPR»

MIE-Maladies Infectieuses Émergentes (Emerging Infectious Diseases)

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The following scientists contributed to drafting the proposed MIE PEPR on emerging infectious diseases

Members of the scientific writing committee

Coordination

Yazdan YAZDANPANAH – Inserm-ANRS-APHP-Université de Paris
Evelyne JOUVIN-MARCHE – Inserm
Claire MADELAINE – Inserm-ANRS

Scientific experts

Xavier DE LAMBALLERIE – Inserm-IRD-Université Aix-Marseille-EFS-IRBA
Eric DELAPORTE – Inserm-IRD-Université Montpellier
Annabel DESGREES DU LOU – IRD-Université de Paris-Inserm
Yves GAUDIN – CNRS
Patrick HASSENTEUFEL – Université Paris-Saclay, CNRS
Roger LE GRAND – CEA
Nathalie MIELCAREK – Inserm-Institut Pasteur de Lille
Hervé RAOUL – Inserm
François RENAUD – IRD-CNRS
Felix REY – Institut Pasteur
Gilles SALVAT – Anses
Nathalie VACHIERY – CIRAD
Muriel VAYSSIER-TAUSSAT – INRAE

Consulted scientists or experts

Benjamin ROCHE – IRD
Christophe CORDEVANT – Anses
Pascale AUGE – Inserm Transfert
Jean-François SICARD – Inserm-ANRS
Marisa PEYRE – CIRAD
Stephane REQUENA – GENCI

Graphic design

ANRS Scientific Communication and Information Department

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Summary

The Covid-19 pandemic, which is currently disrupting our lives, challenging our economic dynamism, and impacting the mental health of many of our fellow citizens, is one of the deadliest emerging infectious diseases of the last 50 years. Emerging related to new pathogens or re-emerging infectious diseases appear regularly and the frequency of their occurrence is increasing. A large proportion of emergences are of animal-origin pathogens that cross the species barrier to infect humans, within which they adapt and optimize human-to-human transmission. Several behavioral and environmental factors facilitate the emergence and spread of these pathogens. These emergences are not specific to low and middle-income regions. Given these observations, it appears urgent to understand the origin and the mechanism of these emergences to anticipate and prevent them, and to implement a global and integrated approach based on the knowledge acquired to control them rapidly and effectively. A strategic and coordinated vision of the fight against emerging diseases must be applied by reinforcing the development of health innovations on a national scale based on academic research and the strengthening of public-private partnerships.

To face these challenges, the national independent Inserm agency “ANRS | Maladies infectieuses émergentes” proposes the deployment of an ambitious program, the “Programme et équipements prioritaires de recherche (PEPR)” “Maladies infectieuses émergentes (MIE)”, fitting into the national strategy for epidemic crises preparedness and management, and comprising 4 main objectives: 1) to accelerate the acquisition of basic knowledge in a coordinated and holistic manner; 2) to strengthen infrastructures and networks; 3) to introduce a preparation and response strategy to limit the effects of emerging epidemic events with all research partners and institutions based on a coordinated approach; 4) to boost innovative public health strategies or early development of innovations possibly up to human proof of principle (diagnostics, vaccines, therapies) at national level. This program is based on interdisciplinary research covering a continuum between basic science and translational clinical research, integrating social and human sciences, as well as mathematical modelling, and including a strong support to innovation. It is by essence multi-institutional, and complementary of the PREZODE PEPR, proposed by CIRAD, INRAE and IRD, with the aim to understand mechanisms leading to zoonotic disease emergence in order to minimize the exposure of human populations. Finally, the PEPR MIE program aims to strengthen European and international cooperation in this area.

Ultimately, this PEPR MIE will contribute to meet the major public health challenges raised by pandemics at the beginning of this century through better anticipation and prevention of infectious diseases. The strategic objective of this program is to enable France to strengthen its position as a key player and essential partner in global health initiatives.

1. CHALLENGES

Emerging or re-emerging infectious diseases appear regularly, some of which cause or lead to epidemics or pandemics, potentially overwhelming social infrastructures before naturally subsiding or being brought under control by human intervention. In the past, most of the major epidemics (e.g., plague, smallpox, measles, and meningococcal meningitis) involved the spread of pathogens already encountered on numerous occasions which then spread geographically because of large-scale population movements, particularly during invasions or wars. Major pandemic-type emerging events have been rare, and largely determined by the size and movement of human populations. These epidemics/pandemics and human infectious diseases in general have been estimated to a large extent to originate from animal reservoirs.[1,2,3,4,5,6] The animal-originated pathogen crosses the species barrier to infect humans. New variants can then develop gene rearrangements or genomic mutations, allowing human-to-human transmission.

Since the 1970s, the rate of emerging or re-emerging infectious diseases in general and those related to zoonotic diseases and vector-borne diseases in particular has been steadily increasing, due to demographic developments, urbanization, increased travels and trade, changes in land use, deforestation, or climate change, including the spatial distribution of species.[7,8] For example, in addition to HIV/AIDS which led to a global pandemic in the twentieth century, and viral hepatitis, we have faced three major epidemics since 2009: Ebola in West Africa, Chikungunya and Zika in Central and Latin America, and the Caribbean (particularly the West Indies), and two pandemics: H1N1 influenza and COVID-19.[9,10,11,12,13,14,15] The diversification and spread of resistance to antimicrobial agents are also now being observed within and between human and animal populations. More in-depth studies and a global understanding of emerging events, taking into account the different components and their continuum (human, animal, and ecosystems) are therefore crucial.[16,17] In addition, bioterrorism with intentional release of pathogens continues to be of concern.

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One of the major roles of the scientific community should be to anticipate and prevent or mitigate the emergence of new epidemics or pandemics, with a view to limiting their health, economic, and social impact.[18,19,20,21,22,23] This requires a perspective that goes well beyond the response to the current crisis, deploying a long-term strategy of coordinated monitoring, preparation, and mobilization of the academic community, public authorities, and industry.

The challenge is twofold: the systematic and generic preparation of the response to future emerging or re-emerging events, while understanding and preventing future emerging or re-emerging events. This research should lead to innovations, by developing new preventive, diagnostic, and therapeutic counter measures, ensuring competiveness of France (through intellectual property for instance), joint development and industrial transfers, and the potential creation of innovative companies with high-added-value to create value for the results of this world-class research, on a national level.

Given the scientific, economic, and public health challenges, along with social expectations associated with the emergence of new epidemics or pandemics, and given France's academic and industrial leadership, we recommend the implementation of a targeted national program "Programme et équipements prioritaires de recherche (PEPR)" as a unique opportunity to amplify the momentum provided on this research topic with the creation of a new agency for emerging infectious disease : "ANRS | Maladies infectieuses émergentes". It aims to allow France to build its independence and to promote a creative dynamics in this field while working in close collaboration with Europe and within the framework of the international effort to fight against epidemics, thereby giving rise to increased safety in terms of public health, patent rights, and economic development.

2. OBJECTIVES

The priority objectives of the "Programme et équipements prioritaires de recherche" (PEPR) will be to prevent and to achieve efficient and integrated control of Emerging Infectious Diseases (EID), both on an individual and global level. **It aims to develop actions that will contribute to shedding light on the basic molecular processes involved in infections by pathogenic microorganisms and their transmission from one individual to another, to predict, prevent, or control emerging phenomena at the global level, and thus directly or indirectly making our communities more resilient to emerging and re-emerging infectious diseases.**

In France, emerging infectious diseases are currently being studied and explored by numerous disciplines, and public and private organizations, across the whole spectrum from basic to applied research. France has all the necessary assets to take its place among the world leaders, notably owing to its multidisciplinary research, with strong links with low-income countries, a robust

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healthcare system, recognized qualifications, an industrial infrastructure, and a dynamic breeding ground for young innovative companies that can be deployed in the field (see Appendix 1).[24,25] It is, however, important to **facilitate partnerships** between the different stakeholders of this continuum, and to **structurally reinforce the collective actions** that can be put in place.

The management of transmissible emerging and re-emerging diseases should be supported from the early stages through interdisciplinary and multi-institutional research. It should consider the interdependent relationship between animal health, environmental health and human health. Links with society should be encouraged by relying firmly on research in the humanities and social sciences, and on participatory research processes.[26]

The proposed approach is structured around two timeframes:

- **response during the acute crisis phase (emerging or re-emerging event, epidemic or, indeed, pandemic);**
- **basic science and applied research in between epidemics, in order to prepare a response to future crises, and to analyze the determining factors of the development and spread of emerging events; preparedness will be the core of this PEPR.**

All these aspects should contribute to defining strategies encompassing more in-depth understanding of emerging infectious diseases and their underlying mechanisms. This knowledge is essential to prevent and manage these emerging events more efficiently. A broader mobilization within the scientific community and an increased allocation of resources are essential to ensure that these efforts are maintained over the long term, beyond their impulsive and ephemeral character coinciding with successive emerging events. For maximum impact, efforts should be made to link preparedness and response strategies with the public policies put in place, particularly in the areas of health, research, education, and measures to support the economy. This concerted action should constitute a reference for all subsequent state-wide cross-sectoral strategies.

3. LINKS BETWEEN THE MIE AND PREZODE PEPR

The environmental, social, economic, ethical, and political factors which characterize a social ecosystem influence the emergence of zoonotic infectious diseases. These different determinants must be considered, both in animals and in humans, in order to understand, prevent, anticipate, and better prepare for the emergence of infectious diseases. To act more effectively against emerging diseases, an integrated, transdisciplinary, cross-sectoral approach, supported by stakeholders in human, animal, and environmental health, both in research and in the field (politicians, decision-makers, veterinarians, doctors, civil society stakeholders, etc.), is essential.

These approaches can be presented in different ways to help understand, prevent, and prepare to respond to emerging and re-emerging events.

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Both the present PEPR MIE and PREZODE PEPR, another PEPR proposed within the EID acceleration strategy, will adopt these approaches, with different but complementary objectives.

The PREZODE (Preventing Emerging Zoonotic Risks nd Pandemics) PEPR will apply its research to the pre-emergence phase, identifying the risks of emerging zoonotic events related to global changes, including the loss of biodiversity, and developing an early warning system, from local to global level, with the aim of jointly creating appropriate risk minimization solutions with and for local stakeholders. The PREZODE PEPR thus aims to develop a research program to minimize human population exposure as much as possible but will not at all target human aspects.

The MIE PEPR applies to pre-emergent, emergent and post-emergent event phases, as part of a "preparedness" and response approach. In addition to the key human aspects which will be extensively considered, this PEPR will adopt a "One Health" approach to shed light on transmission from animal species to humans, focusing in particular on adaptation and spreading within the human population, and considering environment role. It will use research in animal health that can be readily applied to research in human health, based on a comparative approach, allowing each sector to contribute to the other. Thus, the MIE PEPR notably aims to shed light on the mechanisms of transmission of zoonotic diseases to human populations in order to reduce or prevent their occurrence.

The effective coordination of these two programs is essential for future success, and will be achieved through articulated scientific animation, with organization of joint events for instance, by involving common experts, or through sharing of tools and research infrastructures when appropriate.

4. EFFORTS TO FUND RESEARCH ON INFECTIOUS DISEASES AND EMERGING INFECTIOUS DISEASES IN FRANCE IN THE PAST YEARS AND THE STRENGTHS

Prior to 2013 and the creation of the REACTing (REsearch and ACTion targeting emerging infectious disease) consortium within Inserm, which aimed to optimize and coordinate the existing research capacities during emerging and re-emerging infectious threats, little investment had been made in the organization of research in emerging infectious diseases. The French Agence National de Recherche launched calls targeting infectious diseases on a regular basis (annually), however these calls were not directly targeting emerging infectious diseases and, moreover, a retrospective analysis recently conducted, shows that emerging infectious diseases represent a low proportion of funded projects. Some funding has been granted since 2013 in response to emerging infectious diseases and not in preparation and in particular during Ebola or Zika large-scale epidemics. For example, during the Ebola epidemic in 2014-2016 in West Africa, 14 research projects were selected by the scientific board within the framework of the inter-ministerial task force created by the Prime Minister. REACTing has been able to coordinate and take the lead in research, particularly in response to epidemics, despite limited human and financial resources (an annual budget of 500,000 euros), and a political mandate for national coordination which needed to be strengthened.[27]

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Unlike little investment in organization and coordination of research, the establishment of research infrastructures and networks in infectious diseases should be however noted which have played a key role in response to epidemics in recent years (see list of the main infrastructures and networks in Appendix 2).

- The European Virus Archive (EVAg) is the first European infrastructure dedicated to emerging infectious diseases created and coordinated by France. The EVAg is probably one of the largest archive of viruses in the world to date, and is still expanding, including human viruses, animal viruses, and now plant viruses. It has served as a model for the development of other European archives, some of which, such as InfraVEC, also benefited from France's involvement. EVAg has become a privileged partner of WHO during health crises, due to its capacity to distribute reference viral strains, as well as diagnostic tests. During the Chikungunya, Zika, H1N1, MERS and SARS-CoV-2 outbreaks, EVAg provided reference materials to several thousand laboratories around the world (including the USA), and distributed more than a million diagnostic tests, together with thousands of diagnostic test series. Despite its central role in the European strategy for emerging infectious diseases, EVAg has no infrastructure status in France, and needs support to maintain France's leadership in this area.
- The P4 Inserm-Jean Mérieux Laboratory, dedicated to the study of highly pathogenic infectious agents, has been operating under the responsibility of Inserm since 2004, and represents a world-class research infrastructure open to the entire international scientific community. It coordinated the preparatory phases of the pan-European research infrastructure, ERINHA (European Research Infrastructure on Highly Pathogenic Agents), created in July 2017, with the aim of managing ambitious research programs requiring the coordinated participation of multiple European research bodies. The P4 Inserm-Jean Mérieux Laboratory has played a major role in isolating emerging or re-emerging strains, namely Ebola in 2015. Continued support for this resource is vital.
- The IDMIT ("Infectious Diseases Models for Innovative Therapies"), a national biology and health infrastructure, dedicated to preclinical research through the development of new animal models, was created in 2012, and was notably awarded "National Biology and Health Infrastructure" funding from the Investments for the Future (IA) Biology and Health Program. The ANR once again expressed its confidence in this initiative in 2019, during the final evaluation of the research infrastructure by an international jury. With its entire range of equipment and facilities, IDMIT has been fully operational since 2018. This model has widely proven its value for COVID-19 research, with animal models implemented very rapidly, and numerous strategies for prevention evaluated in the course of 2020. The current challenges of this type of infrastructure are as follows: 1) the sustainability of resources after 2025 (additional funding is guaranteed for 2020-2025); 2) safeguarding the supply of animals, particularly non-human primates, mainly originating from breeding facilities outside Europe.
- The IHU Méditerranée Infection, bringing together innovation and expertise, aims at condensing the means of fighting infectious diseases in a major and strategic core at local, national and international levels. To achieve this goal, IHU Méditerranée Infection consists of three poles: 1) Innovative specialized clinical departments at the forefront of technology by bringing together and developing three infectious diseases departments in Marseille, 2) Attracting international first-class researchers to develop research on infectious diseases and 3) Transforming this knowledge into useful tools, such as diagnostic or therapeutic products, and developing special interactions with national and regional industrial partners. In addition, this IHU is committed to

promote North-South exchanges within the field of scientific and clinical research on infectious diseases.

- The ViroCrib emerging technological platform, coordinated by the CNRS, is dedicated to the screening of antiviral molecules in BSL3 containment. The platform, develops innovative high throughput screening in permissive cell lines and, implements the production and sustained supply of human airway organo-cultures (from pluripotent stem cells) for *in vitro* screening of hits relevant human models. This latter development will ensure sustain supply of this essential in vitro model. The platform, created towards the end of 2020 with funding from the MESRI associates three different laboratories with proven expertise in the isolation of clinically relevant viral strains and actively involved in the identification of therapeutic compounds during the COVID-19 pandemic (CEMIPAI, UAR3725; "Centre d'Infection et Immunité de Lille", "Centre International de Recherche en Infectiologie de Lyon") and the laboratory of "Ingénierie cellulaire et tissulaire" (CHU de Montpellier).
- The BIOASTER Technology Research Institute (IRT) created in April 2012 by the Institut Pasteur and the Lyonbiopôle health competitiveness cluster, is working on the development of a unique technological and innovative model to support the latest challenges in microbiology, in particular to fight antimicrobials resistance, improve vaccines safety and efficacy, and quickly diagnose infections at patient bedside. To overcome technological bottlenecks and explore new avenues, this IRT is leading collaborative projects that bring together academics, start-ups, SMEs and industrial groups.
- In terms of animal health, a level 3 containment infrastructure, Emergin, dedicated to the *in vivo* study of zoonoses and animal infectious diseases, in livestock and wildlife, has been included in the national roadmap since January 2018. This infrastructure is coordinating a European project, VetBioNet, and its partners were mobilized in 2020 to identify the susceptibility of different wild and domestic animal species to SARS-CoV-2.
- The establishment of Labex (laboratories of excellence) via the Investments for the Future program, such as:
  - The "Vaccine Research Institute" (VRI), a laboratory of excellence created to conduct research aiming to accelerate the development of innovative vaccines against HIV/AIDS and re-emerging infectious diseases.
  - Integrative Biology of Emerging Infectious Diseases (IBEID) the main objective of which is to develop a structure to anticipate and fight emerging infectious diseases focusing on surveillance, analysis and control of these diseases.
  - Parafrap dedicated to parasitic infections, this Labex develops joint research and training programs that create inter-institutional and scientific links and amplify exchanges between French teams and laboratories in endemic regions in Africa, India and Latin America.
  - The Mediterranean Centre for Environment and Biodiversity Laboratory of Excellence (CeMEB LabEx), which focuses on the dynamics and functioning of biodiversity and ecosystems to anticipate both the biological consequences of global change, and anticipate the evolution of ecosystem services and human societies. Among the Cemeb sustained shared facilities, the Vectopôle IRD has expertise in research on medically significant vectors and pathogens.

- In addition to the Labex, several Equipex (equipment of excellence) have been financed through the "Programmes d'Investissement d'Avenir" (PIA) such as:
  - Equipex I2MC (Strasbourg insectarium) dedicated to the study of vector insects and the pathogens potentially transmitted to humans and animals.
  - Vectopôle Sud in Montpellier, a network of research infrastructures on vector-borne diseases and vectors of interest for human, animal, and plant health, including the CIRAD-INRAE level 2 containment insectarium platform (ticks and mosquitoes). This platform is also part of the European infrastructure project, InfraVEC2.
  - Equipex+ InfectioTron, recently selected, which offers a coordinated network of equipment and platforms for the multi-scale and multimodal analysis of infectious events in living hosts in a high security containment level. It supports the development of new lines of research to carry out integrative projects within the "One Health" paradigm, linking the field to the laboratory.
  - Equipex CACSICE (Partners: Institut Pasteur/CNRS/University of Paris) for the analysis of complex systems in complex environments, such as host-pathogens interactions studied by state of the art cryo-electron microscopy and tomography, including complexes of viruses with cell receptors or neutralizing monoclonal antibodies.

- The structural organization of clinical research networks such as I-REIVAC, a national clinical investigation network specializing in vaccinology; and even support by national institutes and organizations for their research teams (refer to list in appendix 2).

- Several BSL3 facilities have been created in the course of epidemics and have played a crucial role in the current crisis, particularly by allowing immediate isolation of the viral strain circulating in France. However, the current pandemic has shown that the number of such laboratories should be increased, that those already in place should acquire new state-of-the-art equipment to allow research teams a better access to these facilities.

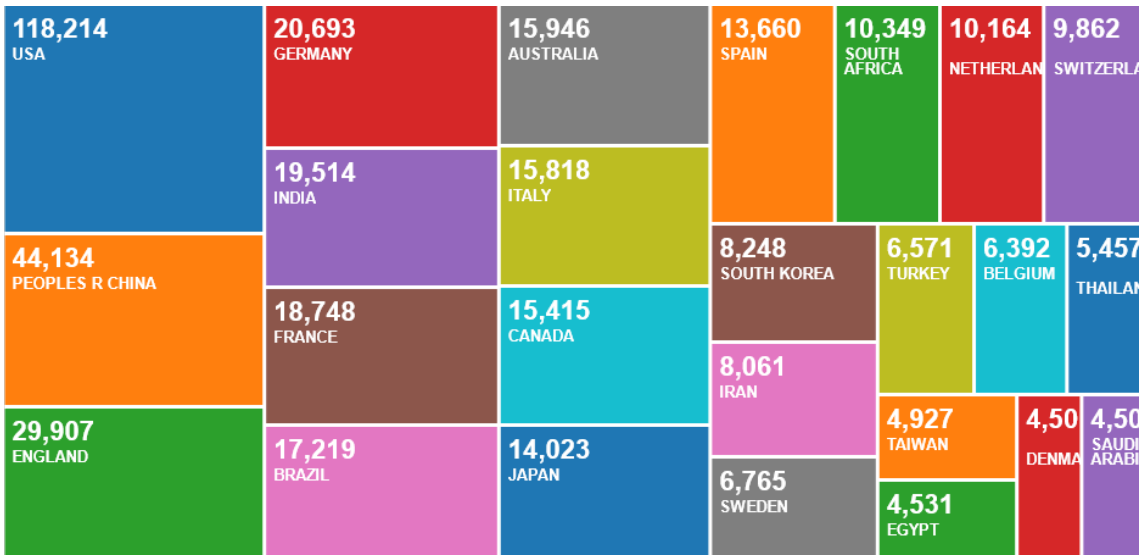
Funding has also been granted for international partnerships. Numerous research partnerships have been in place for several years, with countries in Africa, South-East Asia, and South America, particularly through the ANRS partner sites, institutions that are members of the Institut Pasteur International Network (IPIN), and laboratories working in partnership with IRD (International Joint Laboratories), through projects in partnership with CIRAD (Grease=South-East Asia, CaribVET=Caribbean, OH-OI=Indian Ocean, RP-PCP=Southern Africa), and, more recently, with China for example, through the research program on Nipah virus (Appendix 1). These partnerships that were not mostly targeting emerging infectious diseases at their creation have been reinforced in response to health crises, particularly for the Ebola epidemics with research projects bringing together all these organizations (ANRS, Institut Pasteur, IPIN, IRD, CIRAD, etc.). Of note research infrastructures in the French Guyana, French Antilles, and Reunion Island have been also reinforced to respond to emerging infectious diseases in particular during the Chinkungunya and Zika epidemics.

The institutions working in partnership with the priority research and resources program have also forged numerous links with research institutes and international funding agencies to promote information sharing, identify scientific themes of common interest, and develop alliances. Priority relationships with international public health organizations and international sponsors

(such as WHO, WHO BluePrint, GloPID-R, EDCTP, Isaric, APPRISE, CEPI, GAVI, FIND, ZODIAC-AIEAs, etc.) have been developed in particular to ensure optimal information sharing, with a view to facilitating and accelerating the roll-out of public policies based on scientific results.[28,29]

Funding from national public bodies and funding agencies have contributed to an important production in term of scientific publications, as shown by the bibliometric analysis performed in April 2021 in the field of infectious diseases in human and animal health presented in Appendix 3. Indeed, the analysis, covering all French research teams, highlighted 18,758 publications produced over the period 2016-2020 in infectious diseases in general, and underlined the emergence of following research areas: basic research ; diagnostic evaluation of infections, comorbidities, organization of care, socio-economic and demographic factors, education, epidemiology, vaccination campaigns ; arthropod-borne diseases, zoonoses, phylogenetic analysis ; bacterial and fungal infections, treatments and resistance ; HIV and viral hepatitis, diagnosis, treatments. This cartographic analysis places France in 6th position worldwide as far as the number of publications are concerned (see Figure below) and Inserm in 4th position worldwide behind the University of California, the University of London and Harvard University. In addition, this analysis illustrates that the bibliographic indicators of France are higher than the international averages (regarding the proportion of publications ranked among 1% and 10% of the world ranking in terms of citations, France is in the 3rd position after the United Kingdom and Germany: 3.5% publications among Top 1%, 17.7% among Top 10%). In terms of international collaborations, bibliometric analyses revealed a strong network of collaboration with the United States, United Kingdom, and Germany.

Of note, when excluding scientific publications related to HIV, Hepatitis, and Papilloma virus, over the same period, in infectious diseases, France remains in 6th position worldwide with 15,079 publications. Regarding the proportion of publications ranked among 1% and 10% of the world ranking in terms of citations, France is in the 4th position after the Unites States, United Kingdom and Germany: 3.9% publications among Top 1%, 18.5% among Top 10%.



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5. OBSTACLES AND WEAKNESSES

While as illustrated in the previous section France has all the necessary assets to take its place among the world leaders in research on emerging and re-emerging infectious diseases, a certain number of obstacles have been identified and must be urgently addressed. These obstacles are mainly related to coordination, liaison, structural organization, implementation, and communication issues, together with knowledge acquisition in the field of basic research.

OBSTACLE 1 : Insufficient coordination and a segmented research

Several analyses have reached similar conclusions, particularly following the COVID-19 crisis, on the need to:

- **better structure and coordinate research** across the different health institutions and stakeholders in the field or EIDs, including animal health specialists;
- **strengthen the continuum** between basic research, applied research, drug discovery, medicinal chemistry, medical research, early development and translational research, in response to the needs of society, considering the one health approach.

To address this obstacle, the government has supported plans to create a new national independent Inserm agency as of January 1, 2021, combining the scientific expertise and coordination capability of REACTing in crisis situations, with the operational capability of the ANRS in HIV and viral hepatitis research. This agency will support and ensure coordination of the entire research community focused on emerging infectious diseases and will include in its governance the main research institutions, including animal health institutions. The agency will thus fulfill the role of a permanent authority for research and innovation, where concerted decisions are taken to combine prevention and response to epidemics, in coordination with other major European and global programs. The agency will also ensure the preparedness of the relevant scientific community for future MIE crisis and the strategic research coordination in crisis situation together with other public entities in the frame of the governmental plans.

Obtaining a substantial budget in relation to this program, and in line with the health, economic and social challenges, is crucial to consolidate France's position in an international landscape, and assert its strategic role in European decisions for rapid implementation of health measures, and in the orientation of research and development policies.

OBSTACLE 2 : Inadequate coordination between academic and industrial ecosystems; between research and innovation

Despite the existing substantial foundations for knowledge and interactions between **the academic and industrial ecosystems, research and innovation are currently organized in two parallel and distinct entities that are not well articulated. It is essential to promote this cooperation** in peace time as well as during and in response to the emerging epidemic/pandemic. Synergism should be strongly encouraged between:

- on one hand, acquisition of new scientific and technological knowledge, biomarker or signature identification and validation, target identification and validation and drug/biotherapeutics discovery, by research teams in the academic context;
- on the other hand, the development of predictive, preventive, diagnostic, or therapeutic instruments by all business partners (industrialists, biotech companies, and other potential developers

promoting the advancement of knowledge and health technologies, including companies working on veterinary domains).

Co-construction of early development programs between research teams and business partners should be also encouraged. This will allow an optimal response to urgent needs in an epidemic context, and will help to prepare this response in advance. This also involves adapting the regulations on authorizations and obligations appropriate to the research field (basic and applied research).

OBSTACLE 3 : Inadequate coordination with other countries and insufficient attention to the international sphere

The COVID-19 pandemic clearly illustrates the necessity of supporting strong international scientific cooperation, particularly within Europe, but also with countries on the American continent, in Asia and in Africa. France has set in place European infrastructures allowing exchanges of reference biological materials (pathogens, vectors, blood/tissue samples, etc.) *via* the European Virus Archive and InfraVEC project, and also infrastructures for diagnosis, together with platforms to conduct clinical trials. These infrastructures should be fully integrated into the international research system to guarantee their durability and international status. Equivalent efforts are required for data sharing (epidemiological, genetic data, etc.). There should be important links with initiatives at European level for example the “Health Emergency Preparedness and Response Authority” (HERA) initiative.

OBSTACLE 4 : Insufficient infrastructures, lack of coordination

The availability of research infrastructures is paramount in the implementation of a research strategy dedicated to the fight against emerging infectious diseases: advanced infrastructures for studies in contained laboratories or animal facilities, together with analytical platforms and digital instruments for collecting and sharing data. **We need to rethink our national strategy**: certain highly complex resources should be centralized and pooled due to operating costs and the need to concentrate a critical mass of rare, very high-level expertise, while others should be more widely distributed in order to facilitate local access for teams using these resources (such as access to L3 containment and small animal containment facilities). It is important to set up a coordination system so that, in a crisis, data collection can be immediately implemented and coordinated, allowing rapid access to the scientific community and avoiding duplication. It is also important to guarantee the sustainability of these infrastructures, based on a consolidated economic model and scientific leadership. These infrastructures and advanced biotech equipment should be hosted by research organizations in the field of human health and animal health, and should be pooled as needed. This infrastructure network must cover the international reference archives (e.g. EVAg, InfraVEC) led by or involving France, but also ensure seamless exchanges between diagnostic centers (in coordination with the relevant National Reference Centers) to allow an immediate access to biological specimens, particularly those originating from patients, and removing institutional intellectual property and regulatory obstacles.

OBSTACLE 5 : Failures in collecting and using data

Despite the tremendous progress achieved in data modeling, supported by advances in computational science and the use of big data, the COVID-19 pandemic has revealed several shortcomings

which prevent from reaching the full potential in this field, and where investment is essential. Measures should be taken to improve the collection and use of data, in terms of monitoring, population behaviors including social contact, adoption of at-risk behaviors, compliance with preventive measures, and the perception of risks. It is, moreover, essential to facilitate and guarantee rapid access for various research stakeholders to these data, by allowing data transfer taking into account the open science paradigm, while ensuring compliance with regulatory requirements.

OBSTACLE 6 : Limited dialogue between the scientific community and public health authorities, decision makers, and society

Dialogue between the scientific community, public health authorities, and decision makers is key to ensure that decisions are made taking scientific progress into account and based on an adequate level of evidence. These decisions, in order to be implemented, must also be clear for society and endorsed by the various stakeholders concerned. The COVID-19 crisis has clearly highlighted the need of swift dialogue and interactions between these stakeholders, in the event of an emergency. Minor issues may then suddenly become amplified and have particularly harmful repercussions on the deployment and perception of the actions taken.[30] It is therefore essential that dialogue is organized before a health crisis occurs.

Dialogue improvement should involve 1) better training of researchers and healthcare personnel in sharing knowledge and best practices in health management, as and when these are acquired, before and during an epidemic or a pandemic; 2) better organization of communication, including all stakeholders: scientists, media, civil society stakeholders, and decision makers; and, lastly, 3) implementation of an effective dialogue between government and the population where the concerns of patients, consumers, and those involved can be heard and rapidly taken into account in order to improve messages and actions.

To achieve these goals, conclusions must be drawn from research, in all fields, concerning the current health crisis, to shed more light on the strategic decisions for patients and society, while reducing the extensive consequences of the epidemic, and preparation for future crisis should embark research actions dedicated to tackle these issues.

In France, in the past, response to crisis situations has been made possible thanks to available funding and long-term support. However, better support for ambitious exploratory research and a structural reinforcing of national strategic coordination are essential to prevent epidemic occurrence and when it does occur to drastically curb the health and economic impacts of an epidemic.

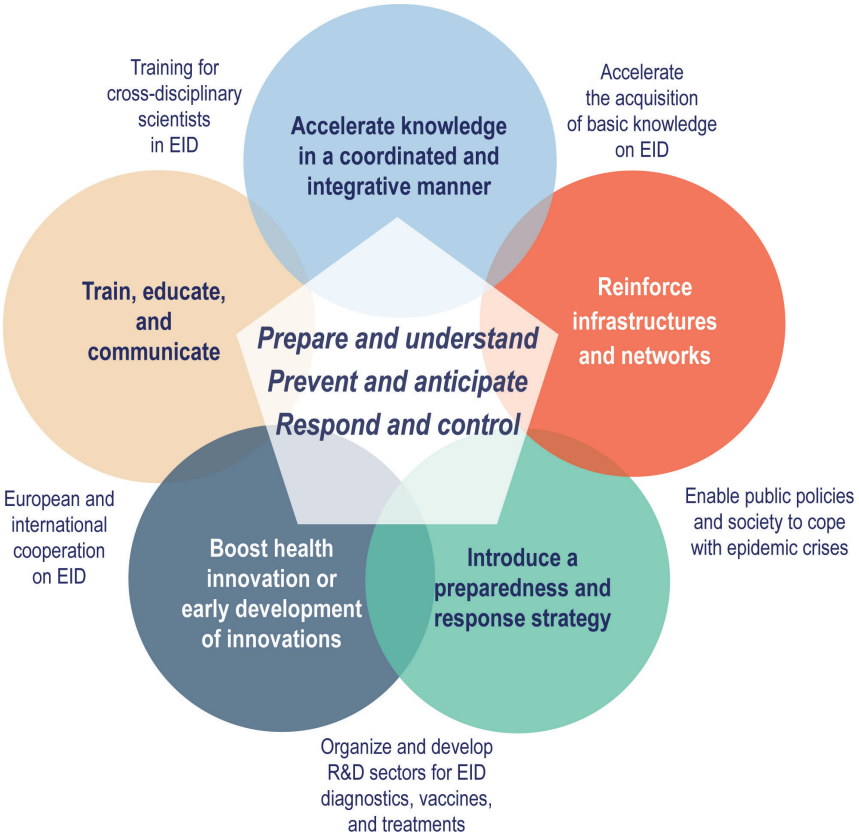
This anticipation capacity is currently limited in France, due to limited coordination and a lack of resources. The creation of an ambitious national priority research and resources program (PEPR) in emerging infectious diseases, led by the new ANRS | Maladies infectieuses émergentes agency, which includes in its governance the most important research institutions in human and animal health, is an appropriate first step response to improve French preparedness and management of epidemic crises.

We propose a research plan with 5 objectives and 12 actions presented in section 6. Some of these actions will be directly funded through the MIE PEPR workpackages that are detailed in section 7, whereas others will benefit from support through different axes of the national strategy for EID while ensuring efficient coordination with the MIE PEPR, in particular beyond research, regarding innovation and training. Research actions of the MIE PEPR will also benefit from other preexisting funding mechanism, through the ANR, National Research Agency, or European funding.

30. Second report on progress by The Independent Panel for Pandemic Preparedness & Response for the WHO Executive Board, January 2021.

6. RESEARCH PLAN ON EMERGING INFECTIOUS DISEASES: OVERALL OBJECTIVES AND ACTIONS

The Figure below represents a global and comprehensive research plan, including several aspects such as innovation and training that will be funded outside of the PEPR MIE, but need proper coordination with the MIE PEPR actions.



1) Accelerate knowledge in a coordinated and integrative manner

ACTION 1 : characterize the mechanisms of emergence in order to anticipate and prevent emerging events "at source"

- By acquiring an in-depth knowledge base on the biology of emerging, re-emerging, or candidate emerging infectious agents, hosts, reservoirs, and vectors (insects, ticks) which cause vector-borne diseases. As a large proportion of emerging events are due to pathogens originating from the animal world, research into agents already identified as having zoonotic potential is therefore essential.
- By characterizing microorganisms with potential for an emerging event.
- By clarifying the environmental, demographic, and biological mechanisms associated with the emerging event and the spread of pathogens in human and animal (mechanisms promoting contact, adaptation, and transmission, etc.).
- By studying the ecology of infectious agents, their interactions with vectors/reservoirs/intermediate hosts, and their secondary spread (water, air).

- By studying the mechanisms allowing pathogens to infect new host species.
- By targeting the geographic zones in which the emergence of disease is more likely due to global changes.

ACTION 2 : characterize the mechanisms of propagation of emerging and re-emerging agents, and their impact on human and animal health

- By clarifying the pathophysiological mechanisms of related diseases, the spread and transmission of pathogens, in humans and animals (target or model).
- By taking into account the host's genetic makeup, including vulnerability and robustness.
- By modeling the spread of these agents in the population.
- By identifying the environmental, socio-anthropological, and epidemiological drivers for epidemic spread.
- By proposing adapted approaches to monitoring and control emerging events, based on these scientific data and modeling techniques.
- By studying and validating effective barrier measures or systems to limit the spread.

It is important to compile an active list of pathogens potentially responsible for emerging or re-emerging events, and to study all the concepts described above relating to these pathogens in 'peacetime'. This fundamental knowledge will be valuable in enabling effective action to be taken during a crisis. For example, the fundamental study of at least one representative of each family of pathogens infecting vertebrates and their vectors could be an objective.

ACTION 3 : develop research on anti-infectious agents in the therapeutic and preventive fields

This includes:

For known emerging and re-emerging agents:

- Identifying the molecular mechanisms essential to the life cycle of the pathogen (including host/pathogen interactions) allowing **identification of the best therapeutic targets and/or the development of vaccines.** This should cover at least one representative of each family identified as likely to emerge.
- Screening of chemical libraries to identify "leads", i.e. molecules capable of blocking the target mechanism. This requires screening infrastructures as described below.
- Major efforts in medicinal chemistry are essential to move from the "leads" identified in the previous step, to compounds with optimal activity.
- The development of preclinical models (*in vitro, ex vivo, in vivo*) allowing the evaluation of these compounds (including pharmacokinetic and toxicity studies).
- Assessment of the risk of emerging resistance to new anti-infective agents, and adaptation of the therapeutic strategy (combination therapy).

Based on taxonomic research:

- Search for anti-infectious compounds covering the spectrum of the main viral, bacterial, parasitic, and fungal families infecting vertebrates, using the instruments described above.
- Search for molecules with an extended spectrum or for biological molecules likely to have

a significant activity on new emerging pathogens, while anticipating tachyphylaxis and the emergence of resistance.

- Cloning and characterization of neutralizing monoclonal antibodies from convalescent individuals for target pathogen families, thereby identifying the most cross-reactive, with high potential to protect against new agents liable to emerge in the target family. The information obtained via these antibodies is also essential for the development of immunogens for new-generation vaccines described below.

- Development of vaccines against emerging and re-emerging agents, ranging from the most conventional (attenuated and inactivated vaccines) to the most modern (vector vaccines and target platforms), also relying on vaccine technologies developed for use in animals. This includes identification of the target antigenic structures, the "design" of vaccine antigens to focus the protective response (reverse vaccinology, design of epitope-based vaccines and next generation vaccines), knowledge of host response mechanisms, development of methods for monitoring the host's response to vaccines, improvement of vaccine platforms (vaccine vectors, nanoparticles, etc.), molecules transported by these platforms (DNA/RNA allowing recombinant gene, protein, peptide expression, etc.), and the development of appropriate preclinical models, notably in a high-security containment facility (BSL3 animal facility).
- Target immunogens: Determining the target of the most potent neutralizing antibodies for each pathogen family is essential. However, these targets are often unstable glycoproteins, which must be artificially stabilized by protein engineering processes. Structural biology studies are thus essential during this step.
- A better understanding of attitudes among the population toward vaccination. Analyze hesitancy to the SARS-CoV-2 vaccine in France, for example, or in other countries such as in some African countries (which are reporting high levels of hesitancy among the populations). Analysis of current hostility will help anticipate potential vaccine hesitancy during a crisis and adapt vaccination strategies as well as their associated message.

These developments will involve both academic laboratories in the field of fundamental biology, human and animal health, associated value-creation organizations, pre-industrial prototypes, and all types of health industries: start-ups, pharmaceutical firms, bioproduction sites, manufacturers of medical devices and *in vitro* devices, third-party manufacturers, generic manufacturers, and veterinary health industries. They will be open to civil society and particularly to patient associations.

2) Reinforce infrastructures and networks

ACTION 4 : develop and strengthen research infrastructures

The availability of research infrastructures is paramount for implementing a research strategy dedicated to the fight emerging infectious diseases.

The crisis related to the emergence of SARS-CoV-2 has highlighted several shortcomings in several areas:

- Research infrastructure containment zones (L3 and A3): few in number, not sufficiently distributed to facilitate access for local teams, and not mutualized between human and veterinary domains.
- Access to reference scientific materials (for instance, the European Virus Archive), including

viral strains, recombinant viruses, serological and molecular diagnostic controls, monoclonal antibodies, etc.

- Development and evaluation of diagnostics, diagnostic supplies for re-emerging events, diagnostic platforms that can be deployed supported by existing systems in the healthcare, including veterinary laboratories.
- Biobanks and difficult access to samples: human, animal, and preclinical samples.
- Molecule banks: requiring coordination between the different banks and standard access conditions.
- Screening platforms for potential therapeutic agents (L2 and L3 lacking in number, and not necessarily adapted).
- Patient immuno-monitoring platforms (insufficient in L2 and L3).
- Preclinical evaluation of treatments.
- Imaging (including live imaging, with appropriate containment).
- Metagenomics and new-generation sequencing.
- Databanks (collection AND processing, including distribution of metadata) and storage facilities, and difficult access to data.
- Expertise and resources for bioinformatic analysis, sorely lacking.
- Animal supply: highly dependent on suppliers with breeding facilities outside Europe.
- Supply of research reagents (enzymes, cones, gloves, masks, etc.).
- Data quality: a vast number of data were collected during the crisis, but usually for "situation management" purposes, rather than for improving knowledge, thus making the data subsequently difficult to process.

Infrastructures already exist in all these areas, but are unable to meet national needs, or lack adequate coordination.

Proposals in terms of infrastructures and resources:

- Centralize highly complex resources due to operating costs and rare expertise ("Infectious Diseases Models for Innovative Therapies" - IDMIT, P4 Inserm-Jean Mérieux Laboratory, insectarium/Vectopôles, *in vivo* synchrotron imaging by PET and MRI, electron microscopy).
- Ensure a supply of non-human primates that has been under severe threat for a year.
- Resources in L2/L3 should be distributed throughout the country to facilitate local access for teams using these facilities, including laboratories dedicated to animal health; they may be however pooled.
- Reinforce and coordinate the omics platforms with existing large national platforms, for instance, with the "National Center for Human Genome Sequencing" (CNRGH), MetaboHub, CellPheDia, the French Institute of Bioinformatics (IFB), and the PASREL-imaging program.
- Strengthen immuno-monitoring platforms and coordinate them at national level.
- Ensure a transparent, correct, and accessible visualization/exploration/representation of epidemic data thanks to dedicated infrastructures which are constantly updated. Their value may go far beyond reporting data, for a transparent and correct analysis of the situation, with a potential impact on risk perception and the adoption of measures among the population.

The actions to be taken to meet the needs should be structured as follows:

- List the existing infrastructures in the different fields.
- Prioritize the needs according to research priorities.

- Participate in the creation of new facilities in fields lacking national capacities (particularly containment zones and data processing platforms).
- Set up a coordination system for those that are dispersed and isolated (concept of distributed infrastructures).
- Develop and reinforce a meta-network to coordinate infrastructures and platforms.
- Ensure the sustainability of these infrastructures (maintenance, human resources, etc.).

It is essential to rethink the national strategy so that, in a crisis, we can immediately coordinate the acquisition of big data (transcriptome/proteome/interactome/molecular screening), and make them rapidly available to the scientific community, to avoid duplication.

We need to organize access to biobank samples, particularly patient samples, to ensure these are rapidly available for research programs, along with the development of diagnostic instruments, treatments, and prevention.

Infrastructures should be pooled and linked as far as possible to different scientific communities (basic and clinical research, as well as human, animal, and environmental research).

In the context of the international ANRS | Maladies infectieuses émergentes network, and French institution networks (IRD, IPIN), support for "strategic" surveillance platforms within reference centers in low-income countries should also be considered. This type of network would be at the forefront of potential emerging events.

ACTION 5 : develop and strengthen monitoring and research networks

Some of these actions such as for example clinical research networks and platform trials will be in part funded through other mechanisms of the national strategy (in particular the 6th measure), but still needs to be strongly articulated with the MIE PEPR, especially in term of coordination.

It should be emphasized that several types of networks in the field of infectious diseases already exist in France, concerning both human and animal health, and the environment:

- Clinical research networks are in place, such as I-REIVAC, the national clinical investigation network specializing in vaccinology, labeled "network of excellence" by the national clinical research infrastructure "F-CRIN"; RENARCI (national clinical research network in infectious diseases), which aims to reinforce France's visibility and attractiveness in clinical research in the field of infectious diseases, and, in particular for the development of new anti-infectious agents; OUTCOMEREA, an association aiming to develop research and teaching activities with a view to improving management of the most seriously affected patients, and CLIN-Net France, a subsidiary of the CLIN-Net European network, which brings together existing investigation networks, together with researchers in infectious diseases isolated so far, with the aim of facilitating the implementation of studies to develop new anti-infective agents. Faced with the COVID-19 pandemic, a number of clinical research platforms have been set up, such as the EU-Response/Discovery platform for phase 2 and 3 trials in French hospitals and within the EU; COVERAGE France, a community-based clinical research platform; and COVIREIVAC, extension and integral part of the "I-REIVAC" network enabling clinical trials on COVID-19 vaccines to be carried out in France.
- A consortium on monitoring and research on infections due to emerging pathogens based on microbial genomics (EMERGEN), coordinated by ANRS | Maladies infectieuses emergentes and Santé publique France, is currently being set up, aiming for the national roll-out of a molecular monitoring system for infections (viral, and also bacterial, fungal, and parasitic infections in

the longer term), which will offer interdisciplinary support for microbiological monitoring and research activities.

- Monitoring or research networks in animal health, such as the animal health epidemiological monitoring platform (ESA), the food chain security platform (SCA), and the plant health platform (ESV) bringing together stakeholders from both health fields, DGAL, and research organizations (CIRAD, INRAE, ANSES).
- Environmental data collection and monitoring networks have also been set up, such as the Obépine network (Epidemiological observational study of wastewater).
- Population cohorts (ELFE, CONSTANCE, etc.) make it possible to monitor health indicators in the general population, and were able to be rapidly mobilized during the COVID crisis (SAPRIS and EPICOV surveys). France is also involved in demographic and health monitoring in southern countries (IRD, INED).

This will involve adopting a coordinated national vision of all these initiatives, strengthening existing meta-networks in the field of infectious diseases (human and animal), promoting interactions with other non-EID networks, which may share their resources and expertise (CNRGH, investments for the future program, imaging, metabolism, pediatric clinical research, neurology, pulmonology, etc.), and rolling out new networks, observational studies, or research platforms in order to respond to the identified needs. This national vision and networks that will be strengthen and developed should have strong links with networks at the European level in particular to conduct clinical trials in hospitals and/or primary care at a large scale in case of emergencies.

3) Introduce a preparedness and response strategy to limit the effects of emerging epidemic events with all research partners and institutions based on a coordinated approach

ACTION 6 : develop the capacity to diagnose, monitor, and limit the spread of emerging infections before health crises (i.e., preparedness)

- By developing and implementing diagnostic instruments and capabilities which are currently lacking, for all known emerging and re-emerging pathogens, with robust quality standards, compatible with the medical and veterinary diagnostics.
- By developing and implementing acceptable surveillance resources to detect emerging pathogens resistant to antimicrobial agents, or vectors resistant to treatment.
- By developing and setting up a generic diagnostic capacity that can be rapidly adapted to an emerging event and deployed at the relevant sites, and in the veterinary field.
- By organizing the collection and availability of diagnostic reference products (strains, natural and synthetic positive controls, specific antibodies), and biological specimens from human and veterinary clinical research programs on emerging events.
- By identifying, for known emerging diseases, predictive biomarkers of the clinical course in the acute phase, and in the medium and long term.
- By developing research in phylodynamics and the use of genomic data for monitoring pathogens in time and space at the molecular level (monitoring of variants). This requires shared systems, together with sequencing, bioinformatics, and *ad hoc* storage platforms.
- By reinforcing the testing capacity to monitor animal reservoirs of zoonotic pathogens.

• By developing physical solutions to limit the spread of pathogens: ventilation, filtration, masks, disinfectants, surface coatings.

ACTION 7 : put in place a strategy to strengthen the links between the scientific community and public health authorities, decision makers, and society

This action will be conducted in coordination with the other axes of the national strategy in particular the 4th axis. Within the MIE PEPR, it will mostly consist in supporting and improving the dialogue between scientists and the authorities, through implantation of research projects results of which will be used by decision makers and in public policy.

a) Define, in advance, how the findings resulting from the latest knowledge and available innovations can be efficiently delivered to national public authorities, in collaboration with European and international authorities (EC, WHO, etc.), possibly by proposing scenarios for public policy which are as precise as possible (efficiency, cost, impact, etc.).

Dialogue between the modeling community and public health authorities and decision-makers is key to reach informed decisions, based on an adequate level of evidence. This usually takes place in an emergency context, when it must be organized in advance, in "peacetime", to achieve mutual understanding. Multiple bodies on different scales operating between modeling and decision makers, typically disseminate data, whereas cohesive, structured interaction is necessary to optimize resources and efficiency.

Modeling is based on rigorous methodological approaches, intrinsically characterized by controlled and acceptable estimates, which can be difficult to communicate outside the modeling context. These estimates are, however, essential for correctly interpreting the modeling results - therefore, misunderstandings can lead to confusion, or even worse, incorrect interpretation of the results.

Communication channels, able to (i) simplify the scientific message while ensuring it remains precise, and (ii) explain the limitations and estimates inherent in the data and models, need to be established through research.

b) Define, in advance, how to involve the different components of society in a coordinated and efficient manner, in the response to the crisis, which involves all public health stakeholders (from local to national level, from associations to health agencies) as part of a social participation approach.

The challenge here is to build trust, before the crisis, and maintain trust during the crisis. The following measures are therefore necessary:

• In "peacetime", encourage "literacy in emerging disease" in society, to develop an understanding of the challenges, mechanisms, and issues raised by these diseases and by research (concept of scientific uncertainty, knowledge building, etc.).

• Promote participatory research, involving patient associations, families, consumer associations, and citizens who may make a useful contribution to area such as health care, research ethics, public health policies, and consideration of scientific uncertainty.

• Learn from past crises, particularly the COVID-19 crisis, by collecting, sharing, and analyzing information from historical and comparative recollections of these crises.

• Develop a communication plan through research to be applied during a crisis, to ensure that scientific opinions have greater visibility, and be expressed by credible spokespersons and in a responsible manner, avoiding too many messages.

ACTION 8 : prepare for research to be conducted in the context of a crisis

This action will be conducted in coordination with 4th axis of the national strategy, which focuses on crisis preparedness. This preparedness will be achieved:

- By setting up general population-based cohorts in mainland France, and in the overseas territories, and via international partnerships forged with ANRS-MIE with proven expertise in monitoring cohorts (HIV, Ebola, etc.). Cohorts with specific diseases should also be set up: for example, immunocompromised patients, the elderly, and healthcare workers.
- By setting up generic clinical research protocols making it possible to study the natural history of the disease and its spread more rapidly, and able to identify promising treatments or non-medicinal interventions to limit the transmission and impact of EID in humans and animals.
- By setting up instruments for biological and epidemiological monitoring (including social indicators).
- By organizing immediate access to biological specimens.
- By proposing a preclinical sector allowing rapid evaluation of new molecules and vaccine candidates.
- By initiating a prior dialog with the regulatory authorities governing diagnostic and medicinal products, and facilities with expertise in scale-up or production of diagnostic and therapeutic products.
- By setting up clinical and veterinary validation platforms, and by pooling infrastructures, particularly during crises.
- By pursuing the development of theories and modeling approaches: new data highlight the limitations of modeling estimates used so far; hence, substantial efforts should be made to overcome these limitations, and create new theoretical frameworks adapted to new data flows. This, in turn, will also guide the choice of data to be collected in order to improve the precision and efficiency of modeling results. Expertise both from human and animal health domains will be mobilized.
- By conducting a critical and comparative review of previous crisis management and decision-making, organization, and communication processes.[31,32] This should notably be used to identify the successes and failures of non-medicinal interventions,[33,34] effective mechanisms for coordinating urgently deployed research teams, and key factors for rapidly assessing the health situation and its critical aspects.[35,36,37] It should, as well as help assessing the necessary resources for estimating the impact of the envisaged measures, and to identify communication points in the crisis, with the logistical chains to be deployed on a national scale.
- By implementing measures to set the scene for health crises, and analyzing the impediments, obstacles, and barriers to a rapid and efficient response, both in terms of health, administrative organization[38] and political action[39].

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32. Zhilin Liu & Iris Geva-May (2021) Comparative Public Policy Analysis of COVID-19 as a Naturally Occurring Experiment, Journal of Comparative Policy Analysis: Research and Practice, 23:2, 131-142.

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ACTION 9 : define, in advance, the procedures for conducting research (notably from a regulatory perspective), for mobilizing all kinds of resources in the event of a health crisis

This action, essential in term of preparedness for research during epidemics, will be covered in the 4th and 3rd axes of the national strategy. It could cover pre-defined political mandate of coordination and regulation, with clearly established responsibilities, facilitated deployment of human, material, and logistical resources; prior budget arbitration; organized and clear communication and information for citizens, etc.

4) Boost health innovation or early development of innovations possibly up to human proof of principle

ACTION 10 : strengthen and structure research and technology resources in the health fields

This involves:

- Define technology transfer instruments adapted to emergency situations, in order to increase our responsiveness, in the preventive and therapeutic fields and also in the field of medical devices, including diagnostics. Mechanisms able to rapidly deploy these resources are also essential (clear procedures and, ultimately, a designated decision maker).
- Establishment of a coordinated organization system between innovative companies and public stakeholders (research laboratories, healthcare institutions, innovation/technology transfer organizations, government), and industry (pharmaceutical companies, biotech companies, diagnostic companies, and start-ups) to:
  - Identify gaps in public and private resources to respond to EID, and promote joint investments in research programs and research infrastructures/facilities;
  - Use and expand product-oriented transfer hubs for the first steps of discovery (hit, lead, identification of therapeutics pharmacological agents) and preliminary validation of biomarker/signature according to international standards;
  - Develop and finance the phases of the projects dedicated to target validation, pharmacological agents obtentions;
  - Develop “early development units” in accordance with international standards to secure early development roadmaps and execution of novel therapeutic innovations up to clinical proof of principle;
  - Accelerate the synergy as well as co-construction between academic research and industry expectations;
  - Reinforce the capacity to assess the performance of innovation and benefit/risk and cost/effectiveness analyzes, so that these can be incorporated more easily into public health procedures and actions;
  - Define specific mechanisms relating to intellectual property resulting from academic or private research, not hampering research or its immediate application;
  - Consider the concept of “global public good” allowing low-income countries to access to essential innovations.

For the rapid implementation and success of the MIE PEPR, it seems essential to include these specific activities to facilitate and enable the transfer of innovations to industry, in the context of

crisis, and in "peacetime". Many tasks within this action fall under other areas of the National strategy for emerging infectious diseases and chemical, biological, radioactive and nuclear risks and the industrial health strategy development. However, within this program we should improve coordination and articulation between academic and industrial ecosystems, between research and innovation and this must be supported in an innovative way.

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

- from the MIE 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 MIE PEPR workpackages and to very quickly link them to other axes of the National strategy focusing on industrial transfer, prematuration and maturation.

5) Train, educate, and communicate on EID

ACTION 11 : support research and innovation efforts by prioritizing a transdisciplinary approach, and by revising student education, and training of healthcare and industry professionals

This action will aim at allowing targeted actors them to acquire new essential skills, in fields such as vaccinology, structural virology, as well as basic and applied immunology.

ACTION 12 : improve information intended to the population, taking into account the diversity of audiences in order to communicate scientific information more clearly

This involves educating the scientific community in communication, and emphasizing the research and development to be conducted, with researchers in the field of human and social sciences and psychology, and with the relevant groups, to improve information intended for the general public and their willingness to accept public health measures, which are major challenges in the management of epidemics[40,41]

Training tasks in Actions 11 and 12 will be funded by different instruments than the PEPR, in particular through the 5th axis of the national strategy.

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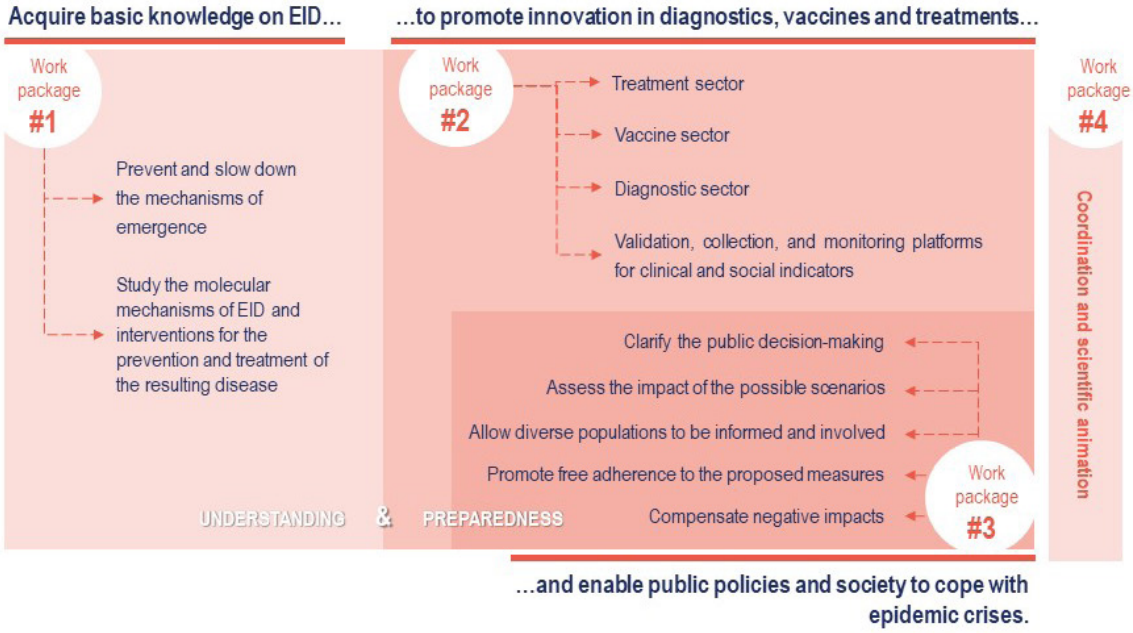
7. "PROGRAMME ET ÉQUIPEMENTS PRIORITAIRES DE RECHERCHE (PEPR)" ON EMERGING INFECTIOUS DISEASES

Based on actions described above, and the articulation between other existing mechanisms on EID, the proposed PEPR on emerging infectious diseases in humans and animals will be divided into four workpackages. Of note the PEPR will focus particularly on research preparedness. Emergency funding for research during epidemic crisis, funding of actions related to several aspects of health innovation, as well as training will be largely covered by other instruments of the national strategy on EID. Coordination between overall funding mechanisms of the national strategy on EID and the MIE PEPR will be essential.



The PEPR program that will be implemented is built on the basis of a budget of 80 million Euros over a 3 to 5 years period. The MIE PEPR will be implemented by the ANRS | Maladies infectieuses émergentes, which leads, coordinates, and funds research on emerging and re-emerging infectious diseases. It will benefit from strong coordination with the other instruments of the national strategy on EID, concerning research with the other PEPR (PREZODE), and the 3rd measure for pre-maturation which will support research projects selected from PEPR MIE with a view to industrial transfer.

Infectious diseases know no borders and cannot therefore be controlled by a single country; COVID-19 has been a dramatic reminder of this fact. Understanding the origin of emerging infections and the factors causing an anthropozoonotic event to turn into an epidemic, and then a pandemic, must be tackled as a global problem, requiring and depending on international partnerships. The MIE PEPR therefore relies on already existing international partnerships and/or to be reinforced according to the health priorities of partner countries, in close collaboration with research centers and national reference laboratories in particular, together with the health authorities in the different countries. This will rely on funding from different workpackages, which could be open to international partners (Low and Middle Income Countries), to develop international research projects sharing responsibility between different teams - in compliance with international

agreements (Nagoya Protocol) and a research ethics and integrity charter (this can be based on the ethics charter developed by ANRS for research in the field of human health in low-income countries with associations and scientists). We also emphasize that additional funding for international collaborations should be encouraged through additional instruments such as Horizon Europe Program, EU-HERA, DIGITAL Europe Program, EDCTP.

Workpackage #1: Accelerate the acquisition of basic knowledge on EID – 37 M€

Two scientific themes are proposed:

Theme 1 - Prevent and slow down the mechanisms of emergence:

- What are the biological mechanisms of emerging events (molecular and cellular aspects, pathogen class, metagenomics study of environmental biodiversity and the host, capacity for replication, evolution, adaptation and transmission, species barriers, animal and human cell receptor structure, vectors, methods of transmission, vector competence and capacity, resistance to treatments, sensitivity to host response, animal reservoirs)?
- What are the monitoring and modeling instruments which should be used to rapidly detect pathogen threats and control infection?
- What are the social, economic, and geopolitical dynamics that favor the spread of EID?

Theme 2 - Molecular mechanisms of EID and interventions for the prevention and treatment of the resulting disease:

- What are the physio-pathogenic mechanisms underlying the infection, and disease severity in humans and animals?
- What are the risk or protective factors for infection and disease severity (genetic factors, age, comorbidities, cross-immunity, sociological factors)?
- What knowledge on emerging pathogens is essential to identify therapeutic or preventive drugs, or to implement diagnostic tests and relevant vaccine strategies?
- What are the protective and preventive measures and resources that should be envisaged?
- How can populations be made aware of the importance of these preventive measures and be encouraged to accept these measures?
- What would be the benefit of comparative medicine in humans and animals for research on antiviral and vaccine treatments?

Efforts on complementarity and synergy with the PREZODE PEPR will be made on this 2 themes.

This will be implemented through:

- 3 successive calls for research projects (targeting multidisciplinary consortia for projects with around 1M€ budget) – **20 M€**
- Call for expressions of interest for infrastructures, to encourage the emergence and development of strategic approaches to replace or acquire advanced, new-generation equipment, and to renovate, develop and coordinate infrastructures; after a first phase of expression of interest and based on the results of the expression of interest a second more targeted call will be organized – **14 M€**
- Reinforcement of human resources with academic Chairs – **3 M€**

Workpackage #2: organize and develop R&D sectors for EID diagnostics, vaccines, and treatments – 31 M€

This second workpackage aims to enable mobilization of knowledge acquired with workpackage 1 of the MIE PEPR to promote innovation. This falls within the scope of an organizational and coordination activity to prepare, in the long term, during "peacetime", innovative treatment technologies, new vaccines and diagnosis, and to accelerate their proof of concept, development, and possible deployment for an emerging event, particularly associated with open, flexible platforms more readily deployed from an individual scale to a mass diagnosis scale, in human and animal medicine. This workpackage will be strongly articulated with the 3rd measure that will support innovative projects with a view to industrial transfer (proof of concept), facilitate the link with product-oriented transfer hubs and early development unit to help anticipate regulatory aspects, improve synergies between academic research work and industry expectations, and promote a de-risked approach to future development in France. It will ensure a continuum with additional maturation funds from other **instruments of the national strategy** on EID to support research teams and infrastructures.

1) Treatment sector

This involves setting up a sector for "early drug discovery" and preclinical research, including selection of molecules or biomolecules with anti-infectious potential from medicinal chemistry and molecular biology, *in vitro* and *in vivo* evaluation, toxicology, and animal models up to use in humans. This sector comprises a selection of therapeutic drug substances, preclinical research, and clinical validation.

In addition to "small" chemical molecules, pharmaceutical and biotechnology industries are developing a growing number of so-called "biological" molecules, notably antibodies, proteins, and nucleic acids, and monoclonal antibodies in particular. More than ever, the complementarity and synergy between public and private stakeholders should allow new therapeutic drugs to emerge. Academic stakeholders should therefore take charge of identifying these therapeutic drug substances. It is essential to expand the molecular nature of medicinal products, and once again to explore the field of chemistry in order to design and rapidly synthesize an arsenal of antiviral, antibacterial, and antiparasitic agents.

To this end, a network of experts should be organized at national level, allowing:

- The design and synthesis of molecules or biomolecules, by supporting research into new synthesis methods, notably miniaturized flow synthesis techniques (microfluidic) which are particularly well suited to the mass production of medicinal products.
- Virtual screening (physical or *in silico*) and molecular modeling or screening in a BSL3 environment, followed by optimization.
- *In vitro* evaluation (cells, organoids, organ-on-a-chip) and *in vivo* evaluation on animal models by developing the preclinical network set up for SARS-CoV-2, with plans for European expansion.
- Platforms for clinical validation of therapeutic candidates (complementary to platforms funded through the 2nd axis – 6th measure of the national strategy, in particular for phase 1 trials).
- Continuation to stages involving optimization, feasibility of industrial scale-up, regulatory toxicology studies, followed by the clinical trial phases.

2) Vaccine sector

As can still be seen with COVID-19, and although depending on the pathogen, vaccination is potentially the most effective means of fighting a pandemic, and the best investment in terms of public health. The vaccine sector of the ANRS | Maladies infectieuses émergentes PEPR program will be inspired by the R&D mechanisms put in place for the COVID-19 vaccines, and should:

- Promote the development of technologies, including vaccine vectors capable of being rapidly adapted to emerging or re-emerging pathogens. Develop preclinical models for evaluating vaccine candidates, particularly in BSL-3 containment. Strengthen links with existing networks and infrastructures, such as the Vaccine Research Institute (VRI), IDMIT, I-REIVAC, and European infrastructures, such as the European Vaccine Initiative (EVI) which coordinates Transvac.
- Support the development of vaccines against emerging and re-emerging diseases, and particularly WHO priority diseases, in accordance with international initiatives (CEPI/GAVI).

It will then benefit from other instruments of the national strategy to:

- Support the creation of start-ups in the field of vaccine in articulation with the BPI France.
- Enable clinical validation of vaccine candidates (although phase 1-2 trials could be funded through the MIE PEPR).
- Support transfer or cooperation in the late stages of vaccine candidate development.

3) Diagnostic sector

The diagnostic sector is essential for detecting and anticipating the response to an emerging or re-emerging disease. This should be based on the extensive mobilization of academic and industrial innovations in diagnosis, both in the human and veterinary field, emerging during the COVID-19 health crisis, and previous crises such as Ebola, together with proposals by Medicen, Eurobiomed, and Lyonbiopole. This should make it possible to:

- Establish a diagnostic capacity which is currently lacking, for all known emerging and re-emerging pathogens, with robust quality standards, compatible with the medical and veterinary diagnostics.
- Set up a generic diagnostic capacity which can be rapidly adapted to an emerging event, and which can be deployed at the relevant sites.
- Develop diagnostic solutions that are less expensive in terms of single-use consumables, and therefore less prone to shortages during a pandemic or panzootic.
- Organize the collection and availability of diagnostic reference products (strains, natural and synthetic positive controls, specific antibodies), and biological specimens from biobanks and clinical research programs on emerging events.
- Identify, for known emerging diseases, predictive biomarkers of clinical evolution in the acute phase, and in the medium and long term.
- Propose biological and epidemiological monitoring instruments, which can be used to monitor the spread of known agents and applied to newly emerging agents.
- Establish secure data management resources for real-time monitoring of changes in the epidemic, and changes in pathogens.
- Optimize the use of patient samples to test and validate diagnostic tests.
- Accelerate the implementation of sequencing, bioinformatics, and storage platforms (with an open science policy) for genomic surveillance of all pathogens in time and space.

4) Validation, collection, and monitoring platforms for clinical and social indicators

This will be in part funded through the 6th measure of the national strategy for the more advanced platforms. The MIE PEPR will play a key role in identification and creation of new platforms, and for the coordination of the different research infrastructures.

It will notably rely on the platforms created for the COVID-19 health crisis which will be used as a pilot:

- EU-Response/Discovery platform for phase 2 and 3 trials in French hospitals and within the EU (EU-Response project), to be opened potentially to company-sponsored trials.
- Covireivac for vaccine trials in coordination with European initiatives, particularly for phases 3 and 4, for postmarketing surveillance.

It will also be important to:

- Based on existing initiatives, create platforms for outpatient and inpatient trials which could be extended to the ANRS-MIE international network.
- Develop cohort studies in the general population, particularly large-scale per- and post-epidemic seroprevalence studies (for instance, using the Epicov, Sapris and COVIDONNEUR studies on COVID-19 as pilots, opening them up to other EID), and in vulnerable populations by expanding existing cohorts, creating new cohorts on target populations, based on management platforms for very large databases with a capacity for complex statistical analysis. Such cohorts could include social indicators.
- Set up a biobank for the collection, storage and sample distribution with simplified procedures.
- Strengthen or create infectious diseases research platforms in the French overseas territories (French West Indies, French Guiana, La Réunion, Mayotte, and New Caledonia) and those belonging to the ANRS-MIE international network, in which populations more frequently face emerging and re-emerging infectious diseases, given the specific characteristics of the tropical climate, the very strong biodiversity, and a very mixed sociocultural context.
- Harmonize the processes and technologies used to promote an effective and robust analysis of the data collected, based on clinical research networks and existing biobanks at the international level to promote sharing of biological specimens in compliance with country-specific and international regulations.

This workpackage will be implemented through:

- 3 successive calls for innovative research projects focusing on counter-measures against EID, and building a continuum with workpackage 1 (targeting multidisciplinary consortia for projects with a minimum 1M€ budget) – **16 M€**.
- Call for expression of interest for biobanks, and for the development of research platforms and infrastructures that can be used for innovation (i.e.; platform trials, cohorts, biobanks…) and are complementary of the more advanced platforms funded through other mechanisms of the EID strategy (measure 6) – **13 M€.**
- Innovation Chairs: Chairs more specifically funded to work on research and innovation articulation – **2 M€.**

Workpackage #3: enable public policies and society to cope with epidemic crises – 10 M€

Controlling an emerging infection at a time when insufficient knowledge is available may require interventions that can severely restrict daily life, social interactions, and the economy. The adopted measures are based on political decisions which should be justified by weighing the epidemic risks against the potential risks of these containment measures. Society should accept and respect these decisions, in order to optimize efficiency and reduce negative impacts in every respect. Research in human and social sciences is therefore essential in order to clarify the public decision-making process, assess the impact of the possible scenarios, allow diverse populations to be informed and involved, promote free adherence to the proposed measures, and compensate negative impacts.

All disciplines of the human and social sciences are mobilized, given the diverse themes to be examined. The following research topics have been identified:

- Public decision-making process, scientific expertise and democracy; interactions between expert scientific organizations and political/governmental decision makers as part of the public policymaking process, procedures for involving citizens and their representatives according to the challenges of health democracy, and the function of democratic institutions during a crisis.
- Development of public policy: legitimacy, efficiency and adaptability of public and private bodies facing an health crisis, which relates both to decision-making processes and the challenges of coordination between institutions, bodies and stakeholders on different levels (local, national, and supranational).
- Health communication and promotion: production and diffusion of scientific information, role of the media, particularly social networks, building trust, attitudes with regard to science, and the problem of conspiracy theories and fake news.
- Assessment of the impact of health measures in the different areas of the daily life among the population: exposure to infection, healthcare consumption, personal and family life, mental health, employment and financial resources, living and working conditions, mobility; and at the macroeconomic level: employment, poverty, human capital.
- Determination of social and regional health inequalities: individual factors and structural aspects of exposure to infection, and treatment.
- Knowledge, perceptions, attitudes, and practices with regard to screening, vaccines, and treatments, in the general population and in different subgroups (by gender, generation, social class, and origin, etc.).
- Transfer of knowledge to future political and governmental decision makers, including the results of this research in the programs led by IHEDN, IHEST, and EHESS, and the future ISP.

Alongside the studies and surveys, which will be based on qualitative methods together with sociometric, psychometric, and econometric quantitative approaches, permanent schemes should also be put in place allowing a proactive response to the problem of emerging events. This is the case for population cohorts, panels and repeated surveys in the population, or in special populations, to determine how specific health challenges feature in the concerns, perceptions, and expectations of populations. Interventions would be also implemented and evaluated using different epidemiological and public health tools.

A few population cohorts and observational studies already exist in France, and in southern countries with which France has a long tradition of research partnerships. These could be restructured

to facilitate links between health data and social data, and introduce new data collection corresponding to the points listed above.

Analytical systems for big data will also be included, in order to characterize, monitor, and assess attitudes among the population faced with EID and emerging phenomena in terms of opinions.

A platform serving as a "digital memory of the COVID-19 pandemic" will be created, to provide a place for archiving and maintaining a collective history of the epidemic in order to promote sharing of knowledge on the social impact of the pandemic, and draw lessons for future emerging events.

Comparative approaches or the creation of international programs are particularly essential and productive in this field.

Implementation of this workpackage will be achieved through:

3 successive calls for research observational studies, cohorts and surveys, and big data analyses (targeting consortia for projects around 0.5M€ budget) – **10 M€**

Workpackage #4: coordination and scientific animation of the MIE PEPR – 2 M€

The MIE PEPR will be implemented by the ANRS | Maladies infectieuses émergentes. The Agency will coordinate the scientific animation at national level with a strong link with international institutions. It will be in charge of organizing the calls for research projects and calls for expression of interest, scientific evaluation, funding and follow-up of funded actions.

This workpackage will support the scientific coordination between the MIE PEPR and other French or international initiatives on EID, in a holistic manner. It will involve joint international scientific animation (e.g. conferences, joint programs, etc...), in particular with the PREZODE PEPR to bring communities to interact, share concepts and elaborate common research questions, as well as sharing of expertise to set up committees and evaluation criteria to select research projects.

The ANRS | Maladies infectieuses émergentes will ensure proper coordination between the MIE PEPR and the other instruments of the national strategy on MIE, in particular with the PREZODE PEPR (through regular meetings for instance) and with the 2nd axis of the strategy (innovation - measures 4 to 6).

Specific funding will be allocated to ANRS-MIE to organize the scientific animation at national and international level, the calls and evaluation of projects, and the coordination of the MIE PEPR – 2 M€.

Overview of workpackages and budget breakdown

We are planning to organize 3 successive calls (AAP) in 2021, 2022 and 2023, pooling calls for workpackages 1, 2 and 3, with a total budget of 46 M€ (around 15 M€ per AAP).

Similarly, successive calls for expressions of interest for infrastructures will be opened, for workpackage 1 and 2, which frequency and budgets will be based on the analysis of existing infrastruc-

tures, seeking for articulation with other funding mechanisms. The total budget for these calls will be 27 M€.

Finally, funding for Chairs will be mutualized, for a total budget of 5 M€.

	Workpackages	M€	Implementation methods	2022	2023	224	2025	2026
#1	Accelerate the acquisition of knowledge on EID	37	AAP		20 M€			
			Equipment & Infrastructur		14 M€			
			Chairs			3 M€		
#2	Organize and develop R&D sectors for EID diagnostics, vaccines, and treatments	31	AAP		16 M€			
			Infrastructure		13 M€			
			Chairs			2 M€		
#3	Enable public policies and society	10	AAP		10 M€			
#4	Coordination, Governance, Evaluation	2				2 M€		

Definition of the calls for proposals and organisation of the evaluation

A list of priority pathogens and pathogen families has been defined at a national level by ANRS-MIE, with experts from multiple institutions including PREZODE stakeholders and partners. This list will be used as a common working basis for the national strategy, and thus the two PEPRs. It will be reviewed on an annual basis.

The themes of the calls for proposals will be proposed by the scientific board of the PEPR-MIE, the text of the call will be drafted by the ANRS-MIE and approved by the steering committee based on the strategic agenda developed in the proposal. For the first call, workshop with the members of the scientific board will be organized in May and June 2022 to propose the different themes to be included in the call.

The content of each call for proposal will be submit to the Joint Directory Board (see Gouvernance) that bring together representatives of PREZODE and PEPR MIE, to avoid any overlaps, ensure the right 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 selection/evaluation committees for projects submitted following calls.

Finally, PEPR pilots will submit the CFPs including modalities and the jury composition to the Ministerial Steering Committee (Comité de Pilotage Ministériel, CPM) for validation.

The selection criteria will be detailed and finalized by the scientific evaluation committee before the launch of the first call, and if needed improved or adapted for the following ones based on the knowledge gained and topic covered after the first call and the potential evolution of the sanitary context. They will at least include:

- Pertinence
- Scientific excellence and ambition
- Quality of the consortium
- Expected impact of the project
- Innovative dimension
- Coherence with the EID/MIE national strategy

The text of the calls will clearly specify that a priority will be given to the proposals that include a transdisciplinary approach and involve the relevant actors.

Upstream research on EID could be addressed without fully covering the One Health approach. Anyway, when relevant, the call will mention that a specific attention will be paid during the evaluation process on projects that includes the three components of the One Health approach.

The goals for WP 2 in the field of treatments is to consider concepts developed in the frame of WP 1 and to push their development for potential industrial use. This includes efficacy and safety testing and pharmacodynamics data definition using preclinical and clinical approaches. The main objective is to strengthen the continuum in R&D.

Involvement of decision makers and affected communities, community engagement and private sector

The ANRS is an agency whose history has begun with the fight against HIV/AIDS; it has made a rooted tradition of its collaboration with patient associations and civil society. Thus, the associations working in the thematic fields of the agency are present:

- In the scientific evaluation committees, where their representatives have the same voting rights as scientific experts;
- In the “coordinated actions” which are the agency’s formal working groups, building its scientific expertise.

The ANRS, since its creation, has a scientific department dedicated to public health and human and social sciences.

Furthermore, the ANRS has recently created an internal department dedicated to innovation, in order to establish a permanent link with the industrial world.

The agency has set up a Council of Partners, a new governance body whose role is in particular to involve the private sector in the agency’s strategic projection.

For the implementation of the PEPR, the agency proposes to strengthen the Scientific Board, in charge of establishing the main orientations of the calls for proposal and part of the selection criteria, by involving patient associations and, if appropriate, other members of civil society. Inclusion of patient associations in the scientific board will be effective before the establishment of the first call for proposals. Their participation will be extended to the evaluation committee before the end of this year.

Private sector involvement will be considered, especially for segment #2, thanks to the evaluation criteria that will be defined. In this way and taking into account the agenda constraints, representatives of the private sector will be included in the evaluation committee for the first call and to the scientific board for the second call.

Obviously, public health and public policies aspects, as well as community engagement will be taken into account in the evaluation and selection process. A particular importance will be given to these aspects.

Articulation and coordination between PEPR PREZODE and PEPR MIE

Several possible interactions have been identified between both PEPR, in particular regarding articulation between workpackages.

First through the WP1 of both PEPRs, the two programmes will contribute to 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 WP3 of MIE that will focus on ways to enable public policies and society to cope with epidemic crisis is linked with the WP2 and 3 of PREZODE. Through its WP3, PREZODE will work on innovative approaches to engage stakeholders to perpetuate over a long-term efficient epidemiological surveillance, this action aiming to engage actors to surveillance will contribute to the involvement of diverse populations as presented in the PEPR MIE. In the WP2 on the identification of sustainable strategies to prevent zoonotic disease emergence, a specific action aim to understand the sociological drivers of the possible adoption of these solutions by the different actors of the society that will help to promote free adherence of proposed measures as planned in the WP#3 of the PEPR MIE.

Then a synergies have been identified through innovation in diagnostics that is included in the WP2 of the PEPR MIE that aim to establish a diagnostic capacity compatible in the human and veterinary field and in WP4 of the PEPR PREZODE that aim to strengthen French capacities to detect zoonotic pathogens from wildlife, domestic animals and environmental samples.

Finally both PEPR have a coordination and scientific animation workpackges (WP4 for MIE and WP5 for PREZODE) that will be in constant interaction through the implementation coordinated animation actions. This coordinating aspect will ensure regular exchanges between WP that need to be articulated between the two PEPR for activities review and identification of overlaps or synergies.

Experts from PREZODE have been involved in the writing of PEPR MIE proposal, and reciprocally. We intend to continue this approach of reciprocal participation within the scientific board which define the calls for proposal as well as in the evaluation committees.

We would favor regular exchanges as well as reciprocal participation of PREZODE and MIE members in selection/evaluation committees for projects submitted following calls. In addition, a joint directory board (JDB) will be constituted and will be in charge to ensure a good synergy, avoid overlap and the continuum of research between the two programs. This board will also identify the key results to be communicated through the «Stratégie d'accélération» actions.

To ensure real-time coordination and communication of important results between the consortia of the two PEPRs, the agency intends to promote the exchange of information and the search for complementarities within its scientific animation system, in particular by setting up a group of One Health experts which could advise the Joint Directory Board, as well as through the use of communication and coordination tools, such as collaborative platforms.

In addition, the ANRS-MIE is currently working on setting up a cross-cutting, high-level project management tool (IT tool). This tool should be operational within eighteen months, and could be used to share information and indicators with PEPR PREZODE, contributing to establishing synergies between the two PEPRs.

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. This will also be closely linked with the already existing young researcher networks at ANRS MIE.

The possibility to organize joint projects for overlapping themes will be considered on a middle-term (upon the first evaluation by the CSTP) to develop a joint call for proposal, for example, the topic of pathogen species jump, where each of the skills of both PEPR teams can be mobilised to answer this important question using interdisciplinarity mixing biological, ecological and sociological approaches. This will be under the responsibility of the Join Directory Board.

Coordination with other PEPRs

The ANRS-MIE is planning to articulate with other PEPRs that could have some overlap, such as « Digital Health", "Bioproduction", or "Healthy diet», both also being coordinated by Inserm. In addition, we are already articulating with PPR Antimicrobial resistance.

Chairs

The PEPR MIE will allow strengthening of research teams through chairs of excellence to develop multi-disciplinary research projects on emerging infectious diseases in France, favoring a One Health approach when possible or relevant.

In this way, calls will be launch at least for the second and third year of the PEPR MIE.

Selection criteria will include:

• Interdisciplinary approach
• One health orientation
• Innovation
• Sustainability of the activity
• Coherence with the EID/MIE national strategy

Evaluation of project progress

The agency's system for the scientific evaluation of projects and the monitoring of the general progress of the PEPR is based on:

- Continuous monitoring by five of the agency's six scientific departments: fundamental research department; clinical research department; innovation department; public health and human and social sciences department ; research support and infrastructure. This monitoring consists in particular in collecting and evaluating the intermediate and final reports of the research teams, publications, and surveilling compliance with the open science approach;

- Scientific monitoring provided by the PEPR MIE Scientific Board.

- Scientific animation and coordination through agency's formal expert groups ("coordinated actions"). This scientific animation is resolutely international and multi-institutional. For the general evaluation of the progress of the PEPR, the agency is working on the creation of a "One Health" working group, which would take part to the synergies between the two PEPRs and would make it possible to promote continuous and high-level scientific evaluation.

- The overall monitoring of the PEPR will be ensured in conjunction with the CSTP and the SGPI, coordinator of the national acceleration strategy.

It should be noted that performance indicators will be set up, including the measurement of medical and environmental impacts.

Data Sharing and Open Science

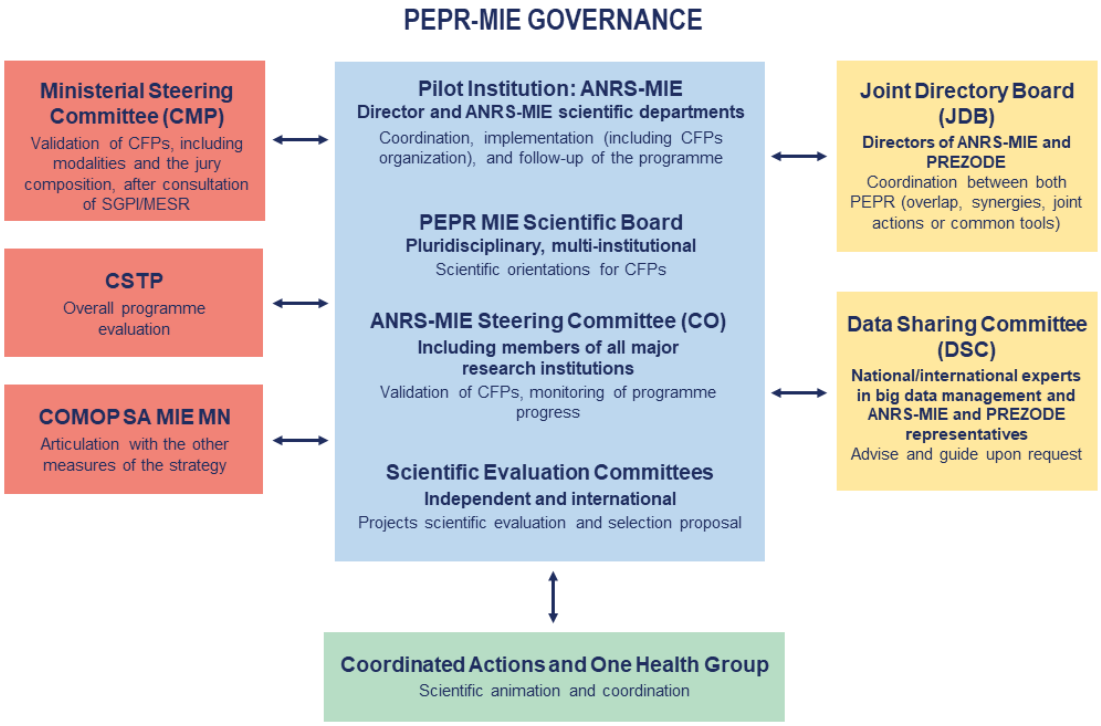
As part of the ANRS|MIE contribution to the promotion and implementation of open science, in accordance with the National Plan for Open Science (PNSO) 2021-2024, and according to the Joint Statement signed with four other French Reasearch Funding Agencies, the National Research Agency (ANR), the National Agency for Food, Environmental and Occupational Health Safety (Anses), the National Cancer Institute (INCa) and the Agency for Ecological Transition (ADEME), the beneficiaries of the ANRS|MIE commit:

- to deposit scholarly publications that result from projects financed by the agency either in the national open archive HAL, or in a local institutional open archive. In addition, the ANRS|MIE recommends that priority be given to publication in native open access journals or books ;

- to draw up a Data Management Plan (DMP) to support management, structuring, access, interoperability and when possible openness and re-use of research data. A first version of the DMP should be provided within 6 months of the start of the project, according to the terms indicated in the grant agreement. It should be updated as necessary, at least at the end of the project and in the mid-term for projects of 30 months duration or more.

In addition to all this, in accordance with both the PNSO, the Joint Statement mentioned above and the recent recommendations of the Cohorts International Evaluation Committee, the ANRS|-MIE will promote data sharing. Regarding the PEPR, the ANRS-MIE' proposition is to create a Data Sharing Committee (DSC) that will be common with PREZODE PEPR (see 8. Governance).

8. GOVERNANCE



The scientific pilot of the PEPR is Inserm – ANRS | Maladies infectieuses émergentes. Consequently, the Director of the ANRS | Maladies infectieuses émergentes is responsible for the organization, arbitration and implementation of actions within the framework of the PEPR.

Since its creation in 1988, in response to the pandemic emergency caused by the spread of HIV, the ANRS has coordinated and funded research in its thematic field. Thus, for nearly 35 years, it has been organizing calls for proposals in this field, which has gradually been opened up to viral hepatitis, sexually transmitted infections, tuberculosis and emerging infectious diseases. These calls for proposals have always been open to all research institutions, according to procedures that are precisely determined with the aim of preventing conflicts of interest.

Following the Covid-19 crisis, several analyses concluded for the need of a better coordination for emerging infectious diseases research across the different stakeholders. To do so, the French government has supported plans to create a new national Inserm's agency by transforming the ANRS into an "ANRS-MIE" ("ANRS-EID"), combining scientific expertise, scientific animation/coordination and funding. This agency is in charge of supporting and coordinating of the entire national research community focused on emerging infectious diseases, and as such, is in charge of the PEPR-MIE.

Accordingly, the governance of PEPR Emerging Infectious Diseases deeply relies on agency frameworks and experience.

• First of all, a scientific board whose composition brings together many reference institutions make a proposal on the scientific orientations of the calls for proposals. The institutions that are currently represented are Inserm, university hospitals, Institut Pasteur, ANSES, Universities, CNRS, CEA, CIRAD, IRD, Inrae with a fair distribution. The scientific board monitor the programme progress in order to adapt the following CFPs.

• The draft of the call for proposal is then submitted to the Joint Directory Board that bring together representatives of PREZODE and PEPR MIE, to avoid any overlaps, ensure the right articulation and define when needed the funding responsibilities between the two PEPR. This body will meet at key periods such as during the elaboration of project calls and then to follow the projects.

• Then the calls for projects are validated by the agency's steering committee. This committee is the PEPR's central governance body; it brings together the major national research stakeholders from human, veterinary and environmental institutions: CEA, CNRS, Inrae, Inserm, Institut Pasteur, IRD, universities, and university hospitals. Each member of the Steering Committee is required to send a public declaration of interest, which is thoroughly analyzed by the agency's services.

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

• The evaluation of projects is managed by following the procedures and standards of the ANRS MIE. For each call for proposals, a Scientific Evaluation Committee is established, made up of high-level relevant scientific experts. Expert reports are written by two experts, at least one of whom, as far as possible, is a foreigner. The prevention of conflicts of interest is organized and traced under the responsibility of the President of each Scientific Committee.

• In accordance with the general PEPR governance scheme, the final funding decision rests with the Prime Minister after consulting the SGPI and the CPM.

• A Data Sharing Committee (DSC), which will operate jointly with PREZODE PEPR, will be created in order to monitor the respect of the ANRS MIE rules, and especially ensure data sharing and interoperability, while safeguarding the protection of intellectual property and equitability of partnerships. This committee will propose tools and support before and during projects' implementation, to ensure FAIR data principles are applied, and then provide guidance on metadata handling, accessibility and utilization. This committee will be composed by national and international specialists, in particular in big data management, PEPR MIE and PREZODE representatives and could be solicited upon request by data owners. The DSC will be operational from beginning of 2023.

The Innovation, Development and Transfer Committee initially planned will not be created within the framework of the MIE PEPR, but within the framework of the measures 3 and 4 of the Acceleration Strategy.

9. EXPECTED IMPACT OF THE MEASURES

- Reduction in the burden of EID thanks to better preparedness for the risk of a pandemic, a faster and more efficient response capacity (detection, prevention, treatment), more appropriate patient care, and increased safety for citizens in terms of public health.
- A significant increase in cohesion and responsiveness among the French scientific community during the next pandemic, notably thanks to its capacity for rapid transfer and industrial scale-up of results and resources from academic research and/or public/private partnerships.
- The creation and development of innovative biotechnology and pharmaceutical companies specializing in the control of EID, and better coordination between research organizations and these industries.
- Faster, more efficient access to quality health care and treatments, and more appropriate implementation of preventive strategies to curb the spread of the pandemic.
- Training of a new generation of scientists, healthcare personnel, veterinarians, analysts, public decision makers, specialized in the control of EID.
- Enable France to become a driving force in terms of preparedness and response at a European level, particularly with the recent creation of the European Health Emergency Preparedness and Response Authority: EU-HERA.

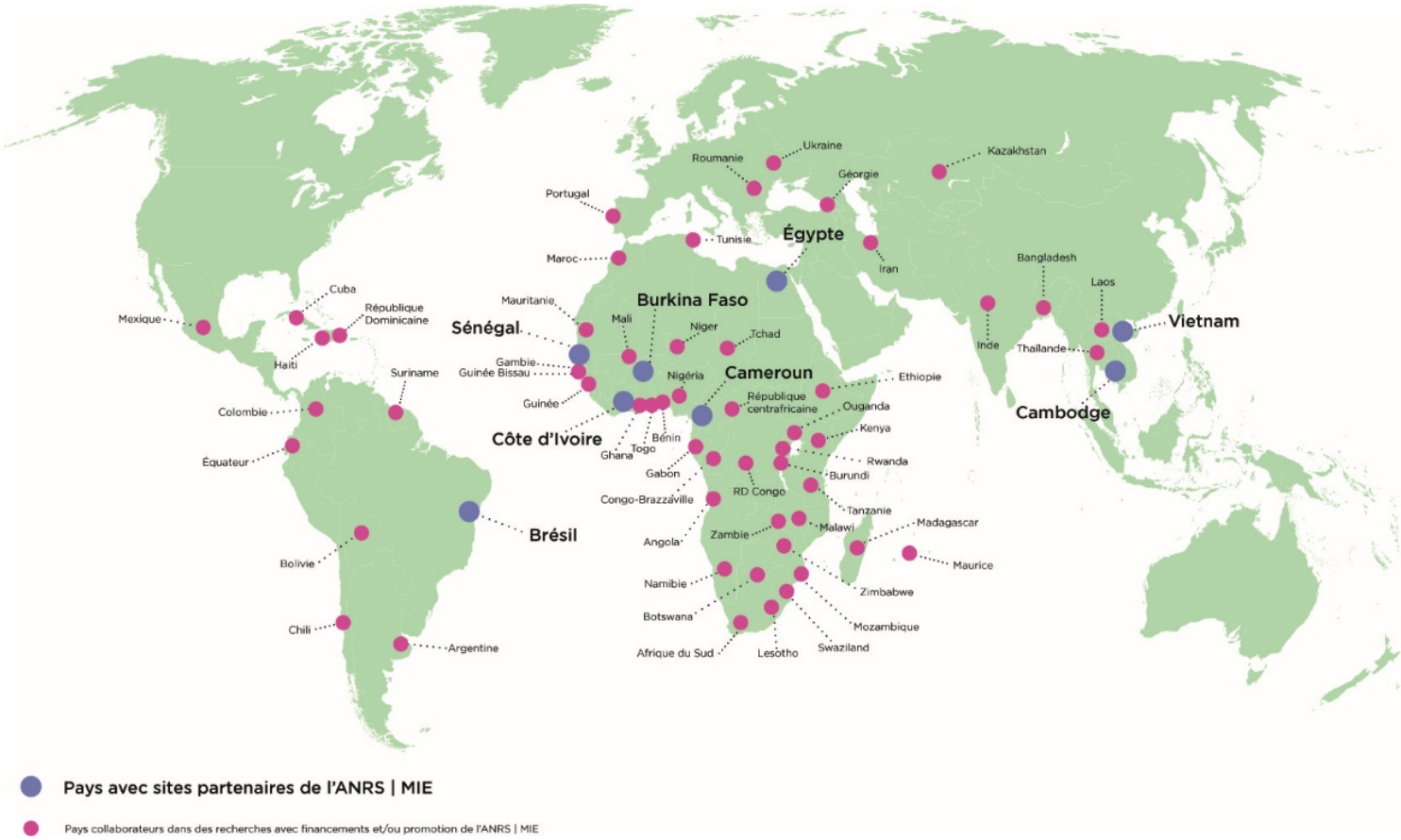
Appendices

Appendix 1 - Research networks within French collaboration

Below is a short description of international research networks of the French institutions involved in the PEPR MIE.

ANRS

All research supported by ANRS in the Low- and Middle-Income Countries (LMIC) is part of a partnership between the French teams and the team(s) in the country or countries where the research is being conducted. In some countries, this partnership is formalized by a signed agreement between ANRS and the Ministries of Health and/or Research defining reciprocal commitments to long-term collaboration: these are the ANRS sites. Depending on the year, between 10 and 25% of research projects in the LMIC are funded outside of ANRS sites.

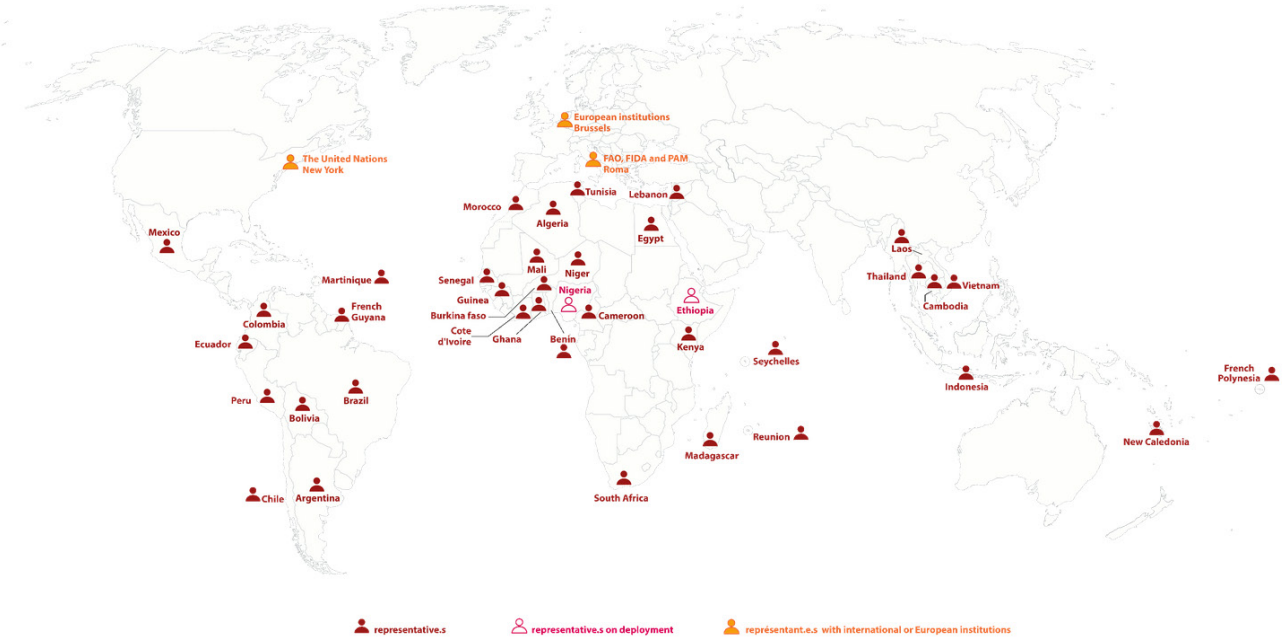


Institut Pasteur International Network

The Institut Pasteur International Network is a unique model of cooperation amongst 33 members based in 25 countries around the world. For the past century, the Network has served as a sentinel for emerging infectious diseases in several endemic regions of the world, leveraging unique multidisciplinary cooperation in the field of health. The Institut Pasteur International Network strives to improve human health by fighting against infectious diseases, through biomedical research, public health activities, training, and innovation.

IRD

IRD relies on its network of french regional delegations and representatives abroad to organise its collaborations.
Thanks to its network of representatives, the IRD can put scientific cooperation with developing countries at the heart of the national and European research and development assistance strategy. The IRD is present both in its immediate management of environmental, health or geostrategic crises and in crisis prevention and preparation measures which require significant interdisciplinary expertise.



CIRAD

The CIRAD network abroad and in the French overseas territories: platform in partnership on research and training in the framework of One Health approach. CaribVET= network on animal health, RP-PCP= Research platform on production and conservation in partnership, DP OH-OI= One Health Indian Ocean network, Grease= Emerging disease in South East Asia.

Appendix 2 – Inventory of infrastructures and networks in France dedicated to infectious diseases

Infrastructures financed by the Programmes d'Investissement d'Avenir PIA 1, 2 and 3)

Infrastructures, LabEx, Equipex, Networks, Animal facility	Project leader	Lead institutions and partners	Description
IDMIT: Infectious Diseases Models for Innovative Therapies	Roger Le Grand	CEA, Institut Pasteur, Inserm, Université Paris Sud	The national infrastructure for biology and health "IDMIT" is dedicated to preclinical research through the development of new animal models.
IHU Méditerranée Infection	Didier Raoult	AP-HM, EFS, Institut Mérieux, IRD, Université Méditerranée, IRBA	The Marseille-Mediterranée University Hospital Institute for Infectious Diseases participates in fighting infectious diseases by bringing together research, surveillance and information on infectious diseases in one place.
IRT Bioster	Nathalie Garçon	Institut Pasteur, Lyon Biopôle, CEA, CNRS, Inserm, Université de Lyon	IRT Bioaster focuses on the development of innovative and technological models to support the latest challenges in microbiology.
Laboratoire P4 Inserm Jean Mérieux	Hervé Raoul	Inserm	This laboratory is dedicated to the study of highly pathogenic infectious agents. This world-class research infrastructure is open to the entire scientific community and has coordinated the preparatory phases of the pan-European research infrastructure ERINHA (European Research Infrastructure on Highly Pathogenic Agents).
Equipex: I2MC	Jean Luc Imler	CNRS, Université de Strasbourg	This insectarium is dedicated to the study and understanding of mosquito-borne diseases and is equipped to work under L3 conditions.
Equipex+ InfectioTron	Fabrice Vavre, François-Loïc Cosset and Fabienne Archer	Université de Lyon, Institut Pasteur, CNRS, Inserm, INRAE, ENS Lyon, Hospices civils de Lyon, VetoAgro SUP	InfectioTron offers a unique and coordinated network of equipments and platforms for the multi-scale and multimodal analysis of infectious events in living hosts in a high security containment level. It supports the development of new lines of research to carry out integrative projects within the "One Health" paradigm, linking the field to the laboratory.
LabEx VRI: Vaccine Research Institute	Yves Lévy	Inserm, ANRS, Université Paris-Est Créteil	Laboratory of excellence created to conduct research aimed at accelerating the development of innovative vaccines against HIV/AIDS and (re-)emerging infectious diseases.

Infrastructures, LabEx, Equipex, Networks, Animal facility	Project leader	Lead institutions and partners	Description
Equipex CACSICE	Michael Nilges	Institut Pasteur, CNRS, Université de Paris	Equipment of Excellence (cryo EM, native mass spectrometry, NMR) to study host-pathogens interactions such as complexes of viruses with cell receptors or neutralizing monoclonal antibodies, infected cells.
LabEx PARAFRAP	Frédéric Bringaud	CNRS, Inserm, Institut Pasteur, Institut Pasteur de Lille, IRD, Cirad and 7 universities	Dedicated to parasitic infections, this laboratory of excellence develops joint research and training programmes that create inter-institutional and scientific links and amplify exchanges between French teams and laboratories in endemic regions in Africa, India and Latin America.
LabEx IBEID: Biologie Intégrative des Maladies Infectieuses Emergentes	Philippe Bastin	Institut Pasteur	IBEID's objective was to develop a structure to anticipate and fight emerging infectious diseases (EIDs), focusing on surveillance, analysis and control of these diseases. Since its creation, partnerships have been established with Santé publique France (formerly InVS), which is responsible for the surveillance and prevention of infectious diseases in France, the École nationale vétérinaire de Maisons-Alfort (ENVA) and the Agence nationale de sécurité sanitaire de l'alimentation, environnement et du travail (ANSES), which focus on infections in the animal world and the study of the mechanisms by which pathogens can cross species barriers.
LabEx: Vectopôle IRD	Fabrice Chandre	IRD	The IRD Vectopole is entirely dedicated to the study of insect vectors and the pathogens they can transmit to humans or animals. It allows the breeding of various species of insects, endemic or invasive, infected or not by pathogens.
LabEx Gral, EUR CBS	Winfried Weissenhorn and François Parcy	CEA, CNRS, Université Grenoble Alpes	A major focus of the Labex Gral is on Molecular Machines and Dynamics: The objective of this program is the comprehensive analysis of molecular machines involved in conserved cellular and pathological processes: (1) Virus host-pathogen interactions will focus on major pathogenic enveloped viruses. Lead research areas will cover replication machines and interaction with cellular complexes, membrane remodeling and budding, ribonucleoprotein complexes, immune response and reverse vaccinology approaches. (2) Bacterial and fungal host-pathogen interactions will focus on pathogens responsible for nosocomial and antibiotic-resistant infections and other life-threatening pathologies.

Infrastructures, LabEx, Equipex, Networks, Animal facility	Project leader	Lead institutions and partners	Description
I-REIVAC, réseau national d'investigation clinique spécialisé en vaccinologie	Odile Launay	ITMO Santé Publique (Inserm)	I-REIVAC, a national clinical investigation network specialised in vaccinology, brings together French clinicians, biologists and academic scientists with a strong interest in vaccinology research. This network of excellence comprises 18 centres including 7 CICs, 2 Clinical Research Centres (CRC), 1 Clinical Research Unit in Immunology, 3 infectious diseases departments, 1 epidemiology and prevention department and 2 immunology laboratories.
Centre d'Immunophénomique (CIPHE)	Bernard Malissen	Inserm	The CIPHE, which is attached to the PHENOMIN National Infrastructure and to CELPHEDIA, has developed a BSL3 with a capacity to house up to 500 cages of mice infected with respiratory pathogens, and equipment for in vitro and bio-imaging experiments.

International Infrastructures and Networks coordinated by France

European Networks and collections	Lead	Coordination	Description
European Virus Archive Global (EVAg)	Xavier de Lamballerie	France	Largest collection of human, animal and plant viruses in the world. Delivered diagnostic tests worldwide during the SARS-CoV-2 health crisis.
European Research Infrastructure on Highly Pathogenic Agents (ERINHA)	Hervé Raoul	France	Pan-European Research Infrastructure dedicated to the study of high-consequence pathogens of Risk Group 4. It is a distributed infrastructure that brings together leading European Bio-safety level 4 (BSL4) facilities and national research institutes with longstanding experience of research in this field, including preclinical developments.
European Research and Preparedness Network for Pandemics and Emerging Infectious Diseases (EU-RESPONSE)	Yazdan Yazdanpanah	France	A 5-year multi-national project, funded by the European Union's Horizon 2020 research and innovation program in order to design and run a new adaptive European platform trial on COVID-19 and emerging infectious diseases.
ERIC : Institut de Biologie Structurale (Grenoble) is an Instruct ERIC Center	Winfried Weissenhorn and Darren Hart	EU-France	Instruct-ERIC is a pan-European distributed research infrastructure providing high-end technologies and methods in structural biology to promote innovation in biomedical science.

National Infrastructures and Networks

National Networks	Lead	Coordination	Description
Emerg'in	Fabrice Laurent et Frédéric Lantier	INRA, Anses, Cirad	National infrastructure dedicated to the in vivo study of infectious animal and zoonotic diseases in livestock and wildlife. Emerg'in provides the scientific community with services and tools for public research and socio-economic partners to improve our knowledge of infectious processes in livestock, wildlife and insect or mite vectors. This infrastructure supports a European VetBioNet project.
Vectopôle Sud Montpellier		IRD, Cirad, INRAE, Université de Montpellier, CNRS, EID Méditerrannée	Research infrastructure network on vector-borne diseases and vectors of interest in human, animal and plant health, including the CIRAD-INRAE level 2 containment insectarium platform (ticks and mosquitoes), which is also part of the European infrastructure project InfraVEC2.
ChemBioFrance		CNRS	ChemBioFrance gathers four different ressources and networks: the national chemical library, a network of screening and ADME (absorption, distribution, metabolism, and excretion) platforms and a distributed chemo-informatics platforms. It is designed to promote and stimulate exchange at the interface between chemistry, biology and computer science to develop new strategies for the discovery and development of bioactive molecules.
IFB		CNRS	National Bioinformatics Infrastructure that provides support, deploys services, organizes training and carries out innovative developments for the life sciences communities. The services provided are grouped into 5 categories: data, tools training, support for research projects in biology and the provision of an IT infrastructure dedicated to life sciences. The IFB federates 36 bioinformatics platforms affiliated to the main French research organizations.
FRISBI-Institut de Biologie Structurale (IBS, Grenoble)	Bruno Klaholz Scientific lead: Winfried Weissenhorn and Darren Hart	France	The French Infrastructure for Integrated Structural Biology (FRISBI) provides an infrastructure for integrative structural biology approaches, from the molecular to the cellular level, integrating multi-resolution data from X-ray crystallography, small angle X-ray scattering, NMR, Cryo-EM and functional data including development for protein expression and crystallization.

Local or regional Infrastructures and Networks

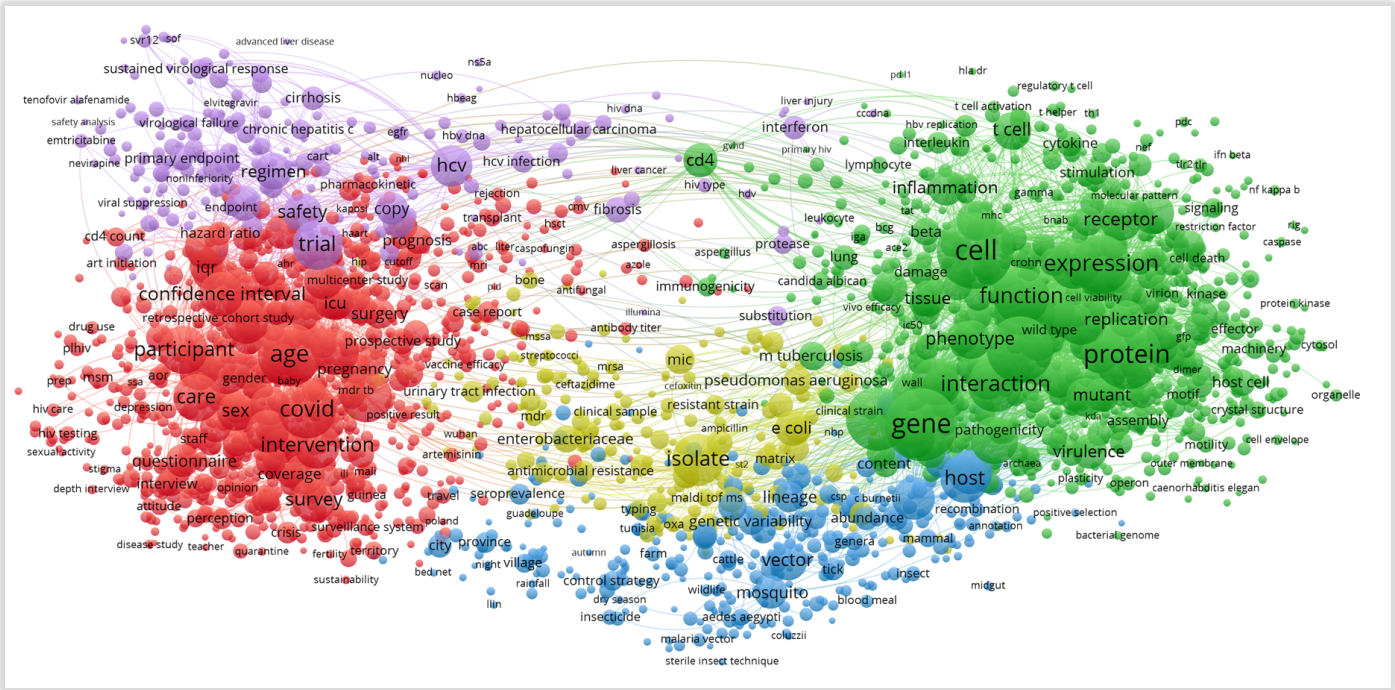
Infrastructure	Lead	Lead institution	Description
BSL3 Montpellier CEMIPAI	Georges Lutfalla	CNRS UMR 5235 LPHI, Université Montpellier, laboratoire Montpelliérain L3 CEMIPAI	Zebravec model and electron microscopy.
BSL3 Tours	Philippe Roingeard	Inserm U1259, Tours	Culture of several SARS-CoV-2 strains.
IBiSA Electron Microscopy Platform	Philippe Roingeard	Inserm U1259 MAVIVH	Electron and confocal microscopy platform.
BSL3 Strasbourg	Catherine Schuster	Inserm UMR S1110 Strasbourg	BSL3 laboratory recently restructured for Covid-19 research.
BSL3 platform managed by the IMAG'IC platform of Cochin, labelled IBiSA	Sophie Vaulont	CNRS UMR 8104 - Inserm U1016 - Institut Cochin	Imaging of living cells by confocal spinning disk microscopy.
Photonic imaging	Florence Niedergang	Institut Cochin	Photonic imaging.
BSL3 animal unit managed by IPBS	Olivier Neyrolles	IPBS Toulouse, CNRS , Université de Toulouse	Dedicated capacity for SARS-CoV-2 experiments of 45 cages, being increased to 65 cages, 3 PSM, equipment for cytometry, cell sorting, confocal microscopy and intravital microscopy.
BSL3 Lille	Jean Dubuisson-Florent Sebban	Institut Pasteur de Lille - Centre d'infection et immunité de Lille (CIIL), Inserm U1019 CNRS UMR 9017, Université de Lille, CHU Institut Pasteur de Lille	*Material*: 10 Biosafety cabinets, Animal facility with 5 gloves boxes, Glove box to study vector-borne infection, anesthesia station for small animals. *Technologies: In vitro Imaging and screening systems*: Incell 6500, Ensight, Viafill (Bulk Reagent Dispenser). *Infection and In vivo Imaging systems*: anesthesia station for small animals, nebulizer for aerosol infection of small animals, FMT 2000 *Microorganisms*: bacteriology (plague & TB) and virology (SARS-CoV1 and Sars-CoV2; MERS-CoV); [MOT] *Animal models to study infectious diseases, find and test new antibiotics, therapies and vaccines*: Mice, rats, guinea pigs, flea-borne transmission model to study bacterial and viral infections.

Infrastructure	Lead	Lead institution	Description
BSL3 Montpellier	David O'Callaghan	Inserm U1047, Université de Montpellier	BSL3 equipped for bacteriology with strictly controlled access due to the presence of Brucella (MOT).
BSL3 Montpellier	Renata Servan de Almeida	Cirad ASTRE	BSL3 equipped for bacteriology/virology with strictly controlled access due to the presence of Rift Valley Fever virus (MOT) and exotic animal and zoonotic pathogens.
BSL3 CHU de Lille	Boulem Sendid	Inserm U1285 - CNRS UMR 8576, Institut de Microbiologie du CHU de Lille	Viral cultures on the Vero CCL-81 line to characterise the glycosylation profile of certain SARS-CoV2 proteins.
Hyperion platform, including the imaging mass cytometer and CytoF technology	Jacques-Olivier Pers	Inserm U1227 (LBAI), Université de Bretagne occidentale, CHRU	A panel already available for the lung including 36 markers (Antibodies) with the possibility to evolve to 60 markers. Currently : CD38, CD21, Vimentin, CD14, Tbet, CD34, CD163, Pan-Keratin, GATA3, PD-L1, CD31, Ki-67, IgD, CD11c, FoxP3, CD86, cKit, CD68, Bcl6, CD20, CD8a, CD138 (syndecan1), MPO, PD-1, CD56 (NCAM1), CD10, CCR6, Collagen Type I, CD3, CD27, Caspase-3 cleaved, podoplanin, HLA DR, CD4, PNAd, SMA.
BSL3 Créteil	Jorge Boczkowski	Inserm U955, Institut Mondor de recherche biomédicale (IMRB), Créteil	Mainly used for handling Sars-Cov2 and COVID19 patient samples. Currently possible to provide 2 MSPs. Outside the IMRB perimeter but nearby, there are 2 A3 animal units at the École Nationale Vétérinaire d'Alfort. They are linked with them to carry out Sars-Cov2 infections on murine lines derived from the transgenic model developed by the IMRB.
Hospital BSL3 et A3 central animal unit	Christophe Combadiere	Centre d'immunologie et de maladies infectieuses (CIMI), Inserm U1135, Sorbonne Université	
CEMIPAI: Centre d'études des Maladies Infectieuses et Pharmacologie Anti-Infectieuses	Delphine Muriaux	CNRS, Université de Montpellier	BSL3 - Level 3 containment laboratory for Level 3 pathogens (and possibly 2, with Level 3 Type B inserts) with state-of-the-art equipment.
BSL3 I Montpellier	Martine Peeters	TransVIHMI IRD, Montpellier	Virology (WHO HIV reference center, Zoonotic pathogens, arboviruses)

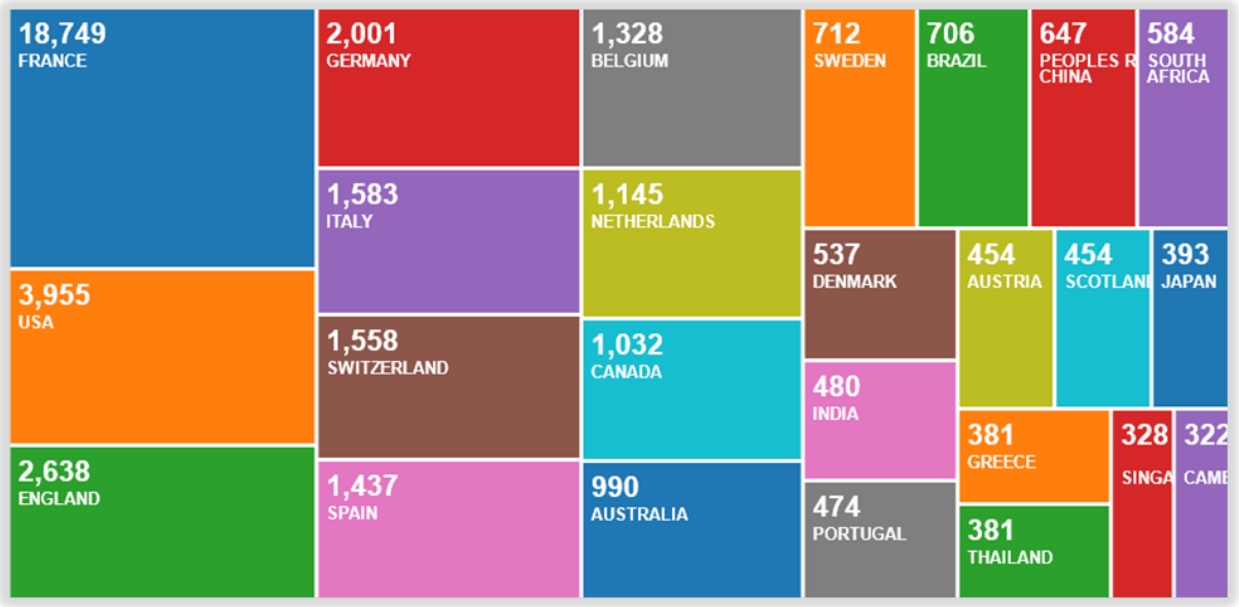
Appendix 3 - State of the art of the Infectious Diseases Research in France

To provide a landscape of the different research activities in the field of emerging infectious diseases in human and animal health, an automated bibliometric analysis of Web of Science data covering all French research teams was performed by Immunology, Inflammation, Infectiology and Microbiology of Inserm Thematic Institute (IT I3M) and Inserm's Department of Program Evaluation and Follow-up. This analysis of bibliometric data highlighted 18,758 publications produced over the period 2016-2020, represented in graphical form (VOSviewer software) and underlined that French research is structured along 5 main axes:
- basic research (virology, bacteriology, microbiology, parasitology and immunology...) (green),
- diagnostic evaluation of infections (viral loads), comorbidities, organization of care, socio-economic and demographic factors, education, epidemiology, vaccination campaigns (red),
- mosquito/parasite-borne diseases, zoonoses, phylogenetic analysis (blue),
- bacterial and fungal infections; Treatments and resistance (light green),
- HIV and hepatitis, diagnosis, treatments (purple).

This cartographic analysis places Inserm in 4th position worldwide behind the University of California, the University of London and Harvard University. The bibliographic indicators are higher than the international averages (average normalized citation index of 1.7 and 3.5% of publications in the Top 1% of the world ranking). In terms of international collaborations, the bibliometric analyses revealed a strong network of collaboration with United States, United Kingdom, and Germany.



French mapping of emerging infection diseases research domains for 2016-2020, based on 18 758 publications. Each keyword is represented by a circle whose size is proportional to the number of times that keyword appears in the titles and/or abstracts of publications. The proximity of the keywords is given by a force of attraction defined by the frequency of their simultaneous occurrence in a publication, making it possible to group them into clusters of different colors. Lines reflect the frequency of the simultaneous citation of two keywords below a frequency threshold that is not as high as that chosen for the circles.



French collaborations with other countries in Europe and worldwide: United States is France's leading partner with 21% of co-authorship. The United Kingdom is in second place with 14%. Germany is the leading European partner with nearly 11% of co-publications.