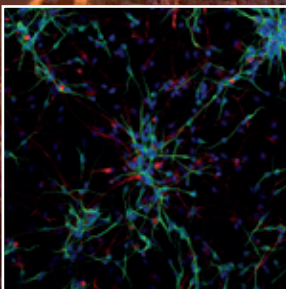


les dossiers d'**AGROPOLIS** INTERNATIONAL

*Expertise of the scientific community
in the Occitanie area (France)*



Global health

*People, animals, plants, the environment:
towards an integrated approach to health*

AGROPOLIS INTERNATIONAL

Agriculture • Food • Biodiversity • Environment

Based in Occitanie, Agropolis International is a non-profit bringing together an exceptional array of institutes and organisations involved in 'green sciences'. Founded by regional research institutes and higher education establishments with support from national, regional and local authorities, since its creation Agropolis International has been a dedicated collective workspace providing links between different collaborators in the areas of agriculture, food, the environment and biodiversity:

- Regional scientific institutes
- International research agencies
- Regional and local authorities
- Civil society organisations

A place for sharing and dialogue, for capitalising on and transmitting knowledge, a laboratory of ideas, a support structure for collective projects and for their promotion abroad, a centre for hosting facilities and events, Agropolis International adapts its three decades of experience to the varying missions requested by its members.

The series of *dossiers d'Agropolis* aim to present the expertise of the scientific community in the region of Occitanie in the major scientific, technological and societal challenges of today, in the fields that concern the organisation and its members.

Each issue is dedicated to a specific topic and gives an overview of the region's research laboratories working in that area, illustrated with concrete examples of projects and the related educational and training offer. They are available in print and digital formats, usually in French and English.

This 25th *dossier d'Agropolis* focuses on integrated approaches to human, animal, plant and environmental health. It was coordinated by a scientific and editorial committee consisting of:

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Cover

Main image: A flock of sheep grazing on a plateau in Lozère © Michel MEURET / INRA

Inserts from top to bottom: Phytophagous insect and disease vector © Bernard AUBERT / CIRAD

Malaria screening test in a school in Benin © Florence Migot-Nabias / IRD

Tsetse fly treated with pink fluorescent marking powder at the Montpellier Vectopole © Patrick LANDMANN / IRD

Human neural cells infected with the Zika virus by fluorescence microscopy © Pauline FERRARIS / IRD

Global health

People, animals, plants, the environment: towards an integrated approach to health

Over the last 40 years, the recurrence of epidemics resulting from known or new infectious agents (AIDS, avian influenza, SARS, Ebola, etc.) has sharply raised awareness about the interconnections between human health and the health of animals and the environment, as well as the effects of global changes on these interactions. In line with the emerging trends in other scientific fields, systemic thinking, strategies and practices have gained ground in the area of health. **In this 25th dossier d'Agropolis, we offer an overview of the expertise of the scientific community in the French region of Occitanie in the manifold areas of health and of the systemic approaches being developed.** Bringing together a critical mass of research in medicine, agronomy, veterinary science and ecological, environmental and social science, this diverse community is fertile terrain for adopting an integrated approach to health and developing innovative concepts and methods. While far from exhaustive, this report provides illustrative examples of research undertaken by scientific teams in the region alongside partners in France, its overseas territories, and around the world. All aspects affecting health are considered: not only human and animal health, but plant health, the environment, and issues linked to diet and food production. **No less than 66 research units are cited in this report, illustrating the diversity and complementarity of the scientific work being carried out from this hub of integrated health research.**

Patrick Caron,
Chair of Agropolis International

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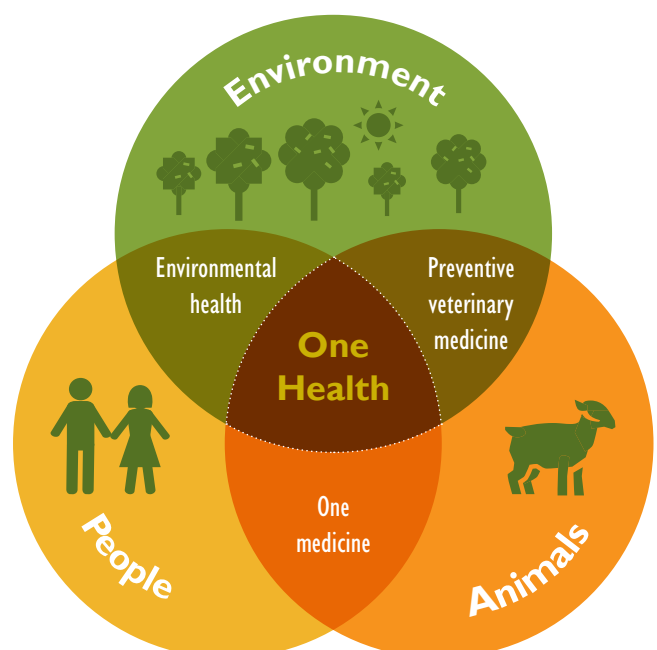
Introduction

At the turn of the 21st century, a trend for considering health in a more integrated way emerged. Taking a more holistic perspective, these integrated approaches identify human health as interconnected with the health of animals and of the environment. This relatively recent upsurge of interest does not mean these human–animal–environment links are new: hunter-gatherers could contract diseases from hunted animals, though it was the domestication of wild species that created the first major epidemiological bridge between animal and human populations with an impact on health¹. The unceasing expansion and progression of animal production systems since then has continued to create contexts that favour the emergence and transmission of pathogens between animals and humans. But at the end of the 20th century, the emergence of known or unknown infectious agents – AIDS, avian influenza, severe acute respiratory syndrome (SARS) and, more recently, Ebola in Africa – accelerated². The factors involved in this phenomenon reflect global changes driven by human activities around the planet: habitat destruction, degradation of natural ecosystems, biodiversity loss, intensification of livestock and crop farming, urbanisation, increased and unprecedented contact between people and wild and domesticated species, climate change that is disrupting certain ecological processes, air and sea transport connecting previously independent ecosystems, etc.

This complexity and the new epidemiological dynamics where humans–livestock–wildlife–the environment intersect are at the centre of the integrated approaches that have sprouted during recent health crises. In its narrowest definition, the ‘One Health’ concept promotes an integrated approach for studying zoonotic diseases (diseases and infections caused by agents that spread naturally between vertebrate animals and people and *vice versa*) in order to improve public health. The ‘EcoHealth’ concept considers the health of people, animals and the state of ecosystems, with more of a focus on the links between biodiversity and health. Lastly, the ‘Planetary Health’ concept takes into account the physical and biological limitations of the Earth in defining the niche in which health, well-being and human equality can develop, taking into account political, economic and social aspects (see box opposite)³. This notion of ‘Planetary Health’ – or ‘Global Health’ – offers an analytical framework for exploring the interrelationships between human activities and well-being in a context of long-term sustainability: a framework that the scientific community studying food systems is starting to adopt. In line with this paradigm shift, an article published by the EAT-Lancet Commission at the beginning of 2019 argued for ‘a healthy diet derived from sustainable production methods’, marking the first attempt at a definition of a set of universal goals to develop a food system that supports human health and environmental sustainability⁴.

While these systemic approaches differ in scope, they share a strategy of building bridges between different disciplines, of investigating different spatial and temporal scales, of enlarging the pool of shared knowledge, of implementing cross-sectoral solutions, and of co-constructing management methods that involve all stakeholders (e.g. through action research), taking into account issues such as gender equality and social justice. These principles are not specific to the field of health; they can be applied to any complex system that includes human populations. One example is natural resource management, a field that was an early adopter of this approach⁵. Educational programmes for future experts in all fields concerned should be designed to take these principles into account.

The scientific community in the French region of Occitanie brings together a critical mass of research in medicine, agronomy, veterinary science, and ecological, environmental and social sciences, making it a fertile terrain for adopting such approaches and developing innovative concepts and methods. This *dossier* aims to illustrate some of the work carried out, from the study of the mechanisms behind the emergence of epidemics, through the implementation of integrated health approaches to prevent and control these outbreaks, to the analysis of the links between human health and diet in all its aspects: nutrition, food security, food safety (both quality and toxicology), and the environmental impact of food production. The final section presents the region’s scientific environment, including its multiple institutes and research units (referred to by their **ACRONYMS** in the text, see pages 44-45 for information on the research units) and the educational and training programmes offered on integrated health approaches.





Integrated approaches to health

Definitions of health

According to the World Health Organisation, **human health** is not only a question of the absence of disease or disability, but is a state of physical, mental and social well-being and a fundamental human right.

Public health concerns the collective management of the health of a population in its community, whether this involves treatment, prevention, education or social hygiene.

International health is the branch of public health focused on the specific issues of developing countries and the aid efforts of industrialised countries.

Global health is a field of study, research and practice that prioritises improving health and achieving health equity for everyone in the world.

Environmental health covers aspects of human health, including quality of life, that are determined by physical, chemical, biological, social, psychosocial and aesthetic factors of the environment.

Animal health concerns both domesticated animals (pets and livestock) and wild animals. It is at once an ethical, economic and health issue as many diseases are zoonotic (i.e. can be transmitted to humans).

The area of **veterinary public health** covers all activities directly or indirectly related to animals (or animal products or by-products) that contribute to the protection, preservation and improvement of human health.

Plant health is a field that focuses on crop pests and diseases (pathogens, insect pests, etc.) that compromise harvests in terms of quantity or quality, as well as methods of crop protection.

Ecosystem health can be defined as a social cross-disciplinary construction which characterises the state of a socio-ecosystem in relation to the array of services that are expected from it.

Integrated health approaches³

The **One Health** concept puts the emphasis on the relationships between human health, animal health and ecosystems, bridging ecology and human and veterinary medicine. The One Health approach focuses mainly on infectious diseases, whether these are transmitted from animals to humans or *vice versa*, on the emergence of these diseases in relation to global changes, on antimicrobial resistance, and on food safety.

The **EcoHealth** concept promotes an ecosystem approach to health, focusing primarily on environmental and socio-economic issues. It was originally formulated by ecologists specialising in diseases and working in the field of biodiversity conservation.

The **Planetary Health** concept takes into account the planet's environmental limits – physical and biological – within which human health, well-being and equality can flourish by examining issues from a political, economic and social point of view. In sum, planetary health – or global health – considers the health of human civilisation and the state of the natural systems on which it depends.

Factors in the emergence and transmission of infectious diseases: the elements for an integrated approach to health

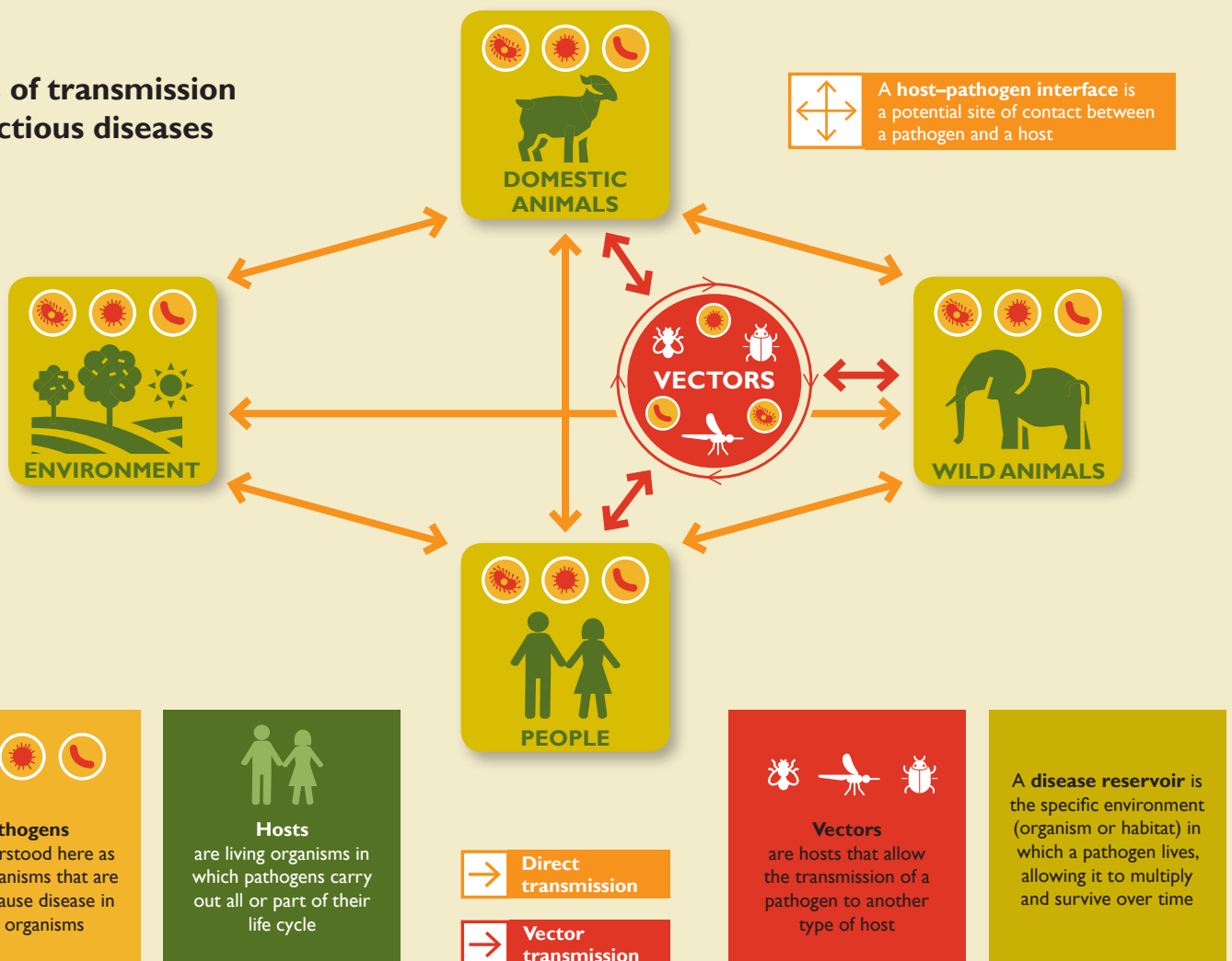
As illustrated in the diagram below, five main mechanisms are involved in the emergence and transmission of infectious diseases:

- the presence and abundance of **pathogens** (1) in **reservoirs** (2) (in humans, animals or the environment);
- their potential spread through **vectors** (3);
- the **interface** (4) between the pathogen and its host: that is, the physical contact between the host and the pathogen and their modes of biological interaction, leading or not to the host's infection, to the proliferation of the pathogen in the organism, and to its transmission to a new host;
- the **evolution** over time (5) of pathogens, their hosts and the potential vectors, related to changes in the environment, which is an additional aspect to take into account.



Studying viruses in the laboratory

Modes of transmission of infectious diseases



While this section focuses on zoonotic diseases, it equally pertains to the emergence and transmission of infectious diseases whether they affect people, animals or plants, as the mechanisms involved are the same, no matter the host. The scientific community in Occitanie is investigating the multiple facets of the pathogen–host relationship for a spectrum of hosts (humans, livestock, pets, wild animals, cultivated and wild plants) and a wide range of pathogenic agents (viruses, bacteria, protozoan and metazoan parasites, prions) responsible for a multitude of diseases (see the table below for examples of some of those affecting humans). The region's laboratories, many of which are nationally or internationally recognised, are conducting research at different spatial and temporal scales to gain knowledge on these multifaceted levels in order to meet the

scientific and social challenges around infectious diseases.

Aside from infectious diseases, viruses, bacteria and parasites are also responsible for around one out of six cancers in humans worldwide. For example, one out of two cases of cervical cancer is attributable to the human papillomavirus, and 80% of cases of liver and stomach cancer are caused by infections (particularly the hepatitis B and C viruses). Some of these oncogenic viruses are studied in Occitanie laboratories: *IRIM* specialises in retroviruses, such as the human T-lymphotropic virus, which causes a form of leukaemia, and the murine leukaemia virus, which affects rodents and is used as a study model, and *MIVEGEC* and *PHARMA-DEV* are studying the ecology and evolution of papillomaviruses.

Some pathogenic agents affecting humans studied by the scientific community in Occitanie

Pathogen and mode of transmission	Disease	Laboratory accreditation
 Viruses: infectious agents that require a host, often a cell, whose metabolism and constituents they use to multiply. In their extracellular form, viruses consist of a core of nucleic acid (DNA or RNA) generally surrounded by a protein coat (a capsid).		
Virus transmitted directly (e.g. hepatitis A, C, E, HIV, influenza, Ebola, etc.)	Hepatitis, AIDS, flu, Ebola haemorrhagic fever	CPTP is a national reference centre for the hepatitis A and E virus TRANSVIHMI is a reference laboratory for the World Health Organisation for HIV ASTRE is a national reference centre for the Rift Valley fever
Virus transmitted to mammals by mosquitoes (e.g. dengue, Zika, West Nile virus, Usutu, Chikungunya, etc.)	Fevers, haemorrhagic fevers, arthropathy, encephalitis, microcephaly	
Virus transmitted by a vector or directly (e.g. <i>Bunyaviridae</i>)	Rift Valley fever, Crimean-Congo haemorrhagic fever	
Viruses whose transmission mechanisms are still not well known (e.g. Coronavirus)	Middle East respiratory syndrome	
 Bacteria: living microscopic organisms, most often unicellular (sometimes multicellular in the case of filamentous bacteria), whose cells have no nucleus (i.e. prokaryotic organisms). Most species of bacteria do not live individually in suspension, but in complex communities embedded in a mucosal gel (or biofilm) that adheres to a surface.		
<i>Escherichia coli</i>	Enteropathy	IRSD participates in expert committees for the French National Agency for Public Health and the National Health & Safety Agency for Food, the Environment and Work (Anses) VBMI is a national reference centre for <i>Brucella</i>
<i>Vibrio</i>	Cholera, enteropathy	
<i>Staphylococcus</i>	Food poisoning, local infections	
<i>Mycobacterium</i>	Tuberculosis	
<i>Mycoplasma</i>	Pneumonia	
<i>Brucella</i>	Brucellosis	
<i>Leptospira</i>	Leptospirosis	
<i>Borrelia</i> (transmission by vector: ticks)	Borreliosis, Lyme disease	
 Protozoans: unicellular organisms whose cells have a nucleus and which live exclusively in water, moist soil or inside another organism.		
<i>Plasmodium</i> (transmission by vector: mosquitoes)	Malaria	MIVEGEC is a national reference centre for <i>Toxoplasma</i> and <i>Leishmania</i> INTERTRYP is a reference laboratory for the World Organisation for Animal Health and a collaborating centre for the World Health Organisation for trypanosomiasis
<i>Toxoplasma</i> (transmitted directly)	Toxoplasmosis	
<i>Trypanosoma</i> (transmission by vector: flies, bedbugs, leeches)	Sleeping sickness, nagana (African animal trypanosomiasis), Chagas disease	
<i>Leishmania</i> (transmission by vector: phlebotomine sand flies)	Leishmaniasis	
<i>Babesia</i> (transmission by vector: ticks)	Babesiosis	
 Parasitic worms: multicellular eukaryotic organisms belonging to diverse groups such as the helminths (flatworms), trematodes (blood flukes) and nematodes (roundworms).		
Schistosomes	Schistosomiasis (bilharzia)	IHPE has the world's largest collection of living strains of schistosomes
Nematodes (transmitted directly and by vector: black flies, deer flies, mosquitoes)	Gastrointestinal parasites, filariasis	
Taenia tapeworms (transmitted directly)	Cysticercosis	
 Prions: pathogenic agents consisting of a misfolded protein that, in contrast to infectious agents such as viruses, bacteria or parasites, do not contain nucleic acid (DNA or RNA) that carries the infectious information.		
Prions (transmitted directly)	Transmissible spongiform encephalopathies	

1. Understanding and characterising pathogens

Integrated approaches to health draw upon a vast body of knowledge in different fields, beginning with microbiology, which is the study of microorganisms – bacteria, fungi, protozoans or viruses – from the point of view of their physiology, their genetics and their interactions with other living organisms. The study of the specific pathogens targeted by the Occitanie scientific community has direct value in a number of fields: for public health, in cases where these agents cause diseases transmissible to humans (see table on previous page); for science, as models to study the mechanisms of transmission and the emergence of diseases; for economics, if these diseases affect crops or livestock; and more broadly for ecology, when investigating the interactions between hosts and pathogens from the point of view of ecosystem equilibrium in a context of global change.

In terms of public health, the pathogens studied by the region's teams can be responsible for endemic diseases (diseases permanently present in a particular region or a certain group of people: for example, the flu, malaria, AIDS, tuberculosis, hepatitis E or multi-resistant bacterial infections), or emerging diseases (diseases whose

incidence has recently risen or risks increasing in the near future and which occur in epidemics: for example, fevers caused by Ebola or Zika), or so-called 'neglected' tropical diseases (diseases that are insufficiently taken into account by policymakers despite their dramatic impact on human and animal health in developing countries: see box below).

Different approaches are deployed to research, identify and characterise pathogens. One approach aims to comprehend all of the pathogenic agents in a given environment: for example, **LBBM** and **MARBEC** focus on marine habitats, **HSM** on freshwater environments, and **MIVEGEC** on tropical forests, for which smart methods are used to gain access to diverse pathogens (see box opposite).

A second approach is to consider pathogens from the point of view of a given group of host species: for example, **IHAP** works on livestock, **PVBMT** on horticultural plants, **BIOAGRESSEURS** on coffee shrubs and cacao trees, and **BIOM** on phytoplankton.

A strong commitment to researching neglected tropical diseases

Due to limited access to clean water, hygiene, sewage systems and health services, low-income populations in developing countries are victims of a variety of diseases termed neglected tropical diseases (NTDs), due to the fact that they receive considerably less attention than the three major world scourges of HIV infection, tuberculosis and malaria. Of the 18 NTDs listed by the World Health Organisation, several are studied by the Occitanie scientific community: rabies, cysticercosis caused by *Taenia solium*, Chagas disease, sleeping sickness, leishmaniasis, lymphatic filariasis, Buruli ulcer, and bilharzia, mainly by **INTERTRYP**, **IHPE**, **MIVEGEC**, **TRANSVIHMI** and **ASTRE**. This research is made available to national and international initiatives that aim to eliminate these infectious diseases in order to improve public and animal health and increase food security. The success of these programmes relies on a better understanding of the mechanisms of transmission, the development of new diagnostic tools, new preventative and therapeutic treatments (including vaccines), innovative strategies for controlling vectors, and informed recommendations for public policy.

Rapid diagnostic test for onchocerciasis (river blindness), a neglected tropical disease, using a testing device coupled with a mobile phone (the 'LoaScope'), during a treatment campaign against onchocerciasis in Cameroon in 2015





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Using biting flies to draw blood from wild animals

MIVEGEC and its partners made use of a smart method to identify the infectious agents circulating in the wild vertebrates inhabiting the tropical forests of Africa: blood-sucking flies were employed as ‘flying syringes’ to obtain blood samples from forest-dwelling animals⁶. In the forests of Gabon, 1,230 blood-filled biting flies were captured, from which one-third of the blood samples were able to be identified as coming from 20 vertebrate species: mammals, birds and reptiles. Almost one sample out of ten was found to be infected with different malaria parasites, some known and others new species. This ingenious method is not only of value for studying the diverse pathogens circulating in wild vertebrates, but could be used as an early detection tool for zoonotic agents.

Through its needlelike proboscis, the tsetse fly transmits pathogens called trypanosomes, agents of sleeping sickness, to humans and animals in Sub-Saharan Africa

Lastly, research can focus on one particular type of microorganism responsible for a given disease: for example, *TRANSVIHMI* studies *HIV*, Ebola and Zika viruses; *VBMI* studies *Brucella* bacteria; *VAP* studies the *Babesia* parasite, and *IPBS* studies mycobacteria.

A detailed understanding of the genetic diversity of pathogens is a first step in the development of diagnostic methods, indispensable for treatment measures as well as for surveillance.

To this end, *LBBM* develops miniature sensors capable of detecting the contamination of bathing water by bacteria⁷ (e.g. *Escherichia coli*, an indicator of faecal contamination, or *Vibrio*, a genus of bacteria with many species that are

pathogenic for humans, notably the bacteria responsible for cholera) by recognising their DNA. In the early 2000s, high-performance molecular tests developed by *CPTP* demonstrated the local transmission in mainland France of the hepatitis E virus. More recently, during the emergence of the Zika virus, the team demonstrated that the protracted persistence of Zika in the sperm of infected men contributes to the risk of sexual transmission alongside the principal vector-borne transmission mechanism^{8,9}. The genetic characterisation of pathogens also allows the contact events and the recombination of different virus strains to be retraced; events that can lead to the emergence of the pathogen. Many pathogenic agents with the potential of generating large-scale outbreaks are thus closely monitored by the scientific community: one example is the coronaviruses responsible for respiratory syndromes (see box below).

Middle East respiratory syndrome (MERS), an emerging disease under high surveillance

This syndrome is a severe, potentially fatal, respiratory disease caused by a coronavirus (MERS-CoV) that affects camels. It is very similar to the severe acute respiratory syndrome virus (SARS-CoV). In 2002, the latter infected 8,000 people in 25 countries extremely rapidly, resulting in 800 deaths. The MERS-coronavirus, since it was first identified in a human in 2012 in Saudi Arabia, has infected more than 2,100 people, resulting in 813 deaths. With a human fatality rate of around 35% and no available treatment or vaccine, this viral disease is today considered by the World Health Organisation as one of the ten highest-priority emerging diseases for research and diagnostics.

To date, only the Arabian Peninsula has experienced cases of human infection, although camels are carriers of MERS-CoV in many African countries. In the framework of an international collaboration led by the Pasteur Institute in Hong-Kong associating *ASTRE* and *MIVEGEC*, genetic differences between the MERS-CoV strains circulating in camels in Africa and in Arabia were revealed, showing that the strains are genetically isolated from each other¹⁰. Research continues in order to clarify other determining factors and cofactors linked to the transmission of the virus to people.



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The camel is a reservoir of the virus that causes Middle East respiratory syndrome (MERS)

2. Understanding and characterising pathogen reservoirs

Once a microorganism is identified, understanding how it spreads disease requires learning about its distribution and mobility. Pathogens can exist freely in the environment in a particular context (e.g. soil, water, air), generally with a limited life span, or within host organism reservoirs. Research into pathogens may focus on a particular type of host as a reservoir: for example, *CEFS* studies large herbivores such as deer and cattle, *CBGP* studies small mammals such as rodents and bats, *IPME* studies cultivated plants, and *MIVEGEC* and *ASTRE* study insect vectors. For instance, by systematically researching the viruses circulating in mosquito populations in the Camargue delta, the presence of a poorly known virus was discovered (see box below). Another approach involves researching all of the reservoirs of the pathogen responsible for a given disease:

for example, *INTERTRYP* is working on trypanosome reservoirs, and *TRANSVIHMI* – after having discovered the origin of HIV in the great apes in Central Africa (see page 21) – recently led a major study on the reservoirs of the Ebola virus (see box opposite). A third approach consists of analysing an environmental compartment as a reservoir of the persistence and transmission of pathogens: for example, *HSM* focuses on urban water systems, and *LBBM* on freshwater and coastal areas, among others.

A comprehensive understanding of proven and potential reservoirs of pathogenic agents is essential in order to put in place preventive measures that limit the spread of epidemics.

Researchers conducted a campaign to identify viruses carried by mosquitoes in the Camargue delta

Hunting down viruses circulating in Camargue mosquitoes

In the research into viruses connected with the mosquitoes in the Camargue wetland of southern France, a consortium led by *ASTRE* and associating EID-Méditerranée (the public agency in charge of mosquito control on the Mediterranean coast) identified two strains of the Usutu virus (USUV), a member of the Flavivirus genus, in the *Culex pipiens* mosquito species^{1,12}. Discovered in 1959 in southern Africa, USUV is transmitted by mosquitoes to certain bird species and can result in significant mortality by attacking the bird's neurological system. Of the two strains of the virus repeatedly detected in the Camargue in several sites between June and September 2015, one is suspected to be the cause of the bird mortalities observed in Europe in 2016, and the other in a case of transmission to a human in the same year in Montpellier, a case studied by the *PCCI*¹³. In total, 49 cases of human infections by USUV have been reported in Europe in the last 10 years, mainly in Italy. None of these were fatal, but certain caused severe neurological disorders such as meningoencephalitis. Largely unknown compared to other viruses with a similar transmission cycle (such as the West Nile virus, responsible for a significant outbreak in Europe in 2018, with more than 2000 cases recorded – including 27 in France – and 181 associated deaths), USUV necessitates close vigilance, as demonstrated by the recent relatively unexpected outbreaks of other Flaviviruses such as Chikungunya and Zika.

This is also crucial in allowing new as yet unknown reservoirs to be identified: for example, *CPTP* was able to identify rabbits as a reservoir of strains of the hepatitis E virus that are transmissible to humans^{17,18}. It equally allows a better understanding of the factors that determine the presence of pathogens in an environment: for example, *HSM* has studied water temperature and the influence of fresh water inflow during rainy periods on the dynamics of the *Vibrio* pathogens in the lagoons of the Gulf of Aigues-Mortes¹⁹. Lastly, it allows the creation of a georeferenced database associating the presence of species to ecological factors in order to evaluate risks: *CBGP* used such a tool to evaluate the risk of the emergence of *Puumala orthohantavirus*, transmitted by the bank vole *Myodes glareolus*, a virus responsible for causing epidemic nephropathy in parts of Europe²⁰.



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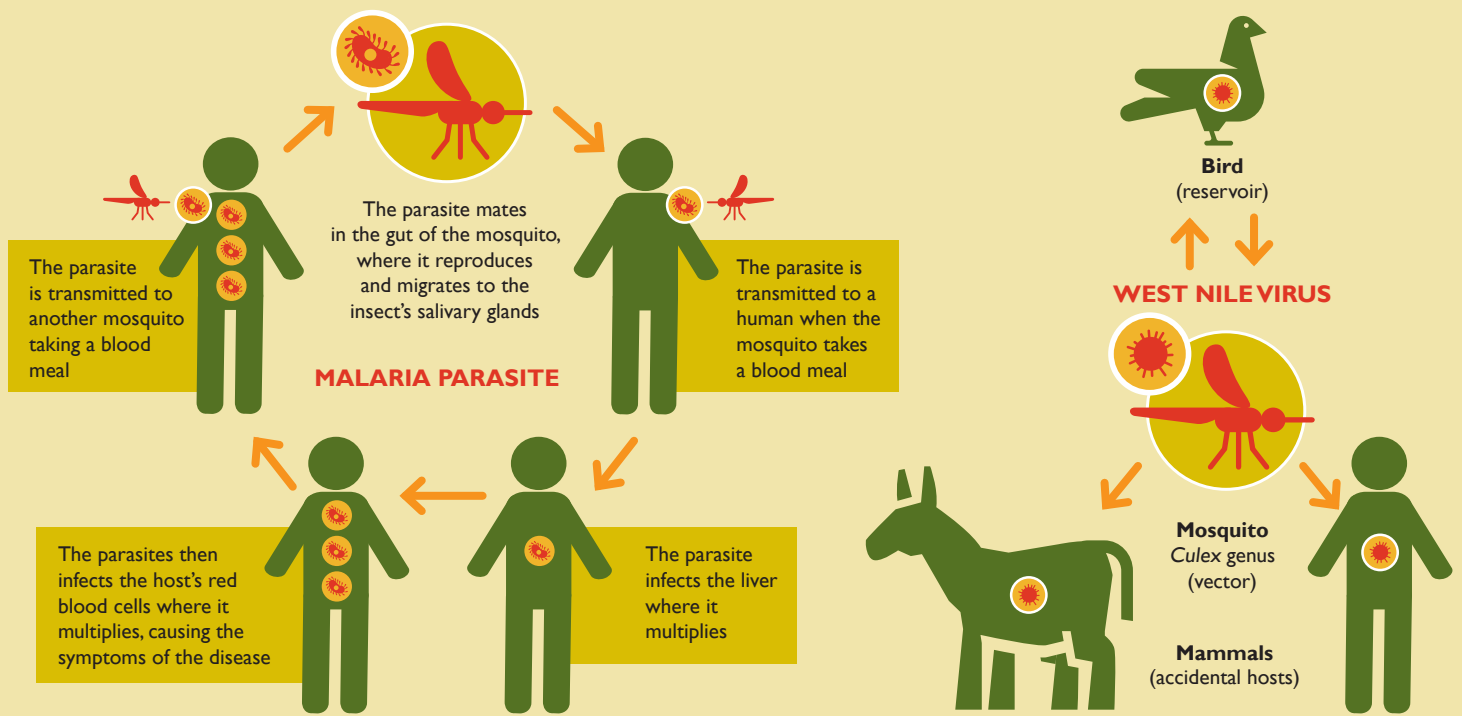
On the trail of Ebola virus reservoirs in Africa

Since the first Ebola epidemic in Central Africa in 1976, 28 outbreaks have been recorded in tropical Africa. The 2015–2016 outbreak in West Africa resulted in more than 11,000 deaths out of 28,000 confirmed, probable or suspected cases. This was followed by three other successive appearances of the virus between May 2017 and July 2018, all in the Democratic Republic of Congo. The virulence and frequency of these outbreaks is a concern for public health authorities, who have encouraged the scientific community to intensify its research into the origins and probability of the transmission of the Ebola virus between animals and human populations.

In response, an international and regional operational research centre into retroviral infections was put in place, bringing together *TRANSVIHMI* and *ASTRE* in Montpellier, the Research Centre for Emerging and Re-emerging Diseases and Nuclear Medicine in Yaoundé (Cameroon), the National Institute of Biomedical Research in Kinshasa (Democratic Republic of Congo), and the Centre for Research and Training in Infectious Diseases in Conakry (Guinea). This joint effort, supported by Montpellier University of Excellence (MUSE: see page 43) aims not only to reinforce the diagnosis and treatment capacities of the countries most at risk, but to better understand the mysterious origin of these epidemics, which make surveillance and prevention even more difficult.

Currently there are four types of Ebola virus (genus *Ebolavirus*, family *Filoviridae*) that are known to be human pathogens. Frugivore and insectivore bats, non-human primates and other wild or domesticated mammals are suspected of playing a role – as a relay or amplifier – in the species reservoir, but many unknowns remain about the modes of transmission of the virus. To shed light on these, two major studies were carried out to try to detect signs of presence or contact with the virus in the blood or droppings of thousands of primates and bats in 21 sites across several countries in Africa^{14,15}. Only one primate was found to have signs of contact with the virus, compared to eight species of bat. This confirms the hypothesis that primates are only intermediate hosts of Ebola rather than reservoirs, while bats seem to play an important role in the epidemiology of the virus¹⁶. Researchers are now working on an even more ambitious project: following the prevalence of the virus within bat colonies over time in order to better understand their role as a reservoir.





Examples of vector-borne pathogen cycles

3. Understanding and characterising disease vectors

Some pathogenic agents are transmitted from one vertebrate (human or animal) to another by the intermediary of a vector, generally a blood-sucking arthropod (e.g. mosquito, tick, sand fly, tsetse fly, etc.). Understanding the biology and ecology of these vectors is a third keystone in integrated approaches to health.

A vector is infected when it bites a host carrying the pathogen; it then transmits the infectious agent to a new host at its next feeding. Some Flaviviruses borne by *Aedes* mosquitoes (e.g. dengue, Chikungunya, Zika) are also transmitted by female mosquitoes to their descendants, due to the ability of these viruses to persist for several months in mosquito eggs. Vectors are also hosts and reservoirs of pathogens. For example, parasites of the *Plasmodium* genus, the causative organism of malaria, carry out their sexual reproduction cycle in the intestine of the mosquito, making the latter, from a biological point of view, the definitive host. For certain arboviruses (arthropod-borne viruses), mammals are an intermediate host – sometimes accidental, sometimes as an amplifier, or sometimes as an epidemiological dead end, when vector transmission between mammals is impossible: this is the case, for example, with the West Nile fever virus, whose main hosts are birds (see diagram above).

Insects and mites that are disease vectors generally have elevated evolutionary potential due both to a short generation time and a mode of sexual reproduction that maintains high genetic diversity in natural populations. They adapt rapidly to changes in the environment, demonstrating a certain plasticity and allowing them to colonise new ecological niches or to become resistant to treatments (insecticides or acaricides). This capacity to evolve relatively rapidly modifies the epidemiology of diseases transmitted by these vectors and plays a key role in the emergence and re-emergence of many diseases around the planet.

The scientific community in Occitanie has internationally recognised expertise in the field, as reflected by the creation in Montpellier of Vectopole Sud, a centre of excellence in France and Europe in crop pests and vector arthropods that transmit pathogens able to cause infectious human and animal diseases. The region's scientists equally collaborate closely with other research teams around the world and have formed long-term relationships that have led to the creation of centres of expertise in key zones (e.g. in West Africa, see box opposite). For example, *INTERTRYP* studies the biology and ecology of the tsetse fly, the vector for sleeping sickness, caused by a parasite of the *Trypanosoma* genus, with a particular focus on the vector's adaptability to anthropized environments. *MIVEGEC* is developing a deeper understanding of the different species of mosquitoes that are vectors of malaria (*Anopheles* mosquitoes) and the dengue, Chikungunya and Zika viruses (*Aedes* mosquitoes). Several research projects are being conducted in Gabon and Brazil on the possible role of the Asian tiger mosquito *Aedes albopictus* as a 'bridge vector' between wild animals, domesticated animals and humans.

By increasing understanding of the biology and ecology of vector species, scientists are contributing to improving systems that prevent and control diseases.

For example, *ASTRE* has analysed the connection between populations of *Culicoides* biting midges, vectors of bluetongue viral disease (a disease that is not transmissible to humans, but affects sheep and other ruminants and has been responsible for massive outbreaks since 1998 in the Mediterranean and elsewhere in Europe), allowing them to retrace the trajectory of the strains of the virus and uncover the transmission pathways of the disease²².

Disease vectors or crop pests: it's the same battle!

While certain insects carry infectious diseases, others feed on plants (stems, leaves, fruits, etc.), resulting in significant crop loss on an international scale. As global changes continue to alter natural systems, the invasive behaviour of certain insect pests risks being exacerbated. As with insects that are disease vectors, the challenge lies in controlling their populations – in this case to protect crops – while limiting the use of insecticides, which are toxic not only to target insects, but to beneficial insects such as pollinators and auxiliary insects that feed on pests.

To tackle the issue from both fronts, research teams in Montpellier working on arthropods of medical, veterinary and agricultural interest joined forces to pool infrastructure and expertise in Vectopole Sud, an international centre of excellence with the aim of developing applications in early warning systems, monitoring and control of arthropod disease vectors and crop pests. In the area of plant health, *DGIMI* is studying three species of noctuid moths: invasive Lepidoptera whose polyphagous caterpillars damage a variety of food crops. The mechanisms driving the interactions between the insects,

the pathogens and parasites associated with them, and the host plants are being decoded. In the area of human and animal health, mosquitoes, ticks, flies and midges that are vectors of diseases with medical and veterinary impacts are the focus of *INTERTRYP*, *ASTRE* and *MIVEGEC*, the latter being the main laboratory of the national centre of expertise on vectors.

A double blow against crop pests and vectors of human pathogens

Some agricultural environments are particularly favourable to the proliferation of mosquitoes, particularly vegetable or rice farms where water is present for extended periods. Female mosquitoes seeking a place to lay their eggs are naturally drawn to these areas of water, and are especially attracted if the water contains fertilisers. *MIVEGEC*, a laboratory accredited as a collaborating centre for the World Health Organisation on pesticides and public health, is studying an innovative approach that incorporates an insecticide in the fertiliser spread in fields that would target both mosquito larvae and crop pests²¹. Agronomists, farmers and vector control services could thus develop joint actions in this shared fight, which would be technically and financially advantageous for all three parties and would also reduce the impact of pesticides on the environment.

Detailed knowledge of vector biology and ecology in a given socio-ecosystem is also essential to implement the sterile insect technique, which consists of releasing sterilised males raised in a laboratory into the wild. These then mate with females, which produce no offspring, reducing the vector population. This technique has been used to eliminate the tsetse fly, the vector of Trypanosomes (which cause sleeping sickness in humans, and animal trypanosomiasis, or 'nagana', in livestock) in a targeted area of the Niayes region in Senegal, through a collaborative project between *INTERTRYP*, *ASTRE*, veterinary services, the Senegalese Institute of Agricultural Research, Senegal's Ministry of Agriculture and the International Atomic Energy Agency. The methods and technologies developed, such as the distribution models, the patented system for aerial release, and quality control guidelines, will be equally valuable in other African countries involved in the Pan-African campaign to eliminate the tsetse fly and trypanosomiasis that was launched in 2001 by the African Union²³.

A similar approach is being developed by *MIVEGEC* to control the population of the Asian tiger mosquito *Aedes albopictus* on the French island of La Reunion^{24,25}. The stakes are high, as this mosquito transmits dengue fever, and outbreaks continue to spread into new geographical areas due to the circulation of viral strains via infected travellers, the introduction and persistence of these vector mosquitoes in new territories, and their increasing resistance to insecticides. More than 100 countries, representing a quarter of the world population, are today considered at risk of dengue epidemics. Evolutionary biology research into the adaptation of mosquitoes to different environments, an area investigated by *ISEM*, opens other possibilities for applied approaches in vector control: for example, the use of the symbiotic bacteria *Wolbachia* (see box).

Bacteria that live in symbiosis with mosquitoes to control virus transmission

Symbiotic bacteria of the *Wolbachia* genus develop in the cells of arthropods and are transmitted generation after generation by the female. In mosquitoes, embryos resulting from crossing a male infected by *Wolbachia* and a female that is uninfected (or infected by another incompatible strain of *Wolbachia*) are not viable due to a phenomenon known as cytoplasmic incompatibility. In addition, it has been demonstrated that mosquitoes with *Wolbachia* are protected against certain viruses such as dengue, thus reducing their ability to transmit these viral diseases to people. By encouraging the reproduction solely of infected females, cytoplasmic incompatibility considerably increases the spread of *Wolbachia*, which can easily reach a prevalence of 100% in a natural mosquito population.

A deeper understanding of the genetic factors of this incompatibility – the research subject of *ISEM* and *PIMIT* – will optimise the use of *Wolbachia* as an agent of vector control^{26,27}. This can be based on one of two mechanisms: a 'suppression' strategy that reduces the density of the vector by releasing male mosquitoes infected by *Wolbachia* into a target population (as in the sterile insect technique) or a 'replacement' strategy that replaces a target mosquito population with individuals infected by a strain of *Wolbachia* with a protective effect against infection by viruses that are human pathogens in the aim of disrupting transmission.

The first approach (suppression) was tested in natural and semi-natural conditions in Myanmar, in French Polynesia and in Kentucky in the United States, resulting in a significant decrease in the target mosquito population. The second approach (replacement) is currently being trialled in Colombia, Brazil, Indonesia and Vietnam in the framework of an international programme with the aim of eliminating dengue fever, and is so far showing promising efficacy.

4. Understanding and characterising interfaces

The infection of a host by a pathogen requires physical contact and a biological interaction between individuals. These interactions require analysis on three interlinked scales: at the cellular and molecular level, at the level of individuals and populations, and at the level of the landscape and the interconnection of species and the environment (see diagram below).

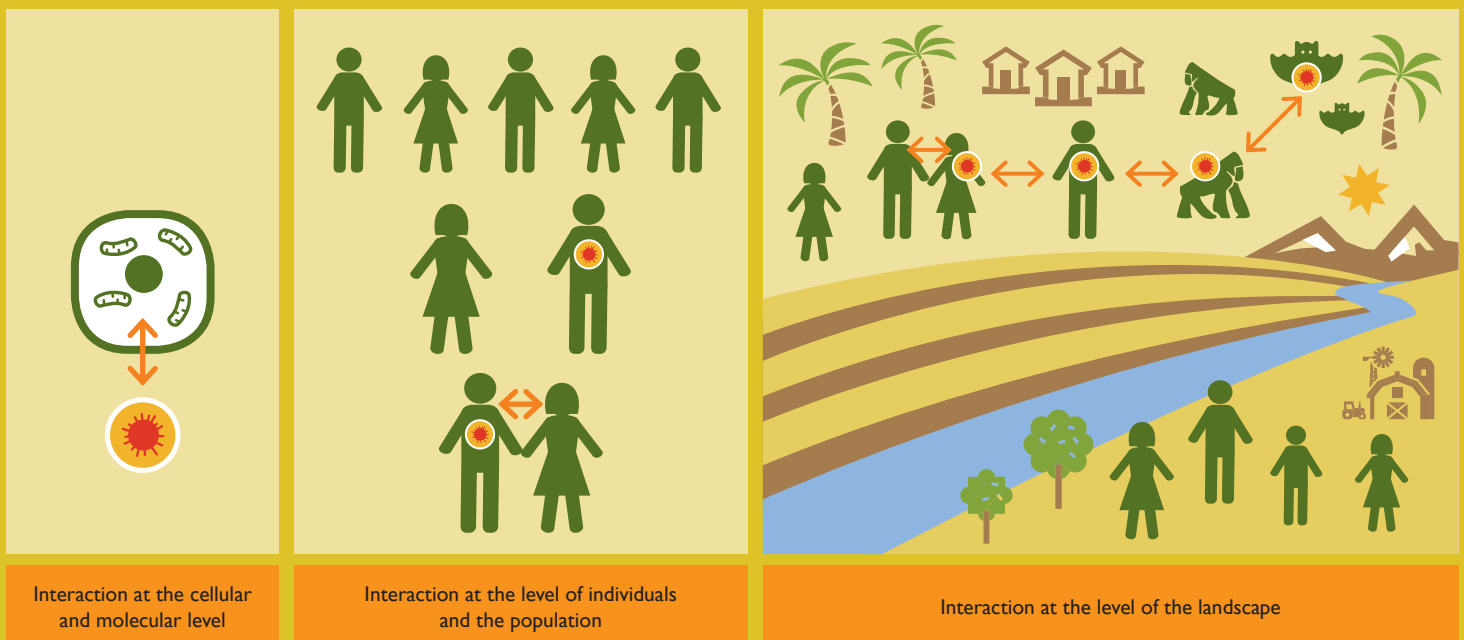
Molecular interactions

The infection of a host by a pathogen occurs on a cellular and molecular level. Many teams of scientists are researching these processes. The goal is to describe the entryways of a pathogen into a host organism, the molecular interactions at work on both sides, the virulence of the pathogen, and the immune response and other defensive reactions activated in the host.

Understanding the molecular interaction mechanisms between the pathogen and the host is crucial in order to identify therapeutic targets and to develop treatments or vaccines.

Research units including *CPTP*, *IPBS*, *IRIM*, *VAP*, *MIVEGEC*, *TRANSVIHMI* and *ASTRE* are studying interactions between animal hosts and pathogenic bacteria (*Brucella*, *Coxiella burnetii*, *Mycobacterium tuberculosis*, *Leptospira*, etc.), viruses (HIV, dengue, Chikungunya, Zika, hepatitis E, influenza, measles, etc.), and parasites (*Toxoplasma*, *Plasmodium*, *Leishmania*, *Babesia*, etc.). Concerning tuberculosis, which is caused by *Mycobacterium tuberculosis* bacteria, *IPBS* has discovered several therapeutic targets for new antibiotics and is participating in major European research programmes into new vaccines that are more effective than the current BCG vaccine. *MIVEGEC* is contributing to investigating how human cells are infected by the Zika virus, with the aim of identifying therapeutic targets (see box opposite). Other research teams such as *LRSV*, *GAFI*, *BGPI*, *IPME* and *LIPM* are studying the interactions between plant hosts and pathogenic viruses, bacteria, filamentous fungi and oomycetes (the latter two are plant pathogens that cause different types of blight and rot).

The different scales of pathogen-host interactions

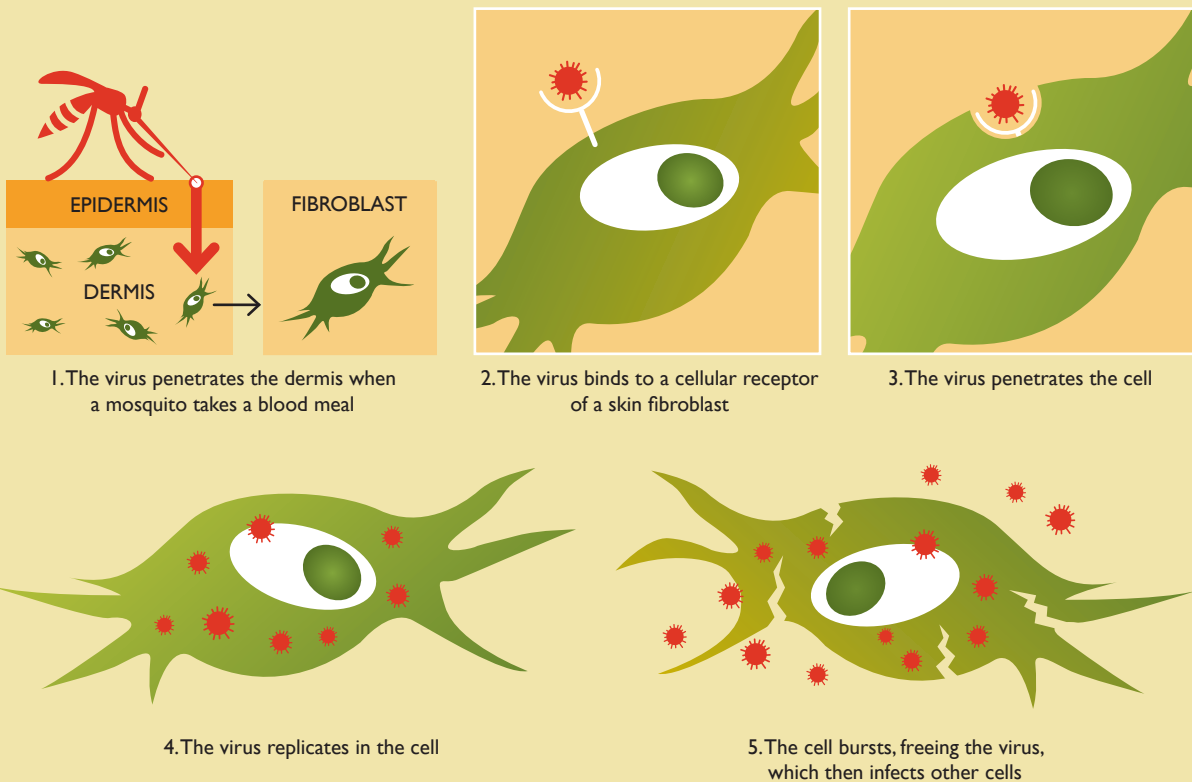


Typically, vaccination acts at different interface levels: a vaccine reproduces on a molecular scale the interaction between the host and the pathogen, stimulating the host's natural defences (the immune response). A vaccinated individual should

thus be resistant to the disease and be individually protected. But the protection of the wider population is only effective when a critical proportion of individuals are vaccinated, limiting the possibility of the survival of the pathogen in its reservoirs

and thus the spread of the disease. Differences in immunisation coverage of a host population in a given region explain why certain diseases have been eliminated in certain regions but not in others.

How the Zika virus infects human cells



Since the first outbreak in Micronesia that revealed the virus in 2007, Zika struck Polynesia at the end of 2013, affecting 55,000 people, and reached Brazil and then the rest of South and Central America in 2015. An international scientific consortium that includes *MIVEGEC* recently revealed how the virus infects humans through the vector of a mosquito (*Aedes aegypti* or *albopictus*) and then propagates in the person affected²⁹. When a mosquito 'bites', it uses its proboscis (a needlelike mouthpart) to search the skin for a blood vessel. When it finds one, it pierces the skin to draw out blood, at the same time depositing viral particles in the victim's skin. The Zika virus particularly infects a type of cell called a fibroblast, where it replicates until the cell self-destructs and bursts. This allows the virus to multiply in the organism and infect other cells, and can eventually reach the foetus and the nervous system. The cellular receptor that allows the

virus to enter a fibroblast has been identified, opening the possibilities for developing a treatment.

Another interesting development has been made by researchers from *PIMIT*: focusing on traditional medicine in La Reunion, they found that extracts from 'bois de gouyave marron' (*Psiloxylon mauritianum*) and 'bois de gaulette' (*Doratoxylon apetalum*), two flowering plants native to the island's forests, have an inhibitory effect on infection by several strains of the Zika virus, as well as on the dengue virus^{30,31}. Experiments on *in vitro* cells show that these plant extracts act on viral entry in the cells, one interfering with the attachment of viral particles to host cells, and the other with the internalisation of viral particles within the cells, with no toxic cellular effects. These plants thus seem good candidates for identifying antiviral compounds that could be used in the fight against Flaviviruses of public health concern.

Microorganisms for treatments

Microbial communities are also an important source of therapeutic molecules: more than one out of two drugs approved since 1940, and over 80% of anti-infection and anti-cancer agents discovered since 1980 have natural origins or were inspired by natural products, the majority from microorganisms. Endophytic fungi, which live symbiotically with plants, are good candidates for these types of molecules. As they compete for their living environment with other microorganisms, some of which are harmful to the plant, it is in their interest to prevent the proliferation of pathogens. This is why natural selection has favoured their capacity to secrete antibiotic molecules whose effect is to eliminate this competition. While the fungi draw resources from the plant, in return

the plant is protected from pathogens, so each mutually benefits. The *PHARMA-DEV* laboratory has isolated new molecules from the achiote (*Bixa orellana*, a plant cultivated in the Amazon for annatto, an orange-red food colouring) that are very effective against leishmaniasis, a vector-borne parasitic disease that affects both humans and dogs in temperate regions and is present in Occitanie²⁸. The development of a medicine for human and veterinary use is being studied. In a similar approach, *LBBM* in Banyuls-sur-Mer is researching the endophytic fungi of *Posidonia oceanica*, a seagrass that is abundant in the Mediterranean. *PIMIT* has also found that extracts from certain plants on the island of La Reunion seem to show promise against the Zika and dengue viruses (see box above).

Genetic mechanisms in human tolerance to sleeping sickness



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Screening for sleeping sickness in Ivory Coast

Interactions between individuals

Beyond the event of host infection, the development and the propagation of the pathogen depend on factors intrinsic to both individuals and the population structure (density, proportion of resistant individuals, etc.). The host's sensitivity to the pathogen and propensity to experience symptoms following infection are variable depending on the individual, on a spectrum that can span, in certain cases, from a total absence of symptoms to death. Exploring these factors, *MIVEGEC* has been able to demonstrate that vector diversity and the variable sensitivity of reservoirs played a key role in the transmission of the West Nile fever virus^{32,33}. These differences in sensitivity can be explained by genetic and physiological factors (notably, the interactions between microorganisms within a host can have positive or negative effects) or environmental factors (see boxes).

Identifying the genetic factors in resistance to pathogens and the physiological and environmental factors that influence this allow the selection of animal breeds or plant varieties and the development of cultivation and livestock-raising techniques that foster disease resistance.

An individual can live for many years with the pathogen *Trypanosoma brucei gambiense*, the causative agent of sleeping sickness, before falling ill or eliminating it. This phenomenon is well known in ruminant trypanosomiasis and has long been taken into account in breeding programmes for resistant breeds. A large-scale review carried out by *INTERTRYP* revealed that in humans, 'healthy carriers' may in fact be much more numerous than people who develop the disease. Partly resulting from a DNA mutation, this tolerance would have been naturally selected in populations living in endemic areas³⁴. Healthy carriers are capable, following a bite from an infected tsetse fly, of limiting the proliferation of parasites within the organism and thus controlling their pathological effects. This discovery allows researchers to study the immune responses that enable the organism to keep the infection in check, opening new avenues for vaccines and therapeutic targets that do not yet exist.

However, people who are contaminated with *Trypanosoma* without realising it slip through public health initiatives and could thus maintain a natural reservoir of these parasites, especially in zones where the tsetse vector is present. The elimination of sleeping sickness in humans by 2020, in line with the World Health Organisation roadmap, will require taking into account the frequency of these healthy carriers in endemic regions of tropical Africa.



A rice field in Kenya studied by researchers

© Eugénie HEBRAD / IRD

Interactions between microorganisms lead to variable effects

An individual is simultaneously exposed to a multitude of microbes – pathogenic and non-pathogenic – which interact with each other with varying effects. In plants, these complex interactions with microbial communities can affect their nutrition, their resistance to various abiotic and biotic stresses, as well as the multiplication of pathogens and the development of their virulence.

In Cambodia, for example, *IPME* has demonstrated that certain soil bacteria reduce infection by parasitic nematodes of the *Meloidogyne* genus, a scourge that seriously affects rice yields. As chemical pesticides aimed at controlling nematodes have been banned in most countries due to their neurotoxicity, these bacteria – in parallel to developing rice varieties that are resistant to roundworms – are an interesting avenue to explore for the large-scale control of these parasites while respecting the environment and human health³⁵.

Elsewhere, in the irrigated rice-growing area of Banzon in Burkina Faso, *IPME* has discovered that it is not rare for plants to be concurrently infected by the rice yellow mottle virus and the pathogenic bacteria *Xanthomonas oryzae*, which attenuates the effects of the virus, while amplifying those of the bacteria³⁶.

Among beneficial microorganisms, arbuscular mycorrhizal fungi are found in all soils and form a mutualistic symbiosis with the majority of plants, playing a major role in their nutrition and their resistance to stress. Research underway at *LIPM* aims to identify the effect of a plant's genotype as well as agricultural practices on the genetic variability of these symbiotic fungi and their ability to stimulate the growth and resistance of model and cultivated grasses. More broadly, the laboratory investigates the relationships between the microbiota and pathobiota and their effects in natural conditions³⁷.

A challenge for researchers is to better understand the manifold interactions between plants and the microbiome in order to develop agroecological methods that stimulate the growth of plants and their resistance to diseases.

Interactions between populations

The ability of a pathogen to propagate also relies on the connectivity of the populations of hosts, vectors and pathogens, which is dependent on the structure of the landscape, the populations, and their means of mobility. Human management of natural systems can thus play a critical role in regulating these transmissions (see box below). The relationships between host populations and disease vectors can be described in mathematical models based on field data that can then be adapted and applied to other combinations of species or situations. For example, based on a study of the transmission of avian malaria to a range of passerine species by a mosquito vector, *CEFE* developed mathematical models to predict the development of the pathogen population in response to the spatial structure of the host population.

Human behaviour also plays a central role in the phenomena of the emergence of epidemics. The health risks – and thus the response to outbreaks – are interpreted differently by populations, who explain them according to socio-political and cultural contexts. An understanding of their experiences, their knowledge and their diverse perceptions, provided through social science research, is essential both for anticipating the propagation of infectious disease and for implementing effective preventive and treatment measures. For example, ethnographic surveys carried out by *TRANSVIHMI* with Ebola survivors in Guinea created a climate of trust that allowed the collection of information that is typically concealed⁴². The interviews revealed a level of non-adherence to recommended treatments by patients received in Ebola treatment centres, which may partly explain the failure of the antivirals tested.

Effective management of health issues requires a collective, territorial perspective, based on scientific approaches that bridge biology, agronomy, ecology and social science.

Integrating knowledge at different scales

A detailed description of the biology and ecology of pathogens, their hosts and their vectors, as well as human behaviour, are thus necessary.

Integrating this knowledge at different scales paves the way to a better understanding of the mechanisms behind epidemics and to the development of methods to halt infections or limit the spread of a disease.

These methods may be preventative (the development of vaccines, the selection of resistant plant varieties or animal breeds, the education of populations), curative (the development of treatments) or predictive (the identification of risk factors, modelling the spread of outbreaks, the development of decision-making tools). In this context, models of host–vector–pathogen relationships, combined with spatial information, can be used to identify zones where the health risks are highest, allowing targeted interventions (see box on following page).

The influence of the landscape on populations of vectors, pests and pathogens

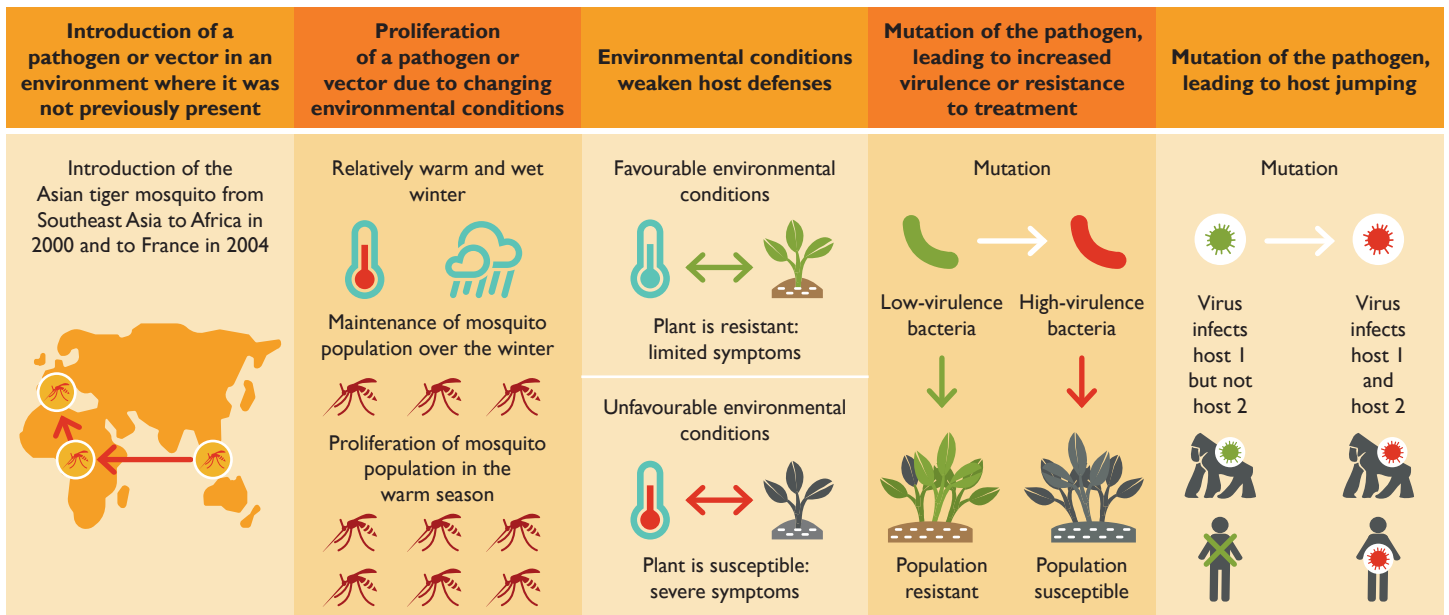
Wild ungulates are both increasing in number and expanding in range by colonising new habitats – in particular anthropized habitats – which is also increasing their contact with livestock and humans. They are hosts for a range of zoonotic pathogens, as well as certain arthropod vectors such as ticks. *CEFS* studies interactions between populations of ungulates, vectors and pathogens. For this it makes use of a ‘field workshop’ in the valleys and hills of Gascony in southwest France, where a population and habitat of roe deer have been monitored for 20 years, as well as an experimental facility where roe deer are raised to study their impact on the ecosystem. A study has shown that the number of houses (indicative of the presence of cats) within the habitat, along with a mild and wet climate, is correlated with an increase in the prevalence of toxoplasmosis in the deer³⁸. Another study has highlighted the role of the landscape (particularly the density of hedgerows and woods) and the climate on the abundance of tick populations (*Ixodes ricinus*, a vector of Lyme disease) and the rodents they parasitize³⁹.

In another context, in the peanut-growing basin of Senegal, *AIDA* along with its Senegalese partners have proven the importance of diversified vegetation at the scale of the agricultural landscape on the natural regulation of the millet head miner, a caterpillar that can cause serious damage to crops. In this agroforestry system where farmers have no access to insecticides, crop loss is only between 2% and 20%, while it rises to over 90% in areas where there is no regulation of this pest by its natural enemies (these include predatory or parasitic insects, birds, bats, etc., which shelter in varied vegetation, particularly in trees)⁴⁰. This regulation is governed by ecological processes on spatial scales much larger than the cultivated plot. Studies such as these demonstrate how agriculture can contribute to the preservation of biodiversity, which in turn can deliver services such as pest control for crops⁴¹.

Agroecology in Senegal



Factors that can lead to the emergence of epidemics



5. Understanding and characterising emergence mechanisms

In addition to the three spatial scales of interactions between hosts and pathogens (molecular/cellular, individual/intra-population, inter-population/landscape), there is a temporal dimension: the modification over time of environments and organisms. The Earth is a dynamic system. Over long periods of time, continents move, the climate changes, populations migrate, species evolve, and a new equilibrium is created.

Microorganisms generally have a short generation time: they reproduce in large numbers, which gives them high evolutionary potential (through genetic recombination, gene transfer or gene mutation) that depends on the environmental and biological pressures they experience. Over the long term, an interaction between a microorganism and its host, whether mutually beneficial, parasitic (beneficial to the parasite and harmful to the host) or commensal (beneficial to the microorganism and neutral for the host), can not only alter, but can change in nature. Likewise, in the context of 'cooperation', a strategy adopted by a large number of species in which individuals generate resources used by the whole community, 'cheaters' can appear who profit from the resources without participating in their production. In a parasitic interaction, the virulence can be modified by increasing the intensity of the pathogenicity. Hosts also evolve in reaction to parasitic pressure, although often over a longer time period (due to a more extended generation time), and can naturally acquire new forms of resistance, which pathogens then adapt to sidestep, and so on.

CEFE, *ISEM* and *MIVEGEC* are developing theoretical and experimental approaches to better understand the evolution of pathogens and their coevolution with hosts. Transposing concepts based on long-term coevolution processes to short time scales sheds new light on the short-term responses of organisms to changes in their environment and *vice versa*. For several millennia, and particularly in recent decades, humankind has considerably accelerated the pace of change on a planetary scale: we have modified environments and land use through agriculture, livestock rearing, urbanisation and deforestation; we have disrupted the climate through the atmospheric emission of greenhouse gases; we have travelled to every part of the planet by every means, bringing in our wake, intentionally or not, a whole array of species; we have introduced chemical substances into every environmental compartment (water, soil and air). The period since the Industrial Revolution at the end of the 18th century, in which human activities have made a significant global impact on the Earth's ecosystems, is considered a new geological epoch, called the Anthropocene.

These disturbances, generally referred to as 'global changes', equally have an impact on the emergence and transmission of diseases, as shown in the diagram above.

Introduction of vectors and pathogens

Global changes can lead to the introduction of a new pathogenic agent or a new vector in an environment where it was not previously present. For example, *MIVEGEC* is studying the introduction and proliferation of the Asian tiger mosquito *Aedes albopictus*, the vector of emerging arboviruses such as dengue and Chikungunya. Native to Southeast Asia, this mosquito species first appeared in continental Africa in the 2000s, on mainland France in 2004, and in southwest France in 2008 – in each of these areas, it has become highly invasive. Aside from the inconvenience caused by this mosquito due to its abundance and aggressiveness, now the risk of viral transmission linked to travellers returning from endemic areas must be considered. In 2014, the city of Montpellier faced an autochthonous episode of infection by the Chikungunya virus⁴⁸, and in 2015, several autochthonous cases of dengue fever were detected in the Gard, a department in Occitanie⁴⁹. Another example is the introduction and proliferation in Thailand of the New Guinea flatworm, a free-living trematode, which has become a vector for a pre-existing nematode that is a parasite of humans and rats and causes meningitis (the local reservoir in Thailand is a snail). This introduction is being studied by scientists at Thailand's Mahidol University and *ASTRE*, who are drawing on a network of Thai citizens to map the presence of the new vector and monitor its evolution in the goal of prevention⁵⁰.

Proliferation of existing vectors and pathogens

Global changes, by modifying the environment, can also favour the proliferation of pre-existing pathogenic agents or vectors, as observed by *MIVEGEC* on the island of La Reunion in 2018 during an outbreak of dengue fever. The dengue virus is present on islands in the southwestern Indian Ocean, which experience recurrent epidemic episodes during the rainy season, with the number of

cases generally decreasing during the austral winter, in line with the reduced density of vector mosquitoes. But at the end of 2017 in La Reunion, observers noted the persistence of dengue transmission hotspots in the west of the island after the winter, leading to a major outbreak in the hot, rainy season at the beginning of 2018⁵¹. The Asian tiger mosquito (*Aedes albopictus*), the dominant species on the island, was the suspected vector in the transmission of this epidemic, although the principal vector species (*Aedes aegypti*) is also present in residual populations restricted to certain zones. These extremely localised populations require monitoring, as expansion is always a risk.

Weakening of host defences

Global changes can also result in weakening a host's capacities of defence, as *LIPM* and *IPME* have shown in plants (see box below). In their natural environment, plants are exposed to both biotic stress (insects, fungi, bacteria, viruses, etc.) and abiotic stress (variations in temperature, the quantity and quality of light, the availability of water and minerals, pollution, etc.), which can occur sequentially or simultaneously. Plant reactions to these types of stress have been widely studied and well described in simple systems, often involving a single plant species and a sole type of stress. However, the response of plants to a combination of stressors remains poorly understood. Climate change scenarios predict an increase in the average temperature of 1.5 to 4.8°C between now and the end of the century along with a rise in the frequency of extreme climate events, which will, in certain contexts, accentuate abiotic stress on plants. Global changes also increase the risk of the emergence of pathogens, amplifying biotic stress. Moreover, various resistance mechanisms employed by plants are inhibited by a constant increase in temperature.

Plant-environment interactions and pathogen resistance

LIPM is researching the impact of rising temperatures on the interactions between the soil bacterium *Ralstonia solanacearum*, which causes bacterial wilt in more than 200 plant species, and the tomato (*Solanum lycopersicum* L.) and thale cress (*Arabidopsis thaliana*). These plants are used as models to address the following questions⁵²: What mechanisms inhibit the immune responses of plants in conditions of increased temperatures? What are the genetic factors in the resistance mechanisms to withstand increased temperatures? What role does the root microbiota play in plant-pathogen-environment interactions?

Another experimental study conducted by *IPME* aims to identify the influence of environmental conditions on the capacity of coffee plants to resist a pathogenic fungi (*Hemileia vastatrix*) that causes coffee leaf rust. The results indicate that, cultivated in an optimal environment, plants that are genetically vulnerable to this fungi were nonetheless able to resist it⁵³. So well in fact that when their needs were met (in terms of water, minerals, temperature conditions, etc.), plants in the field displayed a level of resistance to pathogens sufficient to avoid pesticide use. In contrast, there is concern that stressful environmental conditions (drought, heatwaves, excessive water leading to increased parasitic pressure, etc.) weaken the plant's natural defences and exacerbate harm to its health. Researchers have identified an indicator of the general health of the plant, capable of predicting its ability to resist infection by a pathogen, based on 'chlorophyll fluorescence', which is easily measurable with a small portable tool⁵⁴. The next step is to use this predictive technology directly in the field in order to verify its potential.

Understanding insecticide resistance in mosquitoes

Since World War II, the use of chemical insecticides has drastically reduced mosquito populations and thus the propagation of the diseases they transmit. However, the application of pesticides exposes mosquitoes to selective pressures that have led to an increase in the frequency of resistant individuals. Today this phenomenon poses a serious threat to the prevention of diseases such as malaria, dengue fever and Chikungunya.

Insecticide resistance is conferred by DNA mutations that can have two distinct effects: either the modification of the structure of the proteins targeted by insecticides, making them 'insensitive' to these chemicals, or the modification of the structure of proteins that break down insecticides, making this process more effective. In addition, an increase in the number of copies of encoding genes for these insensitive or biodegrading enzymes is observed. Mosquitoes thus have a range of resistance mechanisms that allow them to rapidly adapt to control strategies and treatment doses.

ISEM and *MIVEGEC* are seeking to better understand the process of natural selection and the influence of genetic mutation on mosquito adaptation^{55,56,57}. By analysing more than 760 genes potentially involved in insecticide resistance in the *Aedes aegypti* mosquito, researchers have demonstrated that resistance processes are different on different continents. These results suggest that, beyond the flow of genes between populations and the appearance of mutations, the environment, such as the use of agricultural pesticides, for instance, plays an important role in the appearance of resistance.

In order to control mosquito populations and the risks of epidemics in the long term, several avenues are being explored: the development of molecular tests to detect multiple forms of resistance, the creation of a world map of resistance mechanisms (with the participation of 40 countries and 10 institutions under the auspices of *MIVEGEC* and with the support of the World Health Organisation), the development of alternatives to chemical insecticides (see page 11), and the adaptation of control methods to each specific context.



Study on mosquito resistance to insecticides

Increased virulence and resistance to treatment

Pressure from global changes can also favour the selection of pathogens that bypass the natural defences of hosts, or of pathogens and vectors that are resistant to treatments. In this area, *BGPI* focuses in particular on parasitic fungi that affect plants (e.g. rice, cacao trees, banana plants) and which adapt very rapidly to constraints, leading to the emergence of new diseases and the recurrent loss of effective control methods (due to resistance to fungicides or circumvention of varietal resistance). Researchers at *IPME* carried out a spatial analysis of the risks of the circumvention of varietal resistance by the rice yellow mottle virus in Africa (see page 27). *MIVEGEC* and *ISEM* are studying the mechanisms of the appearance of insecticide resistance in mosquitoes (see box above).

Host jumping

Lastly, global changes can accelerate the evolving emergence of new pathogens that attack new host species. In Corsica, for example, between 2013 and 2016 the occurrence of human infections by the *Schistosoma* parasitic blood fluke (transmitted by contaminated fresh water) appears to be due to a hybrid. *IHPE's* genetic analysis of the incriminated parasite confirmed that it was a hybrid between an endemic species (*Schistosoma haematobium*, the causative agent of urogenital schistosomiasis, or bilharziasis) and a species of tropical origin (*Schistosoma bovis*, a parasite affecting ruminants and rodents). Following this discovery, ecologists, veterinarians and physicians were brought together in a cross-disciplinary approach in order to understand the origin and persistence of the transmission pathway⁵⁸. Ecologists focused on the infestation process of the molluscs that are the parasite's intermediary host and on the capacity of this pathogen to withstand the low winter temperatures in Europe, as well as the potential

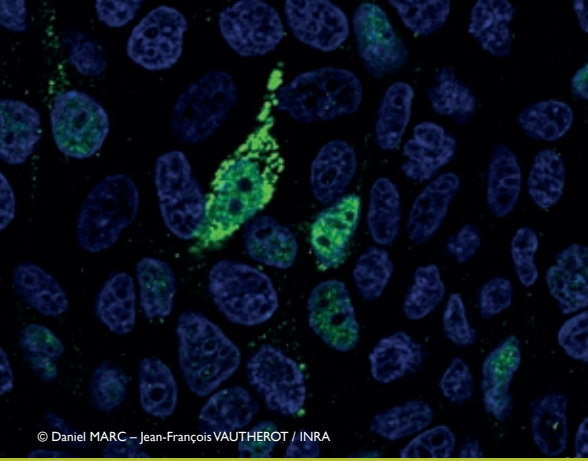
role of rodents as a reservoir. Veterinarians carried out a large serodiagnostic campaign in southern Corsica in which more than 3,500 animals were tested (cows, goats and sheep). Physicians focused on diagnosis issues in exposed patients and demonstrated that the standard diagnostic tests, which typically have a 99% accuracy rate, were less effective at detecting the hybrid parasite. In a collaborative effort with industry, a new test based on an antigen cocktail was developed to reveal infestation by the hybrid.

IHAP and *ASTRE* are working on the plasticity of the avian flu virus and its capacity to cross the species barrier (see box on following page). *IHAP* is also studying the ability of the prions that cause scrapie in small ruminants and chronic wasting disease in cervids to leap to humans, revealing the existence of a previously overlooked zoonotic potential of transmissible spongiform encephalopathies of animal origin (see also page 36).

MIVEGEC is seeking to understand how pathogens of the *Plasmodium* genus genetically adapt to new hosts (e.g. humans, gorillas and chimpanzees).

In the area of plants, *PVBMT* in La Reunion is using agroecosystems characterised by a high density of genetically homogenous plants as models to study the adaptation mechanisms of microorganisms to their hosts, from modifications in the range of hosts (the appearance of epidemics in new plant species) to increased aggressiveness (more severe symptoms).

The AIDS epidemic, on which there is now a vast body of scientific knowledge from several decades of international research, illustrates the dramatic consequences a unique inter-species transmission phenomenon can have on public health in a globalised world (see box page 21).



© Daniel MARC – Jean-François VAUTHEROT / INRA

The influenza virus under high surveillance

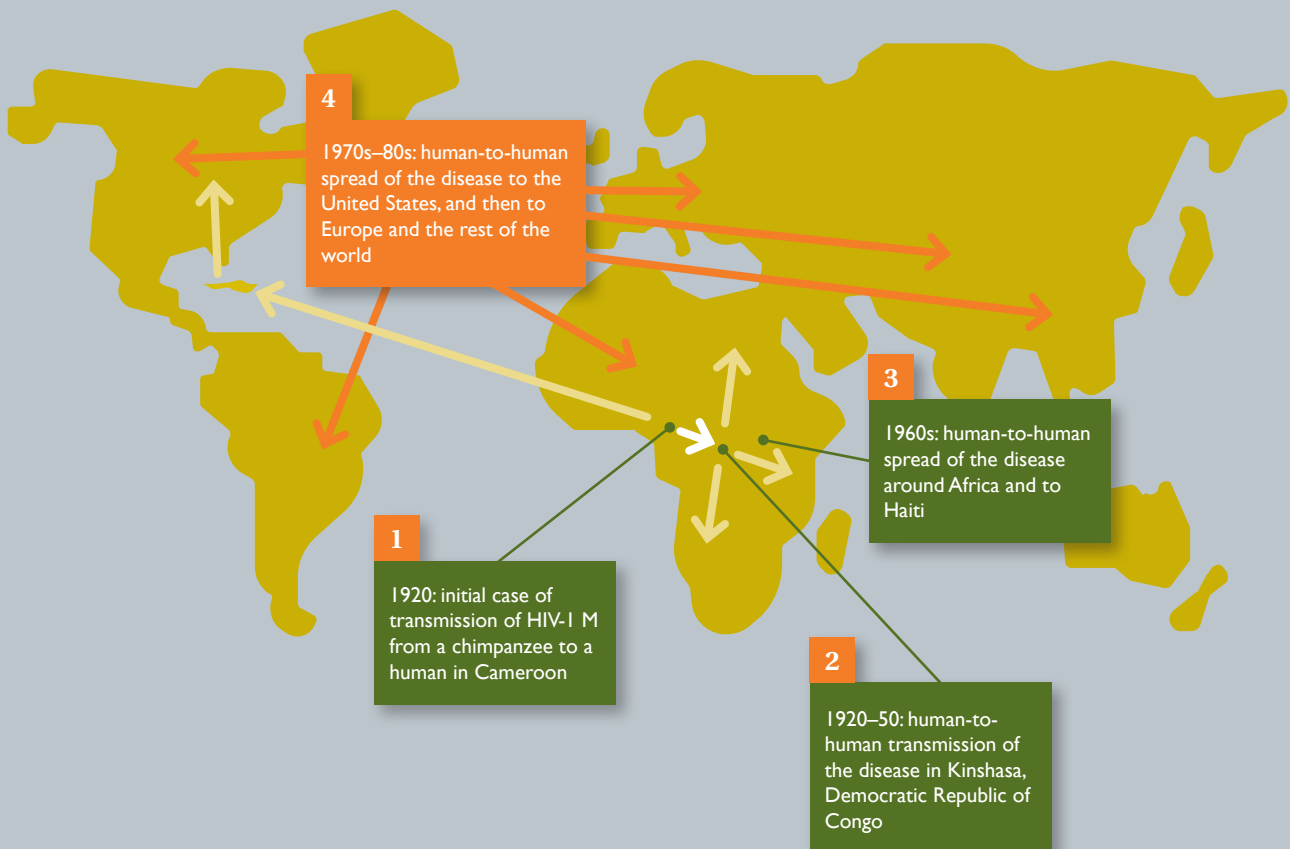
IHAP and *ASTRE* are investigating the risks associated with highly pathogenic avian influenza, in the context of two successive outbreaks in France in the winters of 2015 and 2016⁵⁹ (the focus of *IHAP*) and the epidemics that regularly strike Southeast Asia and Africa (the focus of *ASTRE*). While to date the zoonotic potential of the avian influenza virus identified in France is low, controlling the virus in the animal population is considered essential by the scientific community to limit the cases of human infection and avoid the emergence of a new variant adapted to human-to-human transmission. The emergence of a new pandemic strain of avian or swine origin is a major concern for the World Health Organisation.

Detection by immunofluorescence of cells infected by a flu virus (in green)

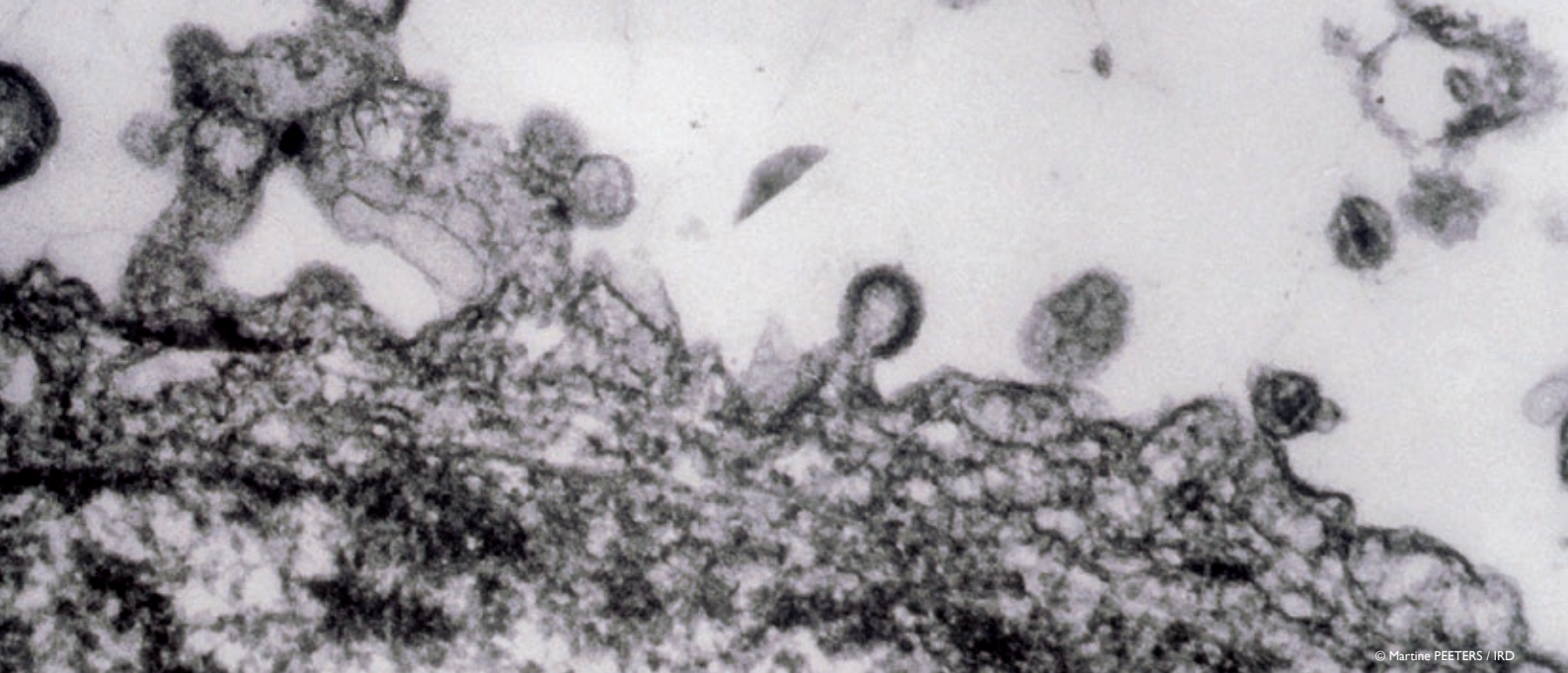
By integrating a continuous-scale approach and combining virology and epidemiology, *IHAP* is studying different aspects of the recent episodes of avian influenza, including the epidemiology of the propagation dynamics of the H5N8 virus in poultry farms, the role of non-commercial farms and wildlife in the introduction and persistence of viruses, the mechanisms affecting the emergence of highly pathogenic variants within a virus population, and the role played by certain segments of viral RNA in giving avian viruses the capacity to cross the species barrier and to modify their pathogenicity in mammals.

Thanks to a surveillance system implemented in Vietnam and based on research in which *ASTRE* was involved – a system that is today coordinated by Vietnamese agencies with support from the Southeast Asian influenza research laboratory and the Pasteur Research Centre at the University of Hong Kong – a new strain of flu was identified in the country in pigs. This strain arises from a reassortment of a H3N2 strain and the pandemic strain in humans, H1N1pdm09⁶⁰.

In addition, research conducted by *ASTRE* and its partners in Southeast Asia and Africa have led to the discovery of the modes of transmission and persistence of the avian influenza virus in wild birds and domestic fowl in these regions – modes which prove to be different than those observed in the northern hemisphere.



Propagation of the HIV-1 M group virus responsible for the global AIDS pandemic



© Martine PEETERS / IRD

Viral particles of an HIV strain budding on the surface of a cell, viewed with an electron microscope (magnification $\times 100,000$)

AIDS: the history of a global pandemic

AIDS is one of the most devastating diseases in human history. Today, 37 million people around the world are infected, 70% of whom live in Sub-Saharan Africa, and every year sees 1.8 million new infections and 1 million deaths. Since the emergence of the epidemic, more than 75 million people have been infected. It has taken several decades since the identification of acquired immunodeficiency syndrome (AIDS) in 1979 in the United States, followed by the isolation of the human immunodeficiency virus (HIV) in 1983, to understand the mechanisms behind this global pandemic. Researchers at *TRANSVIHMI* contributed to these advances, which are the product of work carried out at dozens of laboratories around the world^{61,62}.

In the 2000s, the development of molecular tests allowing the virus to be detected in faeces paved the way for large-scale molecular epidemiology studies on wild populations of great apes. A comparison of the DNA of human and simian viruses revealed 13 independent occurrences of the virus's transmission to humans from chimpanzees or gorillas (HIV-1) or from mangabey monkeys (HIV-2). The most plausible inter-species transmission pathways are exposure to the blood or infected tissue of primates during hunting, cutting up of meat, or from bites or wounds caused by the animals.

Of these 13 cases of initial transmission (4 concerning HIV-1 and 9 concerning HIV-2), one single subtype spread throughout Africa and to other continents (HIV-1 M group); the others remained confined to limited regions (West Africa for HIV-2 A and B groups, and Cameroon for HIV-1 O group), while all the other cases affected only a few individuals and did not propagate.

An analysis of the genetic diversity of HIV-1 M group in humans revealed higher diversity in Kinshasa in the Democratic Republic of Congo, suggesting that this capital city is the epicentre of the epidemic. The closest simian virus was identified by *TRANSVIHMI* in the wild chimpanzees of Cameroon, indicating that this country was the origin of the initial transmission. A retrospective analysis of biological samples taken from patients in the Republic of the Congo confirmed the circulation of the virus in the population from the end of the 1950s. Comparing

the genomes of different strains circulating at different periods, researchers were able to deduce the speed of the evolution of the virus, allowing them to estimate the date of the first occurrences of contamination of humans by primates: the oldest was around 1920.

Colonial-era archives show that in the beginning of the 20th century, there was considerable trade (ivory, rubber, etc.) carried out by river between southeast Cameroon and Kinshasa, which might explain why the epidemic started in Kinshasa while the chimpanzees that initially contaminated humans are found in Cameroon. Then between 1920 and 1950, urbanisation and the development of transport networks, particularly railways, made Kinshasa one of the most connected cities in Central Africa. This explosive cocktail of factors, together with the genetic adaptability of the virus, led to its very rapid spread throughout the country and the establishment of secondary hotspots in southern and Eastern Africa. Following the 1960s, further social changes, such as increased travel, high-risk sexual practices and intravenous drug use, doubtless contributed to transforming small, local infection clusters into a full-blown pandemic.

Today, antiretroviral therapy has dramatically improved patient survival rates, but resistant strains continually emerge. In high-income countries, regular monitoring of patients and the combination of potent molecules restrict the transmission of resistant strains. In low-income countries, the number of people receiving antiretroviral drugs has significantly increased in recent years, particularly in Sub-Saharan Africa, thanks to the World Health Organisation's promotion of a standardised treatment. However, one of the consequences of this strategy is the emergence and transmission of resistant strains; in countries where follow-up care is less frequent, the proportion of new infections from resistant viruses can reach more than 10%. As a World Health Organisation collaborating centre for HIV research, *TRANSVIHMI* is making an important contribution in the surveillance of the emergence of these resistant strains. This threat is to be taken very seriously, and the international community must mobilise to support the necessary public health initiatives in developing countries.

Analysing, preventing and controlling epidemics: integrated approaches to health in action

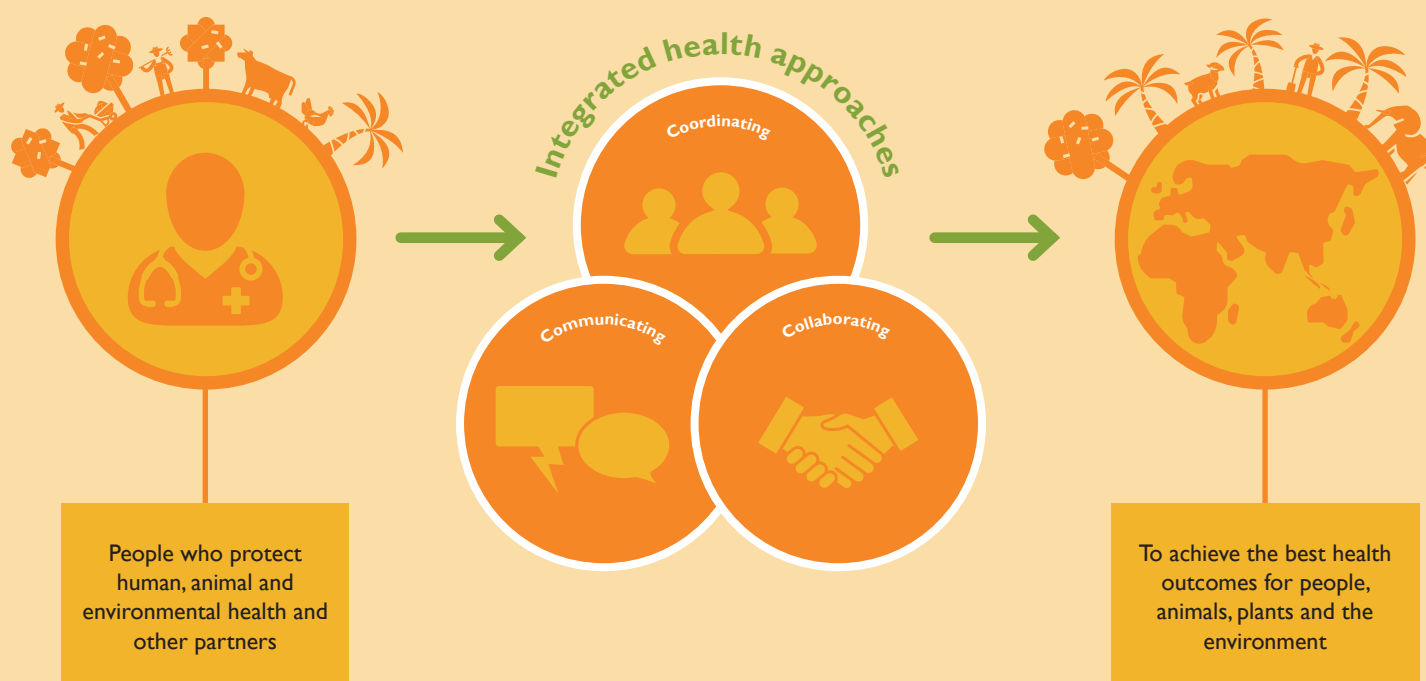
1. Creating a favourable collaborative environment

While integrated approaches to health are essential to enhance health security on national, regional and global scales, their adoption currently remains limited on an operational level. It is crucial to develop relevant tools, methods, standards and recommendations to help countries – particularly those that are less advanced – and institutions to turn a systemic vision of health into reality. These relatively new approaches are not straightforward and require higher awareness by stakeholders, active collaboration, and genuine integration between the disciplines and sectors concerned through strengthened policies and practices at each interface.

Effective pooling of existing infrastructure, information, capacity and skills in different sectors (e.g. policymakers and managers in public, veterinary and environmental

health) and compartments (e.g. human, animal/ plant, environment) is vital. For example, the role of social science in controlling the Ebola epidemic since its outbreak in West Africa (2014–2016) has been recognised by the World Health Organisation. Anthropologists are now included in the rapid response teams deployed in public health emergencies, and international organisations advocate for the inclusion of social sciences in a 'One Health' perspective. Yet there are many challenges: these involve bringing on board researchers from a minority disciplinary field, fostering interdisciplinary dialogue with biomedicine, reinforcing research units in developing countries with insufficient doctoral training, and creating links with specialists in environmental anthropology and health, all while ensuring scientific excellence⁶³.

Integrated health approaches rely on enhanced cooperation between stakeholders and sectors



Source: adapted from a Centre for Disease Control and Prevention

Stakeholder networks

In practice, this means bringing together different stakeholders and sectors within networks, observatories, platforms, training centres, etc. that allow the dissemination of the principles of the integrated approaches to health and facilitate their implementation and their governance. A number of networks have been created to this effect at different levels, for example:

- On an international level, a tripartite collaboration between the United Nations Food and Agriculture Organisation (FAO), the World Organisation for Animal Health (OIE) and the World Health Organisation (WHO) recently reaffirmed its commitment to multisectoral cooperation on the risk of disease at the human–animal–environment interface.
- During the Ebola outbreak in West Africa, anthropologists from a dozen countries created a network that became in 2016 the Anthropology of Emerging Epidemics Network, a space for exchange and mutual support. Based on the comparative approach at the heart of anthropology, the network developed the programme ‘Comparative anthropology of the Ebola epidemic’, in which *TRANSVIHMI* participates. The results of the social science analyses carried out by members of the network were used to adjust and humanise the strategies and procedures of both risk and crisis management put in place post-Ebola by health institutions (Ministries of Health and Health Emergency Operation Centres) in five African countries (Senegal, Burkina Faso, Ivory Coast, Benin, Guinea) and in France (High Council of Public Health). In 2019, this network expanded worldwide to facilitate access, information sharing and the deployment of social sciences in dealing with outbreak risks. Other actions to enhance the integration of social sciences in health strategies are being developed for the benefit of scientists and institutional stakeholders.
- To tackle antimicrobial resistance on a global level, it is fundamental to take into account the problems unique to developing countries and to consider specific local/ regional characteristics. To this end, the French National Alliance for Life Sciences and Health (Aviesan) has started building a research network with developing countries in the framework of the French government’s Priority Research Plan on antimicrobial resistance. In order to facilitate the development of joint projects, countries with a tradition of working with French medical and veterinary research institutes (e.g. IRD with *TRANSVIHMI* and *MIVEGEC*, Cirad with *ASTRE*, Inserm and the Institut Pasteur International Network) have been targeted in priority: Cambodia, Ivory Coast, Madagascar. The more long-term objective is to build on this core group by involving other developing countries, creating a co-financed programme

of operational, multidisciplinary research combining epidemiology, medicine, biology, humanities and social sciences. Three research topics have been prioritised:

- access to community care, irrational distribution and use of antibiotics, and the circulation of counterfeit drugs;
 - hospital care for community-acquired infections and the significant impact of inadequate first-line treatment and empiric therapy protocols;
 - practices around the use of antibiotics in animal health and on farms and the conditions for the transmission of resistance.
- In the Mediterranean basin, the European project ‘MediLabSecure’, coordinated by the Institut Pasteur in Paris and in which *MIVEGEC* participates, aims to reinforce the preparedness in responding to viral outbreaks – medical or veterinary – of a network of laboratories in 19 European and non-European countries around the Mediterranean and the Black Sea. The research topics focus on the evaluation of risks, the optimisation of integrated surveillance and control strategies, in particular of vector-borne diseases, as well as skills development and increasing regional awareness of these diseases through training and information sharing between partners.
 - On the French island of Guadeloupe in the Caribbean, 10 institutes have joined forces in the collaborative project MALIN (including *ASTRE* and *BGPI*) to better control infectious human, animal and plant diseases through a multidisciplinary approach combining microbiology, entomology, epidemiology and socio-economics. This project aims to improve knowledge, diagnosis and surveillance of infectious human, animal and plant diseases that affect the territory; to develop alternative and sustainable control methods for these diseases; to assess their economic and social impact; and finally to transfer the innovations arising from the project to concrete actions and training.

Epidemic preparedness

Health actors, researchers, governmental agencies, NGOs and the United Nations all agree that epidemic preparedness is essential to prevent outbreaks and reduce their damage. Since 2016, health emergency preparedness systems have been put in place in all African countries. These include the establishment of epidemiological surveillance systems – particularly in communities – and early warning systems, the training of health professionals (human and veterinary) for crisis response, the development of diagnostic capacities, the organisation of crisis management structures, and the reinforcement of hospital units that respect biosecurity rules (e.g. triage, isolation) and can provide treatment (prepositioned stocks of medicines and equipment).



Participatory methods are used in the framework of action research projects to take into account the points of view of different stakeholders

International coordination, governed by International Health Regulations, is vertical so that communication between local, national, regional and international levels is rapid and efficient.

However, this global consensus does not guarantee that local experience, skills and resources are always taken into account, giving rise to many anthropological questions as to the efficacy of crisis responses⁶⁴. Researchers at *TRANSVIHMI* alongside colleagues in the United Kingdom, Senegal, Sierra Leone and Uganda are collaboratively exploring these questions to provide information that will make these preparedness systems more equitable and acceptable for local health workers and populations, and thus more operationally effective.

Collaborative tools

Researchers are also developing tools and methods to facilitate cooperation, such as participatory modelling, which allows a shared representation of public health problems to be co-constructed, and to promote the adoption of integrated approaches by stakeholders with different professional backgrounds or from different sectors. This approach understands health – human or animal – as a common good, in the same way as biodiversity, and for which governance must be constructed at different scales. Participatory methods can reveal the collective mechanisms of stakeholder actions, stimulate their construction, and explore links between collective management tools and public policy in relation to social, political, cultural and economic factors. The researchers coordinating the process draw on a combination of methods related to the biological sciences (for a detailed understanding of the ecological and epidemiological dynamics) and the social sciences (to guide communities, defuse power struggles and to understand the social, political and economic issues) (see box).

Evaluation

Lastly, initiatives are also being developed to evaluate and prioritise needs and to document failures and lessons learned from past experiences. Researchers at *ASTRE* participated in an international programme that put forward a general analytical framework to characterise the efficacy of surveillance systems from the point of view of governance and operating procedures, as well as a general framework for evaluating 'One Health' initiatives. The latter has four main elements: (i) the definition of the 'One Health' approach and its context, (ii) the theory of change, taking into account desired and undesired effects, (iii) the evaluation of the operational process and the institutional and infrastructural environment, and (iv) an analysis of the links between the implemented process and the observed effects⁶⁷.

Participatory modelling as a tool for fostering collective action

In Southeast Asia, a research and development project is being implemented to develop the skills of health workers by giving them a comprehensive vision of their sector and to encourage collaboration with other sectors. The project encompasses several issues: the organisation of national and local stakeholders involved in controlling encephalitis in Cambodia and Laos, the health impacts of waste and water management in Thailand, and the control of parasitic zoonoses in the context of family farms in Laos.

To overcome barriers in dialogue and cooperation, essentially related to differences in perception of the issues at stake, the priorities and the processes at work, researchers at *ASTRE* have put forward a methodological framework based on participatory modelling in order to co-construct a shared representation of public health issues and to promote the adoption of the integrated approach to health by stakeholders in different professions and sectors⁶⁵. Various forms of knowledge are shared between stakeholders by means of different tools (risk maps, interaction diagrams, roleplay, etc.) and integrated in models that are co-constructed, improving health risk management. This participatory process allows the development of new multi-actor strategies, involving non-conventional stakeholders such as livestock herders, tribal chiefs and members of the community alongside health risk management professionals.

For example, in the case of the emerging Nipah virus in Southeast Asia, several bat species seem to be its principal reservoir – but as these species are threatened, they are protected by conservation measures. A participatory modelling approach with local people was developed with the aim of raising awareness of the ecological function of bats, of the transmission risks of the virus, and of the preventive measures to put in place⁶⁶. This strategy was based on an analysis of bat ecology, of the presence of the virus in different compartments, and of the perceptions and practices of the local population regarding these bats. It brought together French, Cambodian and international partners, involving researchers from different disciplines, environmental organisations, government agencies, and local communities in Cambodia.

2. Bringing together different disciplines and stakeholders in the analysis and management of health risks

The scientific challenge of integrated approaches to health is to integrate all the acquired knowledge on the study of host-pathogen-vector-microbiota-environment relationships at all levels, in order to support stakeholders in implementing adaptation measures that are capable of increasing the resilience of livestock, agriculture, people and territories to diseases that are sensitive to global changes. Defining the required adaptation measures demands participatory approaches that bring together the different stakeholders in order to:

- prioritise diseases in relation to climatic variations using standard methods (expert opinions) or innovative methods (indicators);
- analyse the risks and build risk maps;
- combine risk prediction maps with vulnerability maps that show the human, animal and plant populations at risk;
- prioritise the zones and populations to target for prevention, monitoring and control actions;
- adapt and reinforce health systems and disease surveillance and control;
- recommend adapted and flexible health policies and regulations.

Most of the research units in Occitanie referred to in this dossier are involved in actions such as these and are making contributions specific to their field. In human and animal health, the units at the centre of the 'One Health' approach include: *MIVEGEC*, *TRANSVIHMI* and *PIMIT* on the persistence, amplification and transmission mechanisms of pathogens and their consequences on populations, in particular in developing countries (the

focus of *PIMIT* is the Indian Ocean region); *ASTRE* and *IHAP* on domestic or wild animal health constraints that may affect humans (*ASTRE* focuses on issues in developing countries); *IRSD* on bacterial hazards related to livestock and pets; *CBGP* on organisms of interest in agronomy, human health and biodiversity; *INTERTRYP* on all organisms in the *Trypanosomatidae* life cycle; and *IHPE* on the interacting biological systems concerning gastropod molluscs of medical or veterinary interest, among others.

In plant health, a number of research units in the region are seeking to understand biotic interactions by investigating a spectrum of scales from the gene to the landscape, with the aim of helping to develop innovative and sustainable agricultural systems that limit crop diseases through: early and effective diagnosis, sustainable management of varietal resistance, the use of biological control agents, and disease forecasting through an understanding of the biology and evolution of pathogens. Of these teams, *PV*, *GAFL* and *LIPM* are working on plants in temperate climates, *BGPI* and *IPME* on tropical and Mediterranean plants, *PVBMT* on challenges encountered in the Indian Ocean, *BIOAGRESSEURS* on tropical perennial crops, and *DGIMI* on the interactions between crop pest insects, their associated pathogens and parasites, and their host plants.

The health risks investigated and the solutions tested are diverse, as illustrated by the following examples (see boxes below and on next pages).

Using health ecology to support public health policy: the case of leptospirosis

At *CBGP*, research is focused on zoonotic diseases transmitted by small mammals (rodents, shrews and bats). These represent 75% of mammal species over a vast ecological range and are major reservoirs of zoonotic agents. This unit is working in particular on leptospirosis, a bacterial disease with a high health impact yet is largely overlooked. *Leptospira* bacteria are carried by mammals, particularly rodents and livestock, which excrete it into the environment, where humans can become infected through contact with contaminated water or moist soil. Different detection techniques for leptospirosis have been developed to identify the rodent reservoirs and characterise the geographical distribution of the bacteria in two cities representative of the explosive urban growth in West Africa: Niamey in Niger and Cotonou in Benin.

Mapping and landscape ecology approaches have demonstrated that the risk of human contamination is high in the irrigated zones used to grow vegetables around Niamey and in the flood-prone informal settlements of Cotonou⁶⁸. Based on these results, local health services were made aware of the need to organise screening campaigns for non-malarial febrile patients potentially infected by leptospirosis. Similar campaigns are also being discussed for monitoring livestock.



Capture and analysis of rodents, vectors of leptospirosis, in Niger

Peste des petits ruminants eradiction

Peste des petits ruminants (also known as the plague of small ruminants) is a highly contagious viral infection that affects almost a billion sheep and goats across Africa, the Middle East and Asia. The disease was recently detected in Bulgaria on the border with Turkey. The virus leads to significant economic losses due to the high morbidity and mortality rates and has a marked social impact, in particular in Sub-Saharan Africa. The role of wild ruminants in the spread of the disease is still poorly known. Although the virus is not zoonotic, an integrated approach is essential. An effective vaccine exists, but large-scale vaccination campaigns are both costly and very complicated to put into practice. A strategy of targeted vaccination in farming systems acting as reservoirs of the virus would overcome these obstacles. This strategy is now within reach, thanks to the development by an international team that includes *ASTRE* of a dynamic model that simulates the dissemination of the virus, based on current knowledge

The effect of bovine tuberculosis on both livestock and human health in Africa is poorly known



Peste des petits ruminants is a major concern in sheep and goat farming

about the disease and a national serological survey carried out in Ethiopia⁶⁹. This model allows an evaluation of the level of viral transmission in endemic zones and the required vaccination coverage to prevent transmission and eliminate the disease. It could thus assist the campaign to eradicate the disease by 2030 launched by the World Organisation of Animal Health and the United Nations Food and Agriculture Organisation, with the support of the European Union, three organisations for which *ASTRE* is a reference laboratory for peste des petits ruminants. If the programme is successful, this disease could be the third infectious disease to be eradicated after smallpox and cattle rinderpest.



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An integrated approach to bovine tuberculosis in Africa

Bovine tuberculosis, caused by the *Mycobacterium bovis* bacteria, is a zoonotic disease that can be transmitted to humans by either wild (e.g. the Cape buffalo) or domesticated (e.g. livestock) animals⁷⁰. One of *ASTRE*'s research areas is the investigation of this disease. Although the large majority of cases of tuberculosis in humans are caused by *Mycobacterium tuberculosis*, for small farmers in Africa the risk of exposure to *M. bovis* is nonetheless higher, and its impact on human health is little known. Likewise, the cost of bovine tuberculosis – a chronic cattle disease – on the livestock sector is poorly assessed. In wild animals, every year new species vulnerable to contracting tuberculosis are identified (essentially bovine tuberculosis in natural contexts, but also human tuberculosis, for example, in zoos). Recent studies have revealed the effects on the host's health linked to interactions between its immune system and the pathogen, as well as between pathogens: for example, between human tuberculosis and HIV. To better understand the interactions between the *M. bovis* pathogen and its biotic and abiotic environment and to be able to provide management options for preventing inter-species transmission and limit its impact on livestock and human health, an integrated approach within this multi-host and multi-pathogen system is vital.

A vaccine for a species at risk

Global changes not only affect the phenomena of epidemics, but the ecology of wild species. Take, for example, the albatross: 18 of the planet's 22 species are threatened, and two are critically endangered. These record-breaking seabirds are perfectly adapted to one of the most hostile zones of the globe, the Antarctic. However, today albatrosses are at risk from modern fishing methods (in particular, longline fishing) as well as from introduced mammals such as cats and rats, which attack the chicks on the islands of the southern hemisphere where they nest. The Nature Reserve of the French Southern Antarctic Territories, created in 2006, is a major reproduction site for many albatross species. This protected area aims to ensure the preservation of

albatrosses on land and in French waters and is strictly regulated. Nonetheless, the Amsterdam albatross, which breeds only on Amsterdam Island in the southern Indian Ocean, remains threatened with extinction. In addition to other threats, the chicks suffer from a high mortality rate due to recurrent epidemics of avian cholera (caused by the *Pasteurella multocida* bacteria). *CEFE* and *PIMIT* have developed and tested a vaccine that reduces the mortality risk by a factor of over 2.5: from a previous rate of only one in seven chicks reaching fledging (the stage of maturity for going out to sea), the vaccine has improved the rate to almost one in two chicks! These encouraging results indicate that implementing vaccination strategies could contribute to the conservation of these seabirds^{71,72}.

Risk mapping of the rice yellow mottle virus

The rice yellow mottle virus is responsible for large losses in yield in the majority of rice-growing countries in Africa. It has significant genetic variation and, over its evolution and spread across the continent, several viral strains have evolved. Currently, one of the only means of controlling it is varietal improvement. Working collaboratively, a team at *DIADE* and AfricaRice have made an important contribution in identifying and characterising the sources of resistance, which appear mainly in the African rice species *Oryza glaberrima*. Nevertheless, certain strains of the virus are able to evolve to bypass defences and infect plants⁷³. By studying the genetic diversity of the virus, the geographic distribution of the viral strains, and their capacity of adaptation to resistant varieties in controlled conditions, a team at *IPME* was recently able to develop a resistance-breaking risk map. This is a very valuable tool for optimising deployment strategies for resistant varieties depending on the locally present strains and thus to safeguard resistance. In addition, a hypervirulent strain, capable of overcoming all known defenses, was identified during the study; it appears to have a wider range than expected in West Africa. The modelling of the spatio-temporal distribution of the virus, made possible by advances in phylodynamics, will allow strain dynamics to be better understood and anticipated, providing information that can then be taken into account in the battle against this pathogen that threatens African rice cultivation.



© Eugénie HEBBARD / IRD

The rice yellow mottle virus causes significant crop losses in Africa

A new tool in the fight against malaria

Malaria remains the world's most deadly parasitic disease, with 435,000 reported deaths in 2017, despite effective control methods being widely deployed in endemic zones. Insecticide-treated bed nets for avoiding *Anopheles* mosquitoes, a vector of the disease, is a case in point, as between 2000 and 2015 their widespread distribution succeeded in reducing morbidity and mortality from malaria. Yet the extensive ongoing use of these nets exerts evolutionary pressure, which is resulting in the emergence

of resistant phenotypes: the mosquito has modified its behaviour by shifting its feeding pattern from what was previously the middle of the night to the beginning of the evening or the morning, or by adopting opportunistic trophic behaviour (biting humans as well as animals). In Burkina Faso, *MIVEGEC* is conducting a study to better understand the physiological mechanisms leading to these behavioural changes.

Managing these evolving forms of resistance, which are responsible for what is known as the 'residual' transmission of the parasite, requires new prevention tools. In this context, treating humans and livestock with ivermectin, which is both an anti-parasite medication and an insecticide, is receiving growing attention. The concept is simple yet original: a host treated with ivermectin delivers the insecticide, present in its blood, to a biting mosquito, which succumbs to it⁷⁴. The use of ivermectin as a complementary method to large-scale vector control measures faces another hurdle, however: its persistence in the blood is limited, requiring recurrent treatments. *INTERTRYP* and *MIVEGEC*, working with the company Medincell, are testing long-acting formulations that would allow the sustained release of the molecule in the blood at predetermined concentrations for up to one year. This approach has the dual advantage of considering both humans and animals in the transmission chain of vector-borne parasitic diseases, which is even more relevant in the mainly rural target context; in Sub-Saharan Africa, human and animal health are closely linked. This promising approach is being pursued in parallel for malaria as well as for neglected tropical diseases of humans and animals, as several other vectors besides *Anopheles* are also susceptible to ivermectin.



© Karine MOULINE / IRD

Dead female *Anopheles* mosquitoes following a blood meal on a cow treated with a therapeutic dose of ivermectin

3. Combatting antimicrobial resistance requires integrated approaches

Worldwide, the emergence of increasingly resistant – including multidrug-resistant – strains of bacteria poses serious problems for human and animal health, threatening public health and food security. According to a 2018 report by the World Health Organisation, in humans, “currently, drug-resistant infections cause at least 700,000 deaths each year; a figure that, if no action is taken, could reach 10 million per year by 2050 according to the most pessimistic projections”. To address this threat, a global action plan to fight antimicrobial resistance was approved by the World Health Assembly in May 2015.

Antimicrobial resistance, which involves one or several genes, occurs through mutation and is passed on ‘vertically’ from one bacterial cell to another during cell division. The emergence of resistance is promoted by the exposure of bacteria to selective pressures within their hosts (for example, during antibiotic treatment in humans or animals) or the environment (for example, the presence of antibiotics in the water or soil). Once resistance is acquired, it can also be passed on ‘horizontally’: that is, through the transfer of genes between bacteria of the same species, or even different species (see diagram below). The spread of resistance is dynamic in nature, as it occurs in a variety of ecosystems that are subject to different

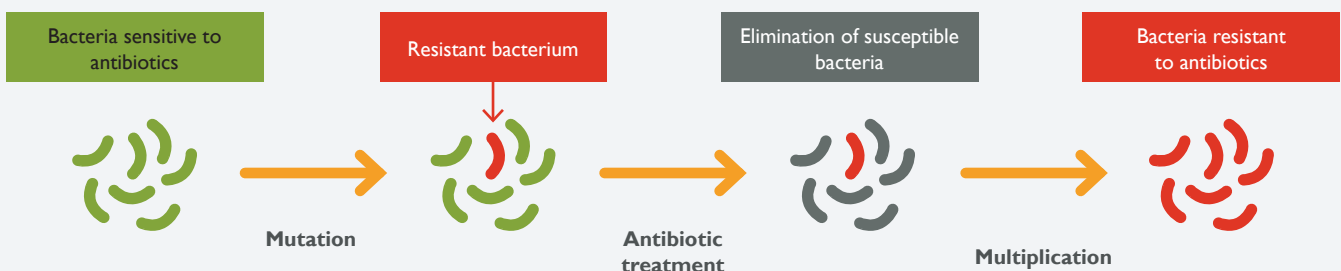
selective pressures (e.g. agricultural environments, urban contexts, hospitals, etc.: see diagram opposite).

Understanding the different evolutionary mechanisms leading to antimicrobial resistance is essential in order to put in place relevant and effective prevention and control strategies.

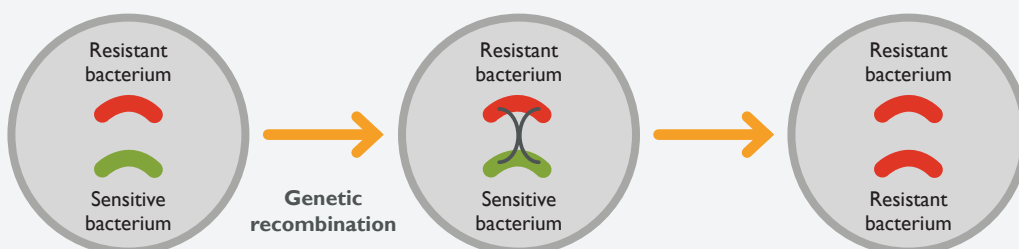
In this objective, the Bioinformatics Platform of Toulouse, along with a number of partners, has embarked on an analysis of all the genomes from the faeces of humans and animals treated with antibiotics, with the goal of identifying and characterising bacterial resistance genes. *INTHERES* is exploring the flow of resistance genes and active molecules within the microbiota of treated livestock and the environment. *LBE*, *HSM* and *ECOLAB* are studying the problem of antibiotic resistance in different compartments (sewage sludge, water, soil), while research carried out by *PVBMT* and *ASTRE* has identified the soil and crops as reservoirs of bacterial resistance genes (see box opposite).

Mechanism of bacterial transmission of antibiotic resistance

Development of resistance and vertical transmission



Horizontal transmission of resistance between bacteria of the same or different species



To combat a phenomenon as complex as antimicrobial resistance, an integrated approach is needed, connecting human, animal, plant and environmental health. It is a challenge that requires coordination at every spatial scale, from local to global, particularly in implementing surveillance systems.

In France, the national 'Antimicrobial Resistance and the Environment' working group has recommended creating a network of complementary sites dedicated to studying this issue, and several research laboratories in Occitanie are working on the topic. *HSM* has put forward the basin of the River Lez – the main river crossing Montpellier – as a workshop site to study antimicrobial resistance in aquatic environments (see box on previous page). *MIVEGEC* is collaborating with the Tour du Valat Research Institute for Mediterranean

Wetlands to study the conditions around the emergence and transfer of multi-resistant bacteria to wildlife within a 'study site for global ecology' in the Camargue, a wetland environment subject to strong anthropogenic pressures. Projects in partnership with international institutions are also focusing on antibiotic resistance, allowing the development of solutions adapted to other contexts potentially prone to the emergence and spread of antimicrobial resistance: for example, in Southeast Asia (see boxes below and opposite).

Of the key actions to implement, the reduction and optimisation of antibiotic use, whether for human, animal or plant health, is a priority.

In this area, *INTHERES*, *GENPHYSE* and *ISEM* are working to develop innovative solutions for managing animal health in the aim of minimising antibiotic use (see box opposite).

Southeast Asia, a region particularly exposed to the risk of antibiotic resistance

The region of Southeast Asia is not only the epicentre of a number of infectious diseases, but is also a major source of antibiotic-resistant bacteria. Several laboratories based in Occitanie focus on this region in partnership with local institutions. In Vietnam, a joint international laboratory between *MIVEGEC* and the Hanoi University of Science and Technology was specifically created to study the mechanisms of the emergence and transmission of bacterial resistance to antibiotics on different spatial and temporal scales. Observational studies allow the collection of data and the characterisation of transmission within and between environmental compartments. These are combined with experimental studies to shed light on the molecular mechanisms of resistance and then linked to mathematical modelling to analyse the data, guide data collection, inform the experimental approach, and test hypotheses for which experimentation is impossible. The results are then applied to develop public health policy, diagnostic tools and new antibacterial molecules, as well as training for students and professionals.

Through an analysis of a multitude of data from several countries in the region, scientists at *ASTRE* were able to show that the recent increase in living standards has resulted in a strong rise in demand for animal protein, intensifying production and also antibiotic use. The result has been that antibiotic resistance has significantly increased, exacerbated by the lack of regulation in sales of antibiotics, inadequate monitoring of their use, and the inexistence of appropriate legislative frameworks^{78,79}. The researchers were able to make several proposals to strengthen the efficacy of health policy, recommending:

- the implementation of integrated surveillance networks aimed at monitoring the use of antibiotics: not only in humans, but also in livestock rearing, fish farming and agriculture;
- the reinforcement of regional partnerships that involve international agencies in order to promote information sharing between countries and multisectoral approaches;
- the education of agricultural users and better application of laws that enforce current regulations concerning antibiotic use.

An analysis of the impediments and leverages in implementing such a cross-sector approach is in progress. This type of study is equally relevant in other socio-economic and legislative contexts poorly adapted to the management of antibiotic use in agriculture, such as Sub-Saharan Africa.



Doctoral student at the Hanoi University of Science and Technology analysing antibiotic resistance genes in the bacteria responsible for tuberculosis

Multi-drug-resistant tuberculosis: a global health crisis

With 10 million new cases a year causing 1.5 million deaths, tuberculosis is today the world's most deadly infection. Increasingly, the bacteria strains responsible for the disease (*Mycobacterium tuberculosis*) are resistant to antibiotic treatment: in 2018, around 500,000 people were infected by strains resistant to rifampicin (the most widely used and effective drug), of which 80% were also resistant to another antibiotic, isoniazid. The therapy to treat multi-drug-resistant forms is complex (involving the combination of several types of antibiotics), long (9 to 20 months), expensive, and can have many side effects that are sometimes serious, for a recovery rate of only 56%. The treatment for the most severe form (resistant to at least four medications) is only employed for one out of three patients, with a success rate of only 30%. It is estimated that 214,000 people die every year from multi-drug-resistant tuberculosis. Worryingly, the discovery of new antibiotic molecules has slowed dramatically: since 2008, only two new medications have been approved for the treatment of multi-drug-resistant tuberculosis.

The challenges posed by the global epidemic of tuberculosis need to be tackled in an integrated way, taking into account both sensitive and resistant strains: the aim is to improve the effectiveness of treatments as well as the performance of diagnostic tools that detect both bacteria and resistance. With this objective, **TRANSVIHMI** is analysing and developing clinical trials to develop new treatment plans for the disease. For its part, **MIVEGEC** is working with the University Hospital in Montpellier to develop a diagnostic kit for resistant strains (in collaboration with the National Institute of Hygiene and Epidemiology in Hanoi, Vietnam, the Christophe Mériex Infectious Disease Centre in Laos and the Institut Pasteur in Cambodia).

Innovations in the fight against antibiotic resistance in livestock farming

While the use of antibiotics in livestock farming contributes to maintaining the health and well-being of animals, it also results in the emergence of bacterial resistance. This calls for the need to develop innovative solutions to prevent and treat bacterial infections. **GENPHYSE** focuses on the role of digestive microbiota in preserving livestock health, with the goal of maximising these microorganisms' beneficial effects on the development and stimulation of the immune system. Two strategies are being studied, one aiming to guide microbiota composition and functioning at an early stage; the other to better take into account the interaction between the host and its microbiota⁸⁰. The main areas of action are animal feeding, in particular the diet transition from milk to solid food, and the use of prebiotics and probiotics. The ecological principle of 'competitive exclusion' is also brought into play to interrupt the vertical transmission of bacterial resistance genes between the mother and her offspring, and thus limit their spread to the environment and to humans⁸¹.

INTHERES is developing precision livestock-farming techniques (sensors, connected devices, videos, etc.) that allow a group of animals to be individually monitored in real time. The mathematicians in the unit are using artificial intelligence technology to analyse the large volume of data collected by the devices, with the aim of creating early detection and warning algorithms to signal disease or animal welfare problems. The early, individual detection of ailments is the first step in allowing targeted interventions that can replace mass administration of antibiotics to an entire group when a disease appears in a few animals (a control treatment referred to as metaphylaxis). The objective of these targeted interventions is to interrupt an infectious event in a group by treating the fewest possible animals. **INTHERES** is also working on combinations of antibiotics and non-antibiotics (e.g. bacteriophages, anti-virulence molecules, etc.), notably for treating bacterial infections associated with 'biofilms' (a multicellular community of microorganisms that adhere to each other and to a surface by secreting an adhesive protective matrix): for example, mastitis caused by *Staphylococcus aureus* in dairy cows.

Phytotherapy in fish farming

Currently, half of the aquatic animals consumed in the world (fish, molluscs and crustaceans) comes from fish farming, which has a global production volume of around 74 million tonnes per year – 90% of which is produced in Asia. However, diseases have a significant impact on aquaculture, leading to the excessive use of antibiotics in many countries to prevent or treat infections or to boost growth. To combat antimicrobial resistance, it is vital to reduce the inappropriate use of antibiotics in fish farms. In producing countries, this objective has generated growing interest in local plants with antibacterial and immunostimulant properties that can strengthen fish resistance to infections or inhibit the virulence of pathogenic bacteria.

An ethnobotanical study conducted by **ISEM** with fish farmers on the island of Java in Indonesia identified 18 species of plant used for therapeutic purposes in local aquaculture. The antibacterial actions of different extracts of these plants (leaves, bulbs or rhizomes) against major pathogenic bacteria of fish in tropical regions (*Streptococcus agalactiae* and *Aeromonas hydrophila*) were then tested in the laboratory⁸². In another study, a diet rich in plant extracts was found to be beneficial to fish health. **ISEM** demonstrated that the use of powdered leaves of *Litsea cubeba*, an evergreen shrub in the *Lauraceae* family, has biological effects on the common carp (*Cyprinus carpio*, a very important aquaculture species with a global production rate of approximately 4 million tonnes per year), notably on growth, non-specific immunity and survival⁸³. These plants traditionally used by fish farmers and derived from plant biodiversity represent interesting alternatives that could promote the ecological intensification of aquaculture systems and the prevention of disease in fish farming.

Traditional aquaculture on the island of Java in Indonesia



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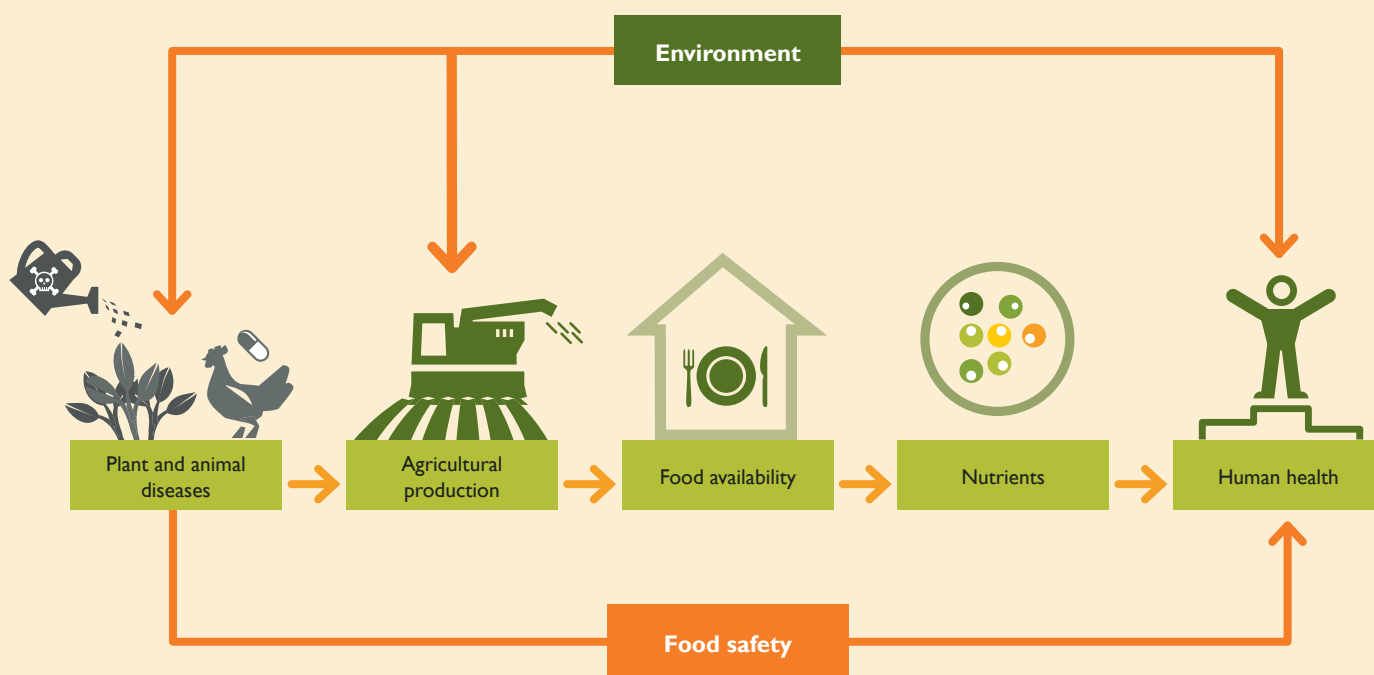
Food, planet, health: the global health concept applied to food systems

Human health is affected not only by infectious and parasitic diseases, but is highly dependent on diet – from both a quantitative and qualitative point of view. Two aspects are particularly important to consider in the diet-health relationship (see diagram below). The first is food and nutrition security: that is, an individual's access to foods and nutrients in sufficient quantity and quality to ensure their essential dietary needs in keeping with their cultural practices. In this context, the health of plants and animals influences the availability of foods and nutrients, the nutritional quality of a diet influences people's health (both directly and *via* their capacity to resist infectious diseases), and people's health influences their ability to feed themselves and to absorb the ingested nutrients. The second aspect in the diet-health relationship concerns

food safety: that is, the hygienic and toxicological quality of food. Ingesting infected plants or animals can be a source of disease transmission or of poisoning for humans. Likewise, food products can be contaminated by microorganisms that are pathogenic to humans and are present in the environment during food production, storage, processing or conservation. Food can also be contaminated during its production by substances in the environment that are toxic to humans, in particular those used to control diseases and pests in crops or livestock.

Lastly, agricultural production is dependent on – and in turn impacts – natural resources and the climate. Thus it is critical to consider the multiple interactions between the environment, food production, diet and human health.

Links between farming, food and human health





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Food systems have a significant impact on both human and environmental health

1. Food and nutrition security and health

Food security and health

In countries where a large part of the population depends on subsistence agriculture and herding, the health of people, animals and plants plays an essential role in the availability of and the access to food, as well as the stability of both. In these countries, where social security systems are often inadequate or inexistent, especially in rural areas, people in poor health are less able to produce food or procure the money to buy it. They also have higher health costs and so less revenue available for food.

Another challenge is that plant and animal diseases reduce agricultural and livestock productivity, and thus the quantity of food directly available for the household and/or the revenue earned through selling what is produced. When these diseases and associated losses in yield are recurrent, they compromise the very sustainability of the means of production and lead to the increasing impoverishment of rural households. If this occurs on a regional scale, which is generally the case in epidemic or invasion events, it decreases the availability of food while simultaneously increasing its price.

In addition, climatic fluctuations, aside from the fact that these also directly affect agricultural yield, can weaken plants and animals, making these organisms more vulnerable to disease (e.g. in the case of droughts and excessively hot temperatures) or encouraging the proliferation of pathogens or vectors (e.g. in the case of heavy rains or flooding). The combination of these factors contributes to limiting food access for rural populations and can lead to malnutrition.

Regions suffering the highest losses in yield from disease or crop pests are also those with the greatest food shortages and strongest population growth.

This is shown by an international study to which *AGIR* contributed⁸⁴. A number of scientific teams in Occitanie are working on the issues specific to developing countries and are contributing directly or indirectly to reinforcing food and nutrition security in a context of global change: (i) by selecting for plant varieties or animal breeds that are resistant to disease and adapted to local environmental conditions (e.g. *AGAP*, *SELMET*), (ii) by developing new methods to control crop and livestock diseases based on knowledge about pathogens, reservoirs, vectors and interfaces, or (iii) by providing socio-economic insights into agricultural production systems, the strategies of stakeholders in these systems, and agriculture and food policy, helping to inform decision-making at different levels (*MOISA*, *INNOVATION*).

Undernutrition and health

One of the dramatic consequences of food insecurity is undernutrition, either from the lack of energy intake or from vitamin or mineral deficiencies (e.g. lack of

iodine, vitamin A, iron, etc.). These can result from a diet temporarily or chronically insufficient in quantity (as a source of energy), and/or in diversity (as a source of nutrients essential to the organism's proper functioning), and/or from an infectious or parasitic disease contracted from the environment that reduces appetite as well as the body's ability to absorb nutrients.

Undernourishment and nutritional deficiencies not only have an immediate health effect on the growth and development of young children, but also play a significant role in morbidity (contracting a disease) and of overall mortality, due to the fact that they weaken the organism and make it more vulnerable to infectious and parasitic diseases. People suffering from malnutrition, children in particular, are much more susceptible to contracting a disease and dying from it, as highlighted by the World Health Organisation:

Undernutrition is responsible for some 45% of deaths of children under the age of five in the world, mainly in low or middle income countries.



Undernutrition and infectious and parasitic diseases are interrelated



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The nutritional quality of diets has a major impact on health

The global impact of undernutrition, affecting 800 million people around the world, is grave. It has serious and persistent social and medical consequences, and also has an impact on economic development, not only for individuals and families, but for communities and countries.

To address this challenge, *NUTRIPASS* is studying the maternal–newborn–child health *continuum* (from pregnancy through birth weight to child growth), using a global approach that integrates nutritional, infectious and environmental aspects. For example, in Cambodia, it revealed a combination of causes of malnutrition arising from diet, environmental and health issues. More than two-thirds of Cambodian children under the age of two do not have access to a sufficient number of meals per day or to sufficiently varied foods⁸⁵. Moreover, the presence of livestock near homes increases the risk of contamination by the intestinal parasite *Giardia duodenalis*⁸⁶, and access to clean drinking water is limited. All these factors contribute to the risk of stunted growth. This type of analysis allows more effective targeting of prevention and maternal education programmes.

Nutritional quality and health

Beyond the issue of food availability, the nutritional quality of a diet has a major impact on health. Worldwide, food systems today are characterised by increasingly processed food products of varying nutritional quality, leading to diets with an excess of simple carbohydrates and saturated fatty acids and lacking in antioxidants.

A diet of low nutritional quality is directly implicated in weight problems, obesity and non-communicable diseases (e.g. diabetes, heart disease, strokes, certain cancers).

The prevalence of these diseases is on the rise all over the world, including in France and in young people. This increase is fuelled by phenomena such as rapid and unplanned urbanisation, the globalisation of unhealthy lifestyles and ageing populations. According to the World Health Organisation, of non-communicable diseases, cardiovascular disease is responsible for the largest number of deaths (17.9 million per year), followed by cancer (9 million), respiratory disease (3.9 million) and diabetes (1.6 million). Every year, 15 million people between the ages of 30 and 69 die of a non-communicable disease, 85% of these in low or middle income countries. Aside from poor diet, smoking, sedentary lifestyles and the harmful use of alcohol are the main risk factors.

Diet also has effects on the intestinal microbiota (leading to a reduction in microbial diversity or even microbial imbalance, called dysbiosis), and research is increasingly

finding that an impaired microbiota is the source of many chronic diseases⁸⁷. The digestive system is the site where micronutrients are absorbed, vitamins are synthesised; it also serves as a protective barrier against pathogens and inflammatory molecules. But its physiological functions can be disrupted or it can be affected by pathologies such as inflammatory bowel disease, celiac disease, intestinal motility disorders, or disturbances in the intestinal absorption of iron, with repercussions on the liver. Conversely, a diet of high nutritional quality, rich in antioxidants (e.g. vitamins, polyphenols, etc.) and polyunsaturated fatty acids (omega 3), has a beneficial impact on health, offering a proven protective effect against certain inflammatory diseases and cancers.

Several scientific teams in Occitanie are seeking to better understand the causes of these nutritional interactions and their consequences, in order to recommend targeted strategies and intervention policies. For example, *MOISA* is analysing the links between food buying/consumption behaviour and health, *NUTRIPASS* is attempting to identify the genetic factors involved in obesity and diabetes, the Nutrition-Diabetes team at Montpellier University Hospital is studying the mechanisms leading to obesity and diabetes, and *I2MC* is focusing on the physiological and molecular mechanisms involved in metabolic and cardiovascular diseases. Dietary changes can also modify mitochondrial function. *DMEM* is seeking to better understand the role of mitochondria in altering skeletal muscle function, demonstrating how this is involved in pathologies linked to nutritional deficiencies. *IRSD* is exploring digestive and metabolic disorders using an integrated approach. A number of other research units, such as *TOXALIM*, *QUALISUD* and *NUTRIPASS*, are also studying the beneficial effects of foods and nutrients.

Chronic disease and environmental factors

Atopic dermatitis is a chronic and multifactorial skin inflammation that is common in children. Its increase in occurrence since the 1950s is explained by the influence of environmental factors. In dogs, the condition shares many clinical characteristics with human atopic dermatitis, such as its prevalence in the general population, the age of appearance, its link with food allergies, etc. Following its development of atopic dermatitis study models on human cells *in vitro* and in mice, *UDEAR* is now focusing on a canine model of the skin condition, with the objective of developing new treatments for both veterinary and human use.

2. Food safety and health

Humans can contract infectious and parasitic diseases through being exposed to pathogenic agents in their immediate environment: through water, air, soil, vectors, or through contact with infected hosts, including the food they eat or the water they drink. Food and water can equally be contaminated by toxic molecules resulting from human activities – molecules that have deleterious effects on health.

Animals as sources of foodborne pathogens

Food can be contaminated 'at the source' by pathogenic agents, and then transmitted: for example, through the consumption of undercooked meat from infected animals. This is the case with the hepatitis E virus, a long overlooked disease in industrialised countries due to the high frequency of asymptomatic forms and the low performance of diagnostic tools. Infecting the liver, the virus is transmitted mainly through eating raw or undercooked meat, through direct contact with infected animals, or through blood transfusions. While the majority of infections by genotypes 3 and 4 of the virus are asymptomatic and resolve on their own, they can persist in immunosuppressed patients, and the virus's presence has recently been found in organs apart from the liver, such as the kidneys and the nervous system. **CPTP** played a large role in the discovery of autochthonous hepatitis E in France, in the characterisation of chronic hepatitis E and in demonstrating the effectiveness of ribavirin, today the benchmark treatment for the disease. Another example of foodborne pathogens is the case of transmissible spongiform encephalopathies (see box below).

Food contamination through production and processing methods

Food can also be contaminated by pathogens in the production or processing chain. For example, cultivated vegetables can be contaminated by pathogens present in irrigation water or in manure. Ruminants (e.g. cows, sheep and goats) are asymptomatic carriers of Shigatoxin-producing *Escherichia coli* (STEC) strains, which can cause severe lesions in the intestinal, renal and cerebral microvascular endothelium in humans. The faeces of these ruminants can contaminate the environment and water, and thus food produced for human consumption (including milk, meat and vegetables). To better understand *E. coli* infections in humans and animals and be able to offer alternative treatments to antibiotics, **IRSD** is studying the variety of genes (related to both virulence and antibiotic resistance) involved in the pathogenesis of STEC, its evolutionary dynamics and its transmission between bacteria.

Food processing techniques can act on microorganisms: cooking eliminates them, fermentation can promote the development of beneficial microorganisms to the detriment of pathogens, etc. Storage conditions also play an important role in the development of microorganisms that are naturally present in food in small quantities. For example, an interruption in refrigeration can cause the proliferation of pathogenic bacteria. Knowing the hygienic condition of food is a key step in developing ways to optimise the stabilisation and processing methods of products. **QUALISUD** is employing global analysis techniques on microbial flora (bacteria, yeasts, moulds)



The zoonotic potential of prion diseases

Internationally recognised for its expertise in prion diseases, **IHAP** recently demonstrated the capacity of the prions responsible for scrapie in small ruminants to cross the species barrier to humans, revealing a previously unrecognised zoonotic potential of transmissible spongiform encephalopathies⁸⁸. These results provide valuable information for the formulation of risk management policies throughout the food production chain, in a context in which Europe is relaxing the security measures put in place at the height of the bovine spongiform encephalopathy (BSE) crisis⁸⁹.

The laboratory is also studying another prion disease, chronic wasting disease (CWD), which affects wild and farmed cervids. Identified in Colorado at the beginning of the 1960s, in three decades CWD spread across almost all of the United States and to three provinces in Canada, and was recently found in Norway (2016), and then in Finland (2017). Current epidemiological data does not show a link between the occurrence of prion diseases in humans and their exposure to CWD (in hunters or people who consume venison); however, experimental data suggests the virus has a certain capacity to cross the species barrier. **IHAP** is characterising the zoonotic potential of prion strains identified in Europe and is researching alleles that are resistant to the disease in French cervid populations, which could contribute to the development of a genetic control strategy against the spread of these forms of transmissible spongiform encephalopathies.

Chronic wasting disease in deer is a prion disease whose risk of transmission to humans is not excluded



Evaluating toxicity risks

Many toxic compounds detrimental to health are found in the environment and in food. Of these, mycotoxins, produced by fungi that contaminate plant-based foods, are a major culprit. *PHARMA-DEV* is studying a particular type of liver cancer in Andean patients that could be linked, among other factors, to the presence of mycotoxins in the grains consumed by the population in this region⁹¹. *TOXALIM* is working on three aspects: the mechanisms behind these fungi's production of toxins⁹², their impact on human and animal health (particularly pigs⁹³), and the development of strategies to control contamination and/or the effects of these toxins.

Analysis at the Toxalim laboratory in Toulouse

The use of fungicides was long the principal control strategy against fungal and mycotoxin contamination of food. However, these substances are toxic for other organisms and, furthermore, targeted moulds now show resistance. Led by *TOXALIM*, and with the participation of civil society, a pilot experiment is being conducted to develop a new evaluation process of the cost-benefit relationship of using fungicides in the framework of an 'EcoHealth' approach. A number of laboratories are collaborating in order to take into account different risk aspects: ecotoxicology (*ECOLAB*), human medicine (in particular renal disease) (*I2MC*), occupational medicine (Toulouse University Hospital), plant epidemiology and health (*LRSV*), animal biology (*TOXALIM*), agricultural economics, and the sociology of risk and epistemology (*TSE*).

Another source of contamination comes from nanotechnology, which involves the use of nanoparticles (ranging in size between 1 and 100 nanometres) for a variety of applications in the food industry, from processing (directly adding nanoparticles to a food product to modify its properties) to packaging (including them in packaging to improve food conservation or to provide information about food safety with the aid of 'nanosensors' for undesirable substances, pathogens or allergens). Ingested by mouth, nanoparticles have potential risks for human health due to their extremely small size, which allows them to cross the biological barrier of the digestive system to circulate in the blood and accumulate in the organs (liver, spleen, brain), where their high chemical reactivity may have potentially toxic effects. It is also suspected that they modify the ecology and/or metabolic activity of the intestinal microbiota, which plays a role in regulating a variety of physiological functions. To better identify and evaluate the health risks linked to nanoparticles, *TOXALIM* and *ECOLAB* are studying their effects on organisms and ecosystems⁹⁴.

Endocrine disruptors are another type of environmental contamination. These interfere with a living organism's natural hormones, and in doing so can affect metabolism, reproduction, development or even cause cancer. *TOXALIM* is developing integrated approaches to evaluate endocrine disruptors and their mechanisms of action⁹⁵. *CBS* and *IRCM* are studying molecular interactions between the major classes of chemical pollutants (e.g. phthalates, parabens, benzophenones, pesticides, alkylphenols, organotins, etc.) and hormone receptors. The results have revealed the mode of action of a large number of these molecules and allowed the development of a bioinformatics tool that predicts if a molecule is an endocrine disruptor. This will steer the development of non-toxic substitutes. 'Cocktail' effects are also being studied by these laboratories, which have demonstrated that different molecules can have combined effects that result in higher toxicity than that of individual molecules. These findings explain certain 'low-dose' effects of endocrine disruptors and call into question the validity of toxicity tests for individual contaminants⁹⁶.

to provide an overview of microbial contamination and monitor it throughout processing. Approaches for improving food safety are being studied, encompassing expertise, training and process optimisation.

SQPOV focuses on bacteria that produce spores, which are widespread in the environment and frequently contaminate food, particularly vegetables. The laboratory is seeking to identify and evaluate the risk these bacteria represent to the health of consumers and to develop solutions to control food contamination.

Food contamination by toxic compounds

The environment is also a source of harmful particles and molecules (from urban, agricultural or industrial pollution) that have damaging effects on health and can cause autoimmune diseases, cancers, respiratory illnesses, etc. These pollutants can penetrate the body through the skin or the respiratory or digestive systems. Many of these molecules are found in food, either secreted by microorganisms contaminating the food (e.g. mycotoxins, toxic compounds produced by moulds growing on fruits

and vegetables), or applied in order to control pathogens that disrupt agricultural production (e.g. pesticides), or that have accumulated in the food chain – in meat, dairy products, eggs, fish – from food consumed by the animals or from pollution in the air, water or soil (e.g. dioxins, heavy metals, etc.).

As with nutrient imbalances, some of these pollutants (fine particulates, N₂O, ammonia, heavy metals, organic compounds, etc.) contribute to the occurrence of chronic diseases by causing low-level inflammation; furthermore, the harmful effects of pollutants and poor nutrition are mutually reinforcing⁹⁰. Several research units in Occitanie are involved in studying the long-term health effects of toxic compounds such as agricultural inputs, pesticides, mycotoxins, chemical migration from food packaging, endocrine disruptors and other food contaminants. Of particular interest is the effect on organisms of chronic exposure to low-dose contaminants, potentially in combination, during critical phases of development and on trophic interactions within communities of organisms (see box above).

The health of a socio-ecological system can be defined as a cross-disciplinary construction resulting from the representations and negotiations around health, biological, economic and cultural norms



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3. Global health applied to food systems

The impact of production systems on the environment and health

Since the 1960s, the objective of global agricultural policy has been to rapidly increase production to ensure food security, which has been relatively successful. This policy has led to the vast expansion of cultivated areas and livestock farming, while economies of scale to lower costs have resulted in the standardisation of agricultural production and the specialisation of farming areas in a few major crops. This simplification and intensification of farming systems has been made possible in part by the massive use of fossil fuels and synthetic inputs such as mineral fertilisers, pesticides and antibiotics.

Yet these modes of production have generated negative externalities for the environment, ecosystem services and human health that are today widely recognised: through air and water pollution, greenhouse gas emissions, and so on. In addition, the huge increase in the global trade of agricultural products (e.g. seeds, livestock feed such as soybean meal, and food products) between specialised regions has led to vast transfers of nutrients, pollutants, carbon, energy and water between the world's regions.

One of the effects of this growth in trade is more standardised and processed agri-food products, leading to more uniform diets. The distance of the consumer from food production has resulted in a loss of a sense of both the quality and the true cost of food. Linked to urbanisation and changing lifestyles, altered diets have had negative health consequences for certain parts of the population, as illustrated by the global epidemic of non-communicable diseases.

All these factors point to the need to transform current food systems and develop alternatives that promote food that is more sustainable from both an environmental point of view (minimising the use of unrenovable resources and avoiding pollution) and a socio-economic perspective (providing healthy food for consumers, allowing producers to make a fair living, and contributing to the development of a territory). The establishment of a local 'circular economy', maximising the reuse of co-products and encouraging crop diversity, contributes

to closing biogeochemical cycles by reducing nitrogen emissions, diversifies the food offer and brings consumers and producers closer together.

Until recently, the general trend in public policy has been to tackle problems independently sector by sector – e.g. water, pesticides, nitrates (environment); or protein, fat content, biofortification (food and health) – or through technology (e.g. anaerobic digestion or precision farming through information technologies) or through 'product-services' (e.g. local food production and distribution). Yet the interdependence of these phenomena calls for the need for structural policy, based on an integrated approach to food systems.

The concept of health, applied to all living organisms and on all analytical scales (humans, animals, plants, soil, the planet), can be enlisted to reconnect agriculture, the environment and food.

This concept can be used to foster exchange between consumers, decision-makers and stakeholders in agriculture, agricultural inputs sector and the agri-food industry. Although the 'health' of an ecosystem cannot be defined *per se*, its condition can nonetheless be characterised from an anthropomorphic point of view in relation to the set of services that it supplies (see box opposite).

The areas to consider here concern (i) land use and biomass management, (ii) material and energy flow management, and (iii) diet. Each of these affects the three following major health vectors: (i) ecosystem services that should be promoted so as to reduce the negative impacts of current agricultural practices, (ii) biogeochemical cycles that need to be closed so as to save resources and avoid pollution, and (iii) human and animal diets that are compatible with health and the quality of the environment. One example is the role of leguminous plants as vectors of health for a transition to sustainable food systems (see box opposite).

Is it possible to talk about the ‘health’ of ecosystems?

On a varying long time scale, all ecological systems are in a transitory state that results from complex processes that are subject to many interactions, making it impossible to objectively define the ‘health’ of an ecosystem. However, we can subjectively describe the dynamic, transient equilibrium of an anthropo-ecosystem and evaluate its trajectory in terms of the range of services expected from the system in a given biogeographic socio-economic context. In this way, the health of a socio-ecological system can be defined as a cross-disciplinary construction resulting from the representations and negotiations around health, biological, economic and cultural norms⁹⁷. A key research challenge is to provide the scientific concepts required to define such systems and to allow their cross-sectoral management. A number of research units in Occitanie are studying these questions (*AGIR, ASTRE, CEFE, DYNAFOR, EDB, ECOLAB, Forêts & Sociétés, GREEN, MARBEC*, etc.).

The benefits of ‘healthy’ soil

Soil is the subject of particular attention in the framework of integrated approaches to health. It can be a vehicle for spreading antibiotic resistance genes; on the other hand, soil microorganisms can be a source of new molecules with antibiotic properties. Aside from that, soil supplies a multitude of ecosystem services. Macro- and microorganisms in the soil contribute to its structure, serving as cement for mineral elements (sand, silt and clay) by lending them cohesive characteristics. A ‘living’ soil is thus better able to retain water, is more resistant to wind and water erosion and protects against flooding. Soil is the basis of all agriculture. Its microorganisms are essential actors in biogeochemical cycles, converting organic matter into minerals that can be absorbed by plants. A soil that is fertile, rich in organic matter and in macro- and microorganisms is a nourishing soil – its opposite is a degraded soil. *ECO&SOLS* is studying the roles of soil organisms and plants, the interactions between them and their environment, and how this affects the biogeochemical cycles of carbon, nitrogen and phosphorous within agroecosystems. Moreover, soil can potentially be a powerful sink for atmospheric carbon, by virtue of its capacity to store organic matter, as well as its role as a substrate for plants, particularly trees, which store carbon through photosynthesis. This capacity is behind the ‘4 per 1000’ idea: a French initiative to promote soil carbon sequestration in the interest of both food security and the climate. Today the initiative has become international, bringing together 360 partners and members, with a Secretariat based in Montpellier.

The value of leguminous plants in the agroecological transition

Forage and grain legumes are key crops for providing a wide range of ecosystem services, whether they are cultivated alone, in association with cereal crops, or as green fertiliser. *AGIR* is carrying out various research studies with the aim of integrating legumes in agricultural systems to increase the latter’s autonomy in terms of inputs. One aspect of this involves working with local stakeholders to co-design development and relocation scenarios for forage and grain legume production, and then to simulate and evaluate the agronomic and environmental impacts of this shift.

From a nutritional point of view, the advantages of a ‘Mediterranean diet’, emphasising fruits, vegetables and pulses while minimising animal protein and ultra-processed foods, have been proven. Increased availability of legume-based foods would thus contribute to the transition to a healthier diet. In this area, *IATE* is working on the inclusion of legumes in processed food products. Substituting a proportion of animal proteins by plant-based proteins would also reduce the impact of our diets on water consumption and greenhouse gas emissions.

MOISA is developing models to evaluate the environmental impact of different types of diets (existing diets or optimised diets) from a nutritional point of view.

Achieving a successful agroecological transition with a real impact on a territory requires effective coordination between stakeholders: horizontally, links must be (re)created between all those concerned by the implications of the transition, and vertically, the production chain must be safeguarded while ensuring the fair redistribution of the value created. To this end, *AGIR* and *INNOVATION* guide stakeholders in defining and evaluating collective governance structures between the different parties.



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Pulse crops have many benefits for animal and human diets, as well as for the environment

Reducing losses in production systems

In the framework of an integrated approach to food systems, the issue of losses due to crop pests or plant or livestock pathogens is of worldwide importance. The highest losses are observed in regions with low food production and high population growth – exacerbating problems of food security – which are also regions where the emergence or re-emergence of diseases and pests are more frequent⁸⁴. These losses concern not only agricultural products, but all the resources used in their production. In addition, the chemical treatments to reduce these losses are often incompatible with environmental quality.

Around the world, reducing production losses while limiting the use of treatments and the emergence of resistance are critical challenges.

These require an understanding of the mechanisms that influence the dynamics of pathogens and pests, the development of resistant varieties and breeds, the creation of control methods against pests and diseases, as well as the optimisation of plant and animal nutrition – all while taking into account the socio-economic conditions of the people concerned.

A number of research units in Occitanie are working on developing and disseminating innovative agricultural practices related to crop health management in accordance with the principles of agroecology – a set of practices based on the use of ecological processes and the development of agro-biodiversity: **AGIR**, **AIDA** and **SYSTEM** are focusing in particular on viticulture and the main crops in temperate and Mediterranean zones (cereals, oleaginous plants and legumes) and tropical zones (cotton, sugarcane and African cereals), as well as on temperate and tropical agroforestry systems; **PSH**, **HORTSYS** and **GECO** on horticultural production (fruit and vegetables) in the Mediterranean (**PSH**), in the tropical zone (**HORTSYS**), and in agrosystems based on bananas and pineapples (**GECO**); **PSCPP**'s research focuses on tropical perennial crops (palm oil, rubber, cacao, coffee and coconut); **SELMET**'s activities are related to pastoral or agro-pastoral (mixed) family farming systems, principally based on ruminants, in Mediterranean and tropical regions; and **INNOVATION** and **AGIR** are studying and developing the methods and tools required to assist the innovation process in temperate, Mediterranean and tropical agricultural systems. Some examples of the design of agroecological practices in agricultural production systems are provided in the boxes below and opposite.

Outwitting red poultry mites

Using an integrated approach, **CEFE** is working to improve the control of the red poultry mite, a problematic hematophagous mite that is omnipresent on egg farms. To optimise the management of this mite while minimising the environmental impact, an innovative agroecological method was developed. As the mite does not live on the host but in recesses and cracks in the hen house, the aim is to limit the population of the mite (i) by disturbing its ability to come into contact with the hen (through chemical ecology and attraction/repulsion) and (ii) by encouraging the regulating action of its natural enemies (through community ecology and biological pest control). To achieve this, it is necessary to untangle the interactions of the red poultry mite with its host and with the other arthropods that thrive in egg-laying systems. The research brings together diverse expertise and investigation tools (e.g. arthropod surveys, phylogenetics and metagenomics, modelling, chemical analysis, behavioural tests and electrophysiology).

In terms of limiting mite populations, a cocktail of five volatile compounds has been developed that has proven to attract red poultry mites and for which a patent has been filed⁹⁸, which in turn could lead to the development of traps. Progress is also being made on biological pest control: around a dozen species of predators of the mite have been identified among arthropods that occur naturally in poultry flooring systems⁹⁹. Research is underway to find ways to make the most of their presence as natural enemies of this pest.

Developing agroecological management methods in crop and livestock systems is a long-term process



An integrated approach to health management in tropical plantations

Despite notable progress, agrosystems remain major users of chemical inputs (herbicides, insecticides, fungicides and fertilisers) that are harmful to both biodiversity and human health. Reintroducing functional diversity into agrosystems allows these artificial inputs to be reduced. This involves maintaining a level of biodiversity in both vegetation (e.g. plants that provide ecosystem services, aromatic plants, native multi-species crops, etc.) and animals (e.g. predators, parasites of insects, pollinators, etc.), while equally considering the spatial and temporal organisation of crops (how they are laid out, crop rotation, leaving land fallow, etc.) in order to control bioaggressors (pests and diseases).

However, the presence of diverse species in a plot can have positive as well as negative effects on plant health. These effects can vary depending on the plant species, on the bioaggressors and their natural enemies, on their life history traits and on their physical environments. The development of bioaggressor populations is closely linked to the characteristics of the host plant, in particular its phenology, which influences resource availability. Assessing these effects at the scale of the associated bioaggressors is very complicated; even more so if the interaction with the environment – especially the climate – is considered. In addition, the spatial expansion of bioaggressor populations depends on their capacity for mobility, and on the nature and structure of the environment – a fragmented or connected landscape – in which the individuals move around. The spatial scale is thus crucial in this approach, as a specific environment can change status, from dangerous to neutral or even favourable, with a change in scale. As a result, implementing health management strategies based on agroecology, while ensuring a high level of production and quality, is not a straightforward matter. Experimentation is necessary to analyse and understand the processes in order to optimise the combinations of species and the crop management techniques before these can be adopted by farmers on a large scale.

In the French Caribbean, *GECO* is working on banana production with a focus on controlling black sigatoka (black leaf streak disease), which is caused by a fungus, using a variety of methods: from the development of resistant varieties, to the adaptation of crop management techniques (for example, necrotic leaf removal) to the introduction of biological control agents. Some of the experiments are carried out directly in the plantations of volunteer farmers, allowing performance to be evaluated in real conditions and facilitating the adoption of methods that have proved their worth.

HORTSYS and *PSH* are developing a computer modelling programme that simulates crop management methods for mango orchards in La Reunion and peach orchards in southeast France. The methods are co-constructed with fruit farmers and then evaluated in terms of their capacity to limit the development of bioaggressors (which include fruit flies, mango blossom gall midges and peach brown rot) and the damage they cause, as well as meet the requirements of agronomic efficiency, economic viability and sustainability.

BIOAGRESSEURS is studying health management in tropical perennial crop systems, in particular coffee, cacao and oil palm plantations. After numerous experiments in Central America, the unit developed an integrated management programme for the coffee borer beetle, the main insect pest of this crop. This strategy is based on three complementary measures: (i) strict sanitation harvesting of the coffee berries; (ii) trapping the insects present in the plantation four months per year (e.g. with the BROCAP© trap developed by the unit), and (iii) rigorous agronomic management (pruning, rehabilitation of the plantation). Thanks to this three-pronged approach, infestations by coffee borer beetles were reduced by 90% in shady coffee plantations in tropical zones with two seasons (dry and wet) and one annual harvest. An adapted protocol is being studied in the region of Toba (North Sumatra, Indonesia), in partnership with the company IndoCafCo, in very different climatic conditions.

Research, education and training in integrated health in Occitanie

1. The organisations involved in integrated health research

The region of Occitanie has a large number of research and higher education institutes (see table below). The scientists working for these institutes in relevant fields collaborate within joint thematic research units. While this report is not exhaustive, 66 research units (see pages 44-45) are cited that are involved more or less directly with integrated approaches to health, whether the focus is on humans, animals, plants, microorganisms or the environment. This wealth, diversity and complementarity of expertise are fundamental to the growing importance of integrated scientific approaches to health in the region. Some of these networks extend beyond the region: in

the area of plant health, the laboratories of INRAE in Avignon (in the Provence-Alpes-Côte d'Azur region) are included in this *dossier* as they have close links with the laboratories in Montpellier, particularly through their co-membership in the 'Agro' laboratory of excellence, accredited by the French Ministry of Higher Education, Research and Innovation and managed by Agropolis Foundation. In the area of animal health, the presence in Occitanie of the National Veterinary School of Toulouse along with partner institutions (INRAE, universities, agricultural schools, etc.) has led to the creation of a national scientific hub of expertise in animal science.

List of umbrella institutions for the research units cited in this report

Umbrella institutions with one or several centres in Occitanie	
APT	AgroParisTech
CHU Montpellier	Montpellier University Hospital
CHU Toulouse	Toulouse University Hospital
Cirad	French Agricultural Research Centre for International Development
CNRS	French National Centre for Scientific Research
EI-Purpan	School of Engineering of Purpan
ENSAT	National High School of Agricultural Sciences of Toulouse
ENVT	National Veterinary School of Toulouse
IAM.M	Mediterranean Agronomic Institute of Montpellier
Ifremer	French National Institute for Ocean Science
IFV	French Institute of Vineyards and Wine
INPT	National Polytechnic Institute of Toulouse
INRAE	French National Research Institute for Agriculture, Food and the Environment
Inserm	French National Institute of Health and Medical Research
IRD	French Research Institute for Sustainable Development
MSA	Montpellier SupAgro
UC-TI	Toulouse Capitole University – Toulouse I
UM	University of Montpellier
UPS-T3	Toulouse Paul Sabatier University – Toulouse III
UPVD	University of Perpignan – <i>Via Domitia</i>
UPVM	Montpellier Paul Valéry University
Umbrella institutions with personnel working in research units in Occitanie	
CBN	National Botanical Conservatory
EHESS	School of Advanced Studies in the Social Sciences
EPHE	Higher Education and Research Institute in Earth and Life Sciences, History and Philology, and Religion
Inria	French Research Institute for Digital Sciences
SU	Sorbonne University
Associated umbrella institutions not based in Occitanie	
UAG	University of the French West Indies and Guiana
UAPV	University of Avignon – Pays du Vaucluse
UR	University of La Reunion

I-site MUSE: mobilising the expertise of 19 scientific institutes in and around Montpellier

In the framework of the Montpellier University of Excellence (MUSE) *consortium*, 19 institutions have joined forces with a shared ambition: to create a research-intensive university that is internationally recognised for its impact in the areas of agriculture, the environment and health, fields in which Montpellier has a significant concentration of research expertise. MUSE rallies the scientific, academic, governmental and business communities to address three major, interlinked challenges for the 21st century highlighted in the United Nation's 2030 Agenda for Sustainable Development and in the Paris Agreement on climate change: **Feed** – promote innovative agricultural solutions that contribute to both food security and environmental quality; **Protect** – foster the transition towards a society that respects the environment; **Care** – improve human health in the context of changing environments.

The time has passed when the planet's resources could be considered inexhaustible – today around the world we must learn to manage limited natural resources sustainably. Global population growth has increased the need for goods and services, risking the degradation of the majority of the Earth's ecosystems and a rise in food security issues for the most fragile populations. In parallel, the world population is confronting new health problems, some of which are related to the environment (e.g. vector-borne diseases) and some of which are related to modern lifestyles (e.g. chronic diseases). The consequences of human activities – biodiversity loss, climate change, disruption of the water cycle, changes in land use (urbanisation, deforestation, intensive agriculture), food and nutrition insecurity, a quantitative increase in toxic agents – is forcing the world to face these challenges. Finding sustainable solutions will demand research: into emerging diseases in humans, plants and animals, into the deterioration of human health, into increased pressure on ecosystems and the environment, into unsustainable management of natural resources arising from farming, forestry and fishery systems, and so on. Integrated approaches to health, in both research and education, are thus one of the priorities of MUSE, being developed by *consortium* members in close collaboration with their regional, national, European and international partners.

The fields of ecology, environmental science and evolution are particularly well represented in the region and have been recognised by the accreditation of two national laboratories of excellence: TULIP in Toulouse and CeMEB in Montpellier. And in the area of human health, the university hospitals in Montpellier and Toulouse, as well as the presence of Inserm, allow the region's expertise in veterinary and environmental science to be linked with human health science. To further leverage the strength of organisations based around Montpellier in the fields of health, agriculture and the environment, 19 scientific partners have joined together in the Montpellier University of Excellence (MUSE) *consortium* (see box above).

The region of Occitanie is also distinguished by its international reach, particularly in tropical zones and around the Mediterranean, essentially through the presence in Montpellier of the major research institutes Cirad and IRD, whose activities specifically focus on the issues of these regions. As a result, this report also includes international joint research units and laboratories based in other countries or in French overseas territories (this is the case of *PIMIT* and *PVBMT*) that are under the umbrella of Cirad or IRD.

This extensive scientific community is supported by state-of-the-art experimental and technological platforms (see box below). All these ingredients make Occitanie a leader in integrated scientific approaches in health.

Innovative facilities and partnership networks

Vectopole Sud, a network in Montpellier for research into arthropods of medical, veterinary or agricultural interest, oversees four experimental platforms and insectariums – available to national and international partners – under the umbrella of five institutes of research and higher education (Cirad, CNRS, INRAE, IRD and the University of Montpellier) together with the main public mosquito control agency in France, EID-Méditerranée. Their objective is to pool facilities and skills in order to develop innovations in the fight against crop pests and pathogen vectors that cause infectious human or animal diseases. Experimental stations further afield are also to become part of the Vectopole Sud network: for example, the Toulouse Experimental Centre for Rabbits, the La Fage Experimental Site for sheep in the Larzac, and the Gardouch site in Haute-Garonne to study roe deer. These sites allow teams working on vector-borne diseases to carry out innovative controlled experiments on animals in conditions similar to natural or livestock-raising contexts.

This network, unique in Europe, is extended by a partnership with foreign institutions. The International Joint Laboratory of Vector-borne Diseases (LAMIVECT) in West Africa, based in Bobo-Dioulasso in Burkina Faso, brings together several of the country's institutes with the French research centres IRD and Cirad, and has recently expanded to include institutes in Bouaké in the Ivory Coast. Today, LAMIVECT is a reference centre in West Africa for research, education and management of vector-borne diseases that affect humans and animals. Other key partnerships are *TRANSVIHMI*'s links in the Democratic Republic of Congo, Cameroon and Guinea with the international laboratories PREVIHMI and RESPIRE, which are reference centres for understanding and preventing the emergence risks of HIV and the Ebola virus. In addition, the Platforms in partnership for research and training created by Cirad with its foreign partner institutions in developing countries bring a unique perspective for integrated approaches to health. Supporting this nexus of scientific expertise is advanced technology (for genomics, sequencing, transcriptomics, phenotyping, metabolomics, imaging, screening, bioinformatics, statistics, modelling, etc.) in state-of-the-art facilities in Montpellier and Toulouse.

Directory of research units cited in this dossier

Acronym Umbrella institutions	Name Website	Main location
AGAP CBN / Cirad / IFV / INRAE / Inria / MSA	Genetic Improvement and Adaptation of Mediterranean and Tropical Plants http://umr-agap.cirad.fr/	Montpellier
AGIR INPT / INRAE	Agroecology-Innovation-Territories https://www6.toulouse.inra.fr/agir	Toulouse
AIDA Cirad	Agroecology and Sustainable Intensification of Annual Crops http://ur-aida.cirad.fr/	Montpellier
ASTRE Cirad / INRAE	Animals, Health, Territories, Risks & Ecosystems https://umr-astre.cirad.fr/	Montpellier
BGPI Cirad / INRAE / MSA	Biology and Genetics of Plant-Pathogen Interactions http://umr-bgpi.cirad.fr/	Montpellier
BIOAGRESSEURS Cirad	Bioaggressors: Analysis and Management of Risks http://ur-bioagresseurs.cirad.fr/	Montpellier
BIOM CNRS / SU	Integrative Biology of Marine Organisms http://biom.obs-banyuls.fr/	Banyuls-sur-Mer
CBGP Cirad / INRAE / IRD / MSA	Centre for Biology and Management of Populations http://www1.montpellier.inra.fr/CBGP/	Montpellier
CBS CNRS / Inserm / UM	Centre of Structural Biochemistry http://www.cbs.cnrs.fr/index.php/fr/	Montpellier
CEFE CNRS / INRAE / EPHE / IRD / MSA / UM / UPVM	Centre for Functional and Evolutionary Ecology http://www.cefe.cnrs.fr/	Montpellier
CEFS INRAE	Behaviour and Ecology of Wildlife https://www6.toulouse.inra.fr/cefs/	Toulouse
CPTP Inserm / UPS-T3	Toulouse Purpan Centre for Pathophysiology https://www.cptp.inserm.fr/	Toulouse
DGIMI INRAE / UM	Diversity, Genomes and Microorganism-Insect Interactions http://www6.montpellier.inra.fr/dgimi/	Montpellier
DIADE Cirad / IRD / UM	Plant Diversity, Adaptation and Development http://www.diade-research.fr/	Montpellier
DMEM Cirad / IRD / UM	Muscular Dynamics and Metabolism https://www6.montpellier.inra.fr/dmem	Montpellier
DYNAFOR INRAE / INPT	Dynamics and Ecology of Agroforestry Landscapes https://www.dynafor.fr/	Toulouse
ECO&SOLS Cirad / INRAE / IRD / MSA	Functional Ecology and Biogeochemistry of Soils and Agrosystems https://www.umr-ecosols.fr/	Montpellier
ECOLAB CNRS / INPT / UPS-T3	Laboratory of Functional Ecology and the Environment http://www.ecolab.omp.eu/	Toulouse
EDB CNRS / IRD / UPS-T3	Evolution and Biological Diversity Laboratory http://edb.cnrs.fr/	Toulouse
ESPACE-DEV IRD / UAG / UM / UPVD / UR	Spatial Dynamics of Socio-ecological Systems in Developing Countries http://www.espace-dev.fr/	Montpellier
Forêts & Sociétés Cirad	Forests and Societies https://ur-forets-societes.cirad.fr/	Montpellier
GAFI INRAE	Genetics and Breeding of Fruits and Vegetables http://w3.avignon.inra.fr/gafi/	Avignon
GECO Cirad	Functional Ecology and Sustainable Management of Banana and Pineapple Agrosystems http://www.cirad.fr/ur/systemes_bananes_ananas	Montpellier
GENPHYSE ENSAT / ENVT / INRAE	Genetics and Physiology of Livestock Systems https://genphyse.toulouse.inra.fr/	Avignon
GREEN Cirad	Management of Renewable Resources and Socio-ecological Dynamics https://ur-green.cirad.fr/	Montpellier
HORTSYS Cirad	Agroecology and Performance in Horticultural Systems http://ur-hortsys.cirad.fr/	Montpellier
HSM CNRS / IRD / UM	Hydrosciences Montpellier http://www.hydrosciences.org/	Montpellier
I2MC Inserm / UPS-T3	Institute of Cardiovascular and Metabolic Diseases http://www.i2mc.inserm.fr/index.php/fr/	Toulouse
IATE Cirad / INRAE / MSA / UM	Agropolymer Engineering and Emerging Technologies https://umr-iate.cirad.fr/	Montpellier
IHAP ENVT / INRAE	Host-Pathogen Interactions http://www.envt.fr/menu-og-32/ihap	Toulouse
IHPE CNRS / Ifremer / UM / UPVD	Host-Pathogen-Environment Interactions http://ihpe.univ-perp.fr/	Montpellier
INNOVATION Cirad / INRAE / MSA	Innovation and Development in Agriculture and Food http://umr-innovation.cirad.fr/	Montpellier

INTERTRYP Cirad / IRD	Host–Vector–Parasite–Environment Interactions in Neglected Tropical Diseases Caused by Trypanosomatids http://umr-intertryp.cirad.fr/	Montpellier
INTHERES ENVT / INRAE	Therapeutic Innovations and Resistance https://www6.toulouse.inra.fr/intheres	Toulouse
IPBS CNRS / UPS-T3	Institute of Pharmacology and Structural Biology http://www.ipbs.fr/	Toulouse
IPME Cirad / IRD / UM	Plant-Microorganisms-Environment Interactions http://umr-ipme.ird.fr/	Montpellier
IRCM Inserm / UM	Montpellier Cancer Research Institute https://ircm.fr/	Montpellier
IRIM CNRS / UM	Montpellier Research Institute of Infectious Diseases https://www.irim.cnrs.fr/index.php	Montpellier
IRSD ENVT / INRAE / Inserm / UPS-T3	Digestive Health Research Institute https://www.irsd.fr/	Toulouse
ISEM Cirad / CNRS / EPHE / IRD / UM	Montpellier Institute of Evolutionary Sciences http://www.isem.univ-montp2.fr/	Montpellier
LBBM CNRS / SU	Laboratory of Microbial Biodiversity and Biotechnology http://lbbm.obs-banyuls.fr/	Banyuls-sur-Mer
LBE INRAE	Laboratory of Environmental Biotechnology https://www6.montpellier.inra.fr/narbonne	Narbonne
LIPM CNRS / INRAE	Laboratory of Plant-Microorganism Interactions https://www6.toulouse.inra.fr/lipm/	Toulouse
LSRV CNRS / UPS-T3	Plant Science Research Laboratory https://www.lrsv.ups-tlse.fr/	Toulouse
MARBEC CNRS / Ifremer / IRD / UM	Marine Biodiversity, Exploitation and Conservation http://www.umr-marbec.fr/fr/	Sète
MIVEGEC CNRS / IRD / UM	Infectious Diseases and Vectors: Ecology, Genetics, Evolution and Management http://www.mivegec.ird.fr/	Montpellier
MOISA IAM.M / Cirad / INRAE / MSA	Markets, Organisations, Institutions and Stakeholder Strategies http://umr-moisa.cirad.fr/	Montpellier
NUTRIPASS IRD / MSA / UM	Food and Nutrition in Developing Countries http://www.nutripass.ird.fr/	Montpellier
PCCI Inserm / UM	Pathogenesis and Management of Chronic Infections https://www.umontpellier.fr/recherche/unites-de-recherche/pathogenese-et-controlle-des-infections-chroniques-pcci	Montpellier
PHARMA-DEV IRD / UPS-T3	Pharmacochemistry and Biology for Developing Countries https://www.pharmadev.ird.fr/	Toulouse
PIMIT CNRS / Inserm / IRD / UR	Infectious Processes in Tropical Island Environments https://pimit.univ-reunion.fr/	Saint-Denis de la Réunion
PSCPP Cirad	Performance of Perennial Plant Cultivation Systems http://ur-systemes-de-perennes.cirad.fr/	Montpellier
PSH INRAE	Plants and Horticultural Systems http://www6.paca.inra.fr/psh	Avignon
PV INRAE	Plant Pathology http://www6.paca.inra.fr/pathologie_vegetale	Avignon
PVBMT Cirad / UR	Plant Populations and Bioaggressors in Tropical Environments https://umr-pvbmt.cirad.fr/	Saint-Pierre de la Réunion
QUALISUD Cirad / MSA / UM / UAPV / UR	Integrated Approach to Food Quality http://umr-qualisud.cirad.fr/	Montpellier
SELMET Cirad / INRAE / MSA	Mediterranean and Tropical Livestock Systems http://umr-selmet.cirad.fr/	Montpellier
SQPOV INRAE / UAPV	Safety and Quality of Plant-based Products http://www6.paca.inra.fr/sqpo	Avignon
SYSTEM Cirad / IAM.M / INRAE / MSA	Tropical and Mediterranean Cultivation Systems http://umr-system.cirad.fr/	Montpellier
TETIS APT / Cirad / CNRS / INRAE	Territories, Environment, Remote Sensing and Spatial Data https://www.umr-tetis.fr/index.php/fr/	Montpellier
TOXALIM EI-Purpan / ENVT / INRAE / UPS-T3	Research Centre in Food Toxicology https://www6.toulouse.inra.fr/toxalim	Toulouse
TRANSVIHMI Inserm / IRD / UM	Translational Research in HIV and Infectious Diseases https://transvihmi.ird.fr/	Montpellier
TSE CNRS / EHESS / INRAE / UC-TI	Toulouse School of Economics https://www.tse-fr.eu/fr	Toulouse
UDEAR Inserm / UPS-T3	Epithelial Differentiation and Rheumatoid Autoimmunity Unit http://www.inserm-udear.cnrs.fr/	Montpellier
VAP UM	Anti-Parasite Vaccines https://www.umontpellier.fr/recherche/unites-de-recherche/laboratoire-de-biologie-cellulaire-et-moleculaire-lbcm	Toulouse
VBMI UM	Bacterial Virulence and Infectious Disease https://u1047.edu.umontpellier.fr/	Montpellier

2. Education and training in integrated health approaches

With their extensive scientific expertise, the research and higher education institutes in Occitanie have developed a unique educational offer in integrated health approaches. Alongside the standard academic degrees in human health, veterinary science and phytopathology available at the region's universities and engineering schools, interdisciplinary Master's degrees have been designed that put particular emphasis on cross-fertilisation between fields. There are also a range of training modules aimed at both students and practicing professionals (see table below). Two international Master's degrees are being developed, one of which (*One Health & Infectious Diseases*) will be a distance learning course, and the other (*Global Health*) will be taught on site. Aside from degree courses, scientists in the region have developed or participate in various targeted short courses for students and/or professionals (see boxes opposite).



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Degrees in Occitanie on integrated health approaches

Acronym	Degree title Website	Site Institutions delivering the degree	Description
DIPHE	Master's in biology, ecology and evolution, with specialisation in parasite-host-environment interaction dynamics https://biologie-ecologie.com/master-b2e/parcours/diphe/	Montpellier University of Montpellier IRD	This degree provides an understanding of the ecological and evolutionary processes that shape the dynamics of host-parasite interactions.
EPI	Master's and International Master's in biology, ecology and evolution, with specialisation in emergence of parasitic and infectious diseases https://biologie-ecologie.com/presentation-du-master-epi/	Montpellier University of Montpellier IRD	This degree offers the tools to analyse the different factors involved in an epidemic or the emergence of a disease and to identify the challenges, contexts and societal issues involved in managing these events.
GIMAT	Master's in biology, with specialisation in the integrated management of tropical animal diseases http://www.masterbiosante.ups-tlse.fr/m2-gimat-596888.kjsp?RH=1298890088210	Toulouse/Montpellier National Veterinary School of Toulouse Toulouse Paul Sabatier University - Toulouse III Cirad	This degree trains animal health epidemiological experts and/or risk managers in the emergence and spread of animal and zoonotic diseases of particular interest in Mediterranean and tropical countries.
IMHE	Master's in agriscience, with specialisation in microorganism-host-environment interactions https://bioagro.edu.umontpellier.fr/master-biologie-agrosiences/interactions-microorg-hotes/	Montpellier University of Montpellier IRD INRAE	This degree, part of a specialisation in microbiology, gives students in medicine, pharmacy, dentistry, biology or agronomy a global, integrated vision of microorganisms in relation to their hosts (humans, animals – including insects – and plants) and their natural and anthropized environments.
INTERRISK	International Master's: assessment and management of health risks at the human, animal and ecosystem interface http://www.onehealthsea.org/interrisk	Bangkok, Thaïlande Cirad National Veterinary School of Toulouse Toulouse Paul Sabatier University - Toulouse III Kasetsart University	This degree offers academic training in risk management related to emerging and endemic diseases based on the 'One Health' interdisciplinary approach (see box opposite).
SEMHA	Master's in public health, with specialisation in epidemiological surveillance of human and animal diseases http://aeema.vet-alfort.fr/index.php/2013-04-12-00-34-41/ces-master	Maisons-Alfort / Montpellier National Veterinary School of Alfort Paris-Sud University Paris-Est Créteil University Cirad	This degree provides the basic methods and the tools for developing, coordinating and facilitating surveillance systems.

Tailormade training

The scientific expertise of the region's laboratories is also capitalised on to develop short tailormade training courses for students or professionals in different contexts. For example, an international university degree supported by Montpellier University of Excellence (MUSE) is delivered by a consortium of partners (CNRS, Cirad, IRD, Inserm, University of Montpellier and the Interstate School of Veterinary Science and Medicine of Dakar in Senegal). The course, *Emerging infections: a 'One Health' approach*, is aimed at health professionals, entomologists, ecologists, economists, sociologists, etc.

In another example, *ASTRE* organised an international four-week summer school in 2018 on 'One Health' approaches in the fight against antibiotic resistance for ten Master's students interested in pursuing doctoral degrees in France. Professors and researchers in Occitanie also participate in an annual summer school on operational approaches to implementing 'Global One Health' concepts, which is held every year in the framework of the joint European 'One Health' programme and is aimed at bachelor and Master's students, doctoral students and researchers.

Training sessions are also organised in the framework of specific projects: for example, the EBO-SURSY project funded by the European Union, led by the World Organisation for Animal Health in partnership with Cirad, IRD and the Institut Pasteur, aims to reinforce surveillance capabilities for the Ebola virus and priority zoonotic diseases. Training is delivered to professionals on sample collection, diagnostics, epidemiology, risk evaluation, surveillance and communication. Seminars on zoonotic diseases are also held for local educational establishments, markets, community leaders, religious groups and public sector personnel in human and animal health.

In 2017, *TRANSVIHMI* and the Guinean Centre for Research and Training in Infectious Diseases at the Gamal Abdel Nasser University of Conakry organised the first collective training in Guinea in a university context with the objective of 'social preparedness' for emerging and re-emerging epidemics. This first session was an opportunity to define the needs for future sessions, which will be integrated in a broader programme aimed at different groups and will include courses in anthropology, community health and public health intervention⁶⁴.



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An International Master's in 'One Health' in Southeast Asia

'InterRisk' is an International Master's degree that provides academic training in assessing and managing risks related to emerging and endemic diseases. Based on the 'One Health' approach, the programme encourages students in different disciplines – veterinary science, medicine, biology and agricultural science – to work together. Coordinated by

Cirad in partnership with the National Veterinary School of Toulouse and the Veterinary Department of Kasetsart University in Bangkok, graduates are awarded two diplomas, one from Kasetsart University (Thailand) and the other from Toulouse University (France). The degree is based on active learning methods, combining interventions from health professionals and different pedagogical approaches – problem solving based on real cases on the ground relevant to the health situation in the field (e.g. Nipah virus, H5N1 virus, rodents and pathogens, etc.), laboratory work, field visits and investigations of outbreaks – providing invaluable practical experience. Particular importance is given to developing students' interpersonal skills through group work and discussion forums around issues of ethics, parity and leadership. The course is held at the Veterinary Department of Kasetsart University in Bangkok, offering a unique opportunity for students to receive *in situ* training in Southeast Asia. The programme focuses on the study of five specific diseases (rabies, Japanese encephalitis, leptospirosis, cysticercosis and influenza) and antimicrobial resistance, looking at these topics in all their dimensions – epidemiological, sociological and economic – and putting students in direct contact with networks of professionals involved in the 'One Health' approach in Southeast Asia. The degree enables students to develop and evaluate health risk surveillance and management programmes, integrating epidemiological, ecological and socio-economic approaches.

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EHESS - School of Advanced Studies in the Social Sciences

EI-Purpan - Purpan School of Engineering

ENSAT - School of Agricultural and Life Sciences

ENVT - National Veterinary School of Toulouse

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IFV - French Institute of Vineyards and Wine

INPT - National Polytechnic Institute of Toulouse

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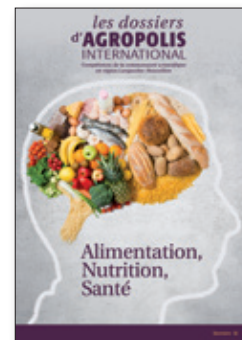
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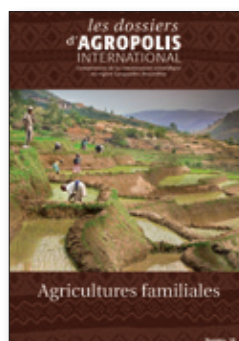
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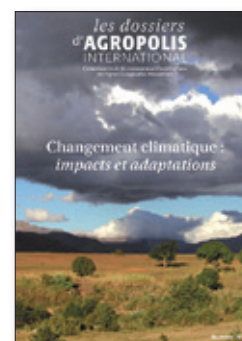
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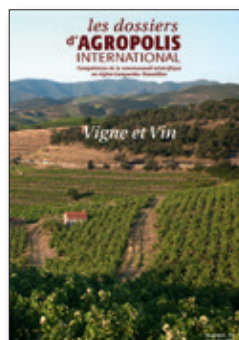
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